Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial

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Summary

Background Continuation of empirical antimicrobial therapy (EAT) for febrile neutropenia in patients with haematological malignancies until neutrophil recovery could prolong the therapy unnecessarily. We aimed to establish whether EAT discontinuation driven by a clinical approach regardless of neutrophil recovery would optimise the duration of therapy.

Methods We did an investigator-driven, superiority, open-label, randomised, controlled phase 4 clinical trial in six academic hospitals in Spain. Eligible patients were adults with haematological malignancies or haemopoietic stem-cell transplantation recipients, with high-risk febrile neutropenia without aetiological diagnosis. An independent, computer-generated randomisation sequence was used to randomly enrol patients (1:1) to the experimental or control group. Investigators were masked to assignment only before randomisation. EAT based on an antipseudomonal β-lactam drug as monotherapy (ceftazidime or cefepime, meropenem or imipenem, or piperacillin-tazobactam) or as combination therapy (with an aminoglycoside, fluoroquinolone, or glycopeptide) was started according to local protocols and following international guidelines and recommendations. For the experimental group, EAT was withdrawn after 72 h or more of apyrexia plus clinical recovery; for the control group, treatment was withdrawn when the neutrophil count was also $0{\cdot}5\times10^9$ cells per L or higher. The primary efficacy endpoint was the number of EAT-free days. Primary analyses were done in the intention-to-treat population. Efficacy and safety analyses were done in the intention-to-treat population and the per-protocol population. This trial is registered with ClinicalTrials.gov, number NCT01581333.

Findings Between April 10, 2012, and May 31, 2016, 157 episodes among 709 patients assessed for eligibility were included in analyses. 78 patients were randomly assigned to the experimental group and 79 to the control group. The mean number of EAT-free days was significantly higher in the experimental group than in the control group (16·1 [SD 6·3] *vs* 13·6 [7·2], absolute difference −2·4 [95% CI −4·6 to −0·3]; p=0·026). 636 adverse events were reported (341 in the experimental group *vs* 295 in the control group; p=0·057) and most (580 [91%]; 323 in the experimental group *vs* 257 in the control group) were considered mild or moderate (grade 1–2). The most common adverse events in the experimental versus the control group were mucositis (28 [36%] of 78 patients *vs* 20 [25%] of 79 patients), diarrhoea (23 [29%] of 78 *vs* 24 [30%] of 79), and nausea and vomiting (20 [26%] of 78 *vs* 22 [28%] of 79). 56 severe adverse events were reported, 18 in the experimental group and 38 in the control group. One patient died in the experimental group (from hepatic veno-occlusive disease after an allogeneic haemopoietic stem-cell transplantation) and three died in the control group (one from multiorgan failure, one from invasive pulmonary aspergillosis, and one from a post-chemotherapy intestinal perforation).

Interpretation In high-risk patients with haematological malignancies and febrile neutropenia, EAT can be discontinued after 72 h of apyrexia and clinical recovery irrespective of their neutrophil count. This clinical approach reduces unnecessary exposure to antimicrobials and it is safe.

Funding Instituto de Salud Carlos III, Spanish Ministry of Economy (PI11/02674).

Introduction

Understanding the optimal duration of empirical antimicrobial therapy (EAT) for patients with haematological malignancies and febrile neutropenia of unknown origin is still a challenge. The classical approach is to continue the initial regimen of EAT in neutropenic patients with unexplained fever until neutrophil recovery, especially for high-risk patients with neutropenia lasting for more than 7 days. This approach is recommended by the Infectious Diseases Society of America (IDSA) in the

Lancet Haematol 2017

Published Online November 15, 2017 http://dx.doi.org/10.1016/S2352-3026(17)30211-9

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Research in context

Evidence before this study

We reviewed guidelines published by relevant international scientific societies for empirical antimicrobial therapy (EAT) in patients with febrile neutropenia. We also searched the Cochrane Database of Systematic Reviews and the PubMed database using the search terms "febrile neutropenia", "empirical antimicrobial", "empirical therapy", "withdrawal", "discontinuation", and "hematologic". Studies published until March 6, 2017, were considered. Most relevant articles within the scope of our study were individually analysed. We found no published meta-analyses. The evidence for discontinuation of EAT in patients with haematological malignancies and febrile neutropenia was considered moderate in the two main clinical guidelines (Infectious Diseases Society of America [IDSA] and European Conference of Infections in Leukaemia [ECIL]). The IDSA guideline recommends the standard approach of continuing the initial regimen of EAT in patients with unexplained fever until clear signs of marrow recovery are observed, with the traditional endpoint of an increasing neutrophil count that exceeds $0{\cdot}5 \times 10^9$ per L. The quality of the recommendation is level B II, and is based on the fact that "years of experience have proven this approach to be safe and effective". The ECIL guideline recommends discontinuation of empirical antibiotics in patients who have been haemodynamically stable from presentation and afebrile for 72 h or more, regardless of their neutrophil count. The quality of the ECIL recommendation is level II, based on few studies, most of them observational, with a non-comparative design and variable criteria for antimicrobial discontinuation. Additionally, some of these studies involved low numbers of patients. To date, no published trials have confirmed the efficacy and safety of discontinuation of EAT in high-risk patients with neutropenia and fever of unknown origin after apyrexia and clinical recovery.

Added value of this study

This study builds on the existing evidence by clarifying the optimal duration of EAT in patients with haematological malignancies and febrile neutropenia without microbiological documentation. These findings provide evidence supporting the ECIL recommendations.

Implications of the available evidence

This insight could contribute to changes in clinical practice, resulting in a reduction in antibiotic pressure in these patients without increasing the frequency of recurrent fever, secondary infections, or mortality. Additionally, these results favour the development and implementation of strategies for antimicrobial stewardship to improve the use of antimicrobials and decrease bacterial resistance in this vulnerable population.

2010 update of its "Clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer",[1] although the scientific evidence (classified as level BII) supporting this recommendation is questionable,[2] since the guidelines are simply based on the fact that "years of experience have proven this approach to be safe and effective".[1] However, this recommendation could result in unnecessarily prolonged EAT in routine clinical practice in patients diagnosed with haematological malignancies who have continued post-chemotherapy neutropenia. Two large clinical trials of EAT have been done, involving nearly 2000 patients with haematological malignancies and febrile neutropenia; the mean duration of EAT was 16 days in one trial (15·8 [SD 9·6] in the cefepime group and 15·7 [8·8] in the piperacillin–tazobactam group)[3] and 12 days in the other trial (13·0 in the caspofungin group and 12·5 in the liposomal amphotericin B group),[4] which is longer than the recommended duration of 8 days or less for treatment of most serious infections.[5] In an era of growing antimicrobial resistance, this approach highlights the urgent need to optimise antimicrobial therapy.[5,6] This issue is particularly important in management of patients with haematological malignancies, who receive consecutive courses of chemotherapy and are repeatedly exposed to the collateral damage of prolonged broad-spectrum antimicrobial therapy.[7] The main reason for this recommendation is the potential risk of recurrent fever and sepsis. However, recurrence of fever is frequent when neutropenia persists, regardless of whether antibiotic therapy is continued or not.[2,8,9]

The available scientific evidence supporting the alternative approach of stopping antimicrobial therapy before neutrophil recovery in afebrile adult patients with negative cultures is scarce. Two randomised studies[8,10] have shown that discontinuation of antibiotics before neutrophil recovery does not increase mortality due to bacterial infections, but both of these studies involved paediatric populations at low risk of bacterial infection and with heterogeneous criteria definition for treatment discontinuation. Several further prospective and retrospective observational studies in adults and children, including patients with haematological malignancies and prolonged neutropenia, have shown that, although discontinuation of EAT during neutropenia is associated with recurrent fever in a variable proportion of patients, mortality does not increase if antimicrobials are restarted.[11–16] Based on these studies, the 4th European Conference on Infections in Leukaemia (ECIL-4) recommendation is to discontinue empirical antibiotics after resolution of fever of unknown origin in high-risk patients with haematological malignancies, despite persistence of neutropenia.[17] However, although this approach is being increasingly implemented, to the best of our knowledge no published trials are available to confirm the efficacy and safety of this approach in adult patients with haematological malignancies. Additionally, a report has suggested that this approach might not be

ethical because of the high rate of fever recurrence and bacteraemia.[18]

The aim of the How Long study was to test whether recovery of neutropenia as a criterion for EAT discontinuation in patients with haematological malignancies and febrile neutropenia unnecessarily prolongs antibacterial treatment, and whether EAT discontinuation driven by a clinical approach regardless of neutrophil recovery would optimise duration of therapy, thus reducing the potential negative effects for patients without increasing recurrent fever episodes, secondary infections, or mortality.

Methods

Study design and participants

The How Long study was an investigator-driven, open-label, randomised, controlled phase 4 clinical trial designed to prove the superiority of a clinical approach versus the standard approach of neutropenia recovery to decide discontinuation of EAT in patients with haematological malignancies and febrile neutropenia without microbiological diagnosis. The study was done in six public academic hospitals in Spain and led by investigators from the University Hospital Virgen del Rocío (Seville, Spain). The other participating centres were the University Hospital of Bellvitge (Barcelona, Spain), the Hospital Clinic and the University Hospital of Vall d'Hebron (Barcelona, Spain), the Hospital of Jerez (Cádiz, Spain), and the University Hospital of Salamanca (Salamanca, Spain). All participating centres regularly treat patients with haematological malignancies and carry out haemopoietic stem-cell transplantation. Details of the principal investigator and the number of patients included at each site are provided in the appendix (p 3).

The planned target population was adult patients (aged ≥18 years) admitted to haematology wards of the participating centres, receiving treatment for haematological malignancies or undergoing haemopoietic stem-cell transplantation, with high-risk febrile neutropenia (defined as expected neutropenia of $\leq 0 \cdot 5 \times 10^9$ cells per L for ≥7 days) with no aetiological (microbiological) diagnosis, including clinically documented infection or unexplained fever.

Potential eligible patients were pre-selected through daily systematic checks of temperature curves and records of neutrophil blood counts of all patients admitted to each haematology ward. Every patient assessed for the study received EAT at the onset of fever after blood culture sample collection. After 72 h (±24 h) those patients without an aetiological diagnosis based on available microbiological results and meeting all the remaining inclusion criteria were considered for inclusion in the study. Patients with an aetiological diagnosis were excluded. Patients receiving antimicrobial therapy for any reason before onset of fever were also not included in the study. Inclusion and exclusion criteria are detailed in the appendix (p 4).

All participating patients or their legal representatives provided written informed consent before enrolment in the study. The informed consent form and patient information sheet are included in the appendix (pp 5–8).

The trial was started after obtaining approval from the Andalusian Central Ethics Review Committee, the authorisation of the Spanish Agency of Medicines and Health Products (AEMPS), and conformity from the directors and local ethics committees at each participating centre. The study protocol is available at ClinicalTrials.gov.

For the **study protocol** see https://clinicaltrials.gov/ProvidedDocs/33/NCT01581333/Prot_ICF_000.pdf

Randomisation and masking

Enrolled patients were assigned in a 1:1 randomisation procedure to one of two groups. In the experimental group, patients received EAT until all the following criteria were met for 72 h or more, regardless of the neutrophil count: apyrexia, resolution of all symptoms and signs of infection, and normal vital signs (blood pressure, heart rate, respiratory rate, arterial O_2 saturation, and daily diuresis). In the control group, EAT was discontinued when patients met the same criteria and also had a neutrophil count of more than $0 \cdot 5 \times 10^9$ cells per L.

Following verification of the informed consent signature and the inclusion and exclusion criteria by one investigator in each centre, the randomisation procedure was done at the clinical trial unit at the coordinating centre by means of a list of randomly generated numbers from a computer system (EpiData version 3.1). The local investigator did not know the assigned study group until formal communication by the clinical trial unit was completed.

Procedures

Evaluation of patients comprised a complete physical examination, assessment of severity signs and source, biochemistry and haematology samples, two sets of blood cultures (collected from the central venous catheter, if present, and from the peripheral vein site or two sets from separate venepunctures), and additional samples from infected sites as clinically indicated. After obtaining cultures, EAT based on an antipseudomonal β-lactam drug as monotherapy or as combination therapy was started according to local protocols in each centre and depending on individual factors such as severity signs, risk of resistant bacteria, or presumed source of fever. All local protocols followed international guidelines and recommendations.[1,17] Predefined antimicrobial agents for EAT and doses were cefepime and ceftazidime 2 g three times a day, meropenem 1 g three times a day, imipenem 500 mg four times a day, piperacillin-tazobactam 4 g three times a day, amikacin 20 mg/kg every day, ciprofloxacin 400 mg twice a day, levofloxacin 500 mg twice a day, vancomycin 15–20 mg/kg twice a day (after a loading dose of 25–30 mg/kg), teicoplanin 6 mg/kg twice a day for the first three doses and every day thereafter, and aztreonam 2 g three times a day. In those patients who remained febrile 72 h after the start of EAT, the diagnostic work-up was done in accordance with international recommendations[1,17] and

See **Online** for appendix

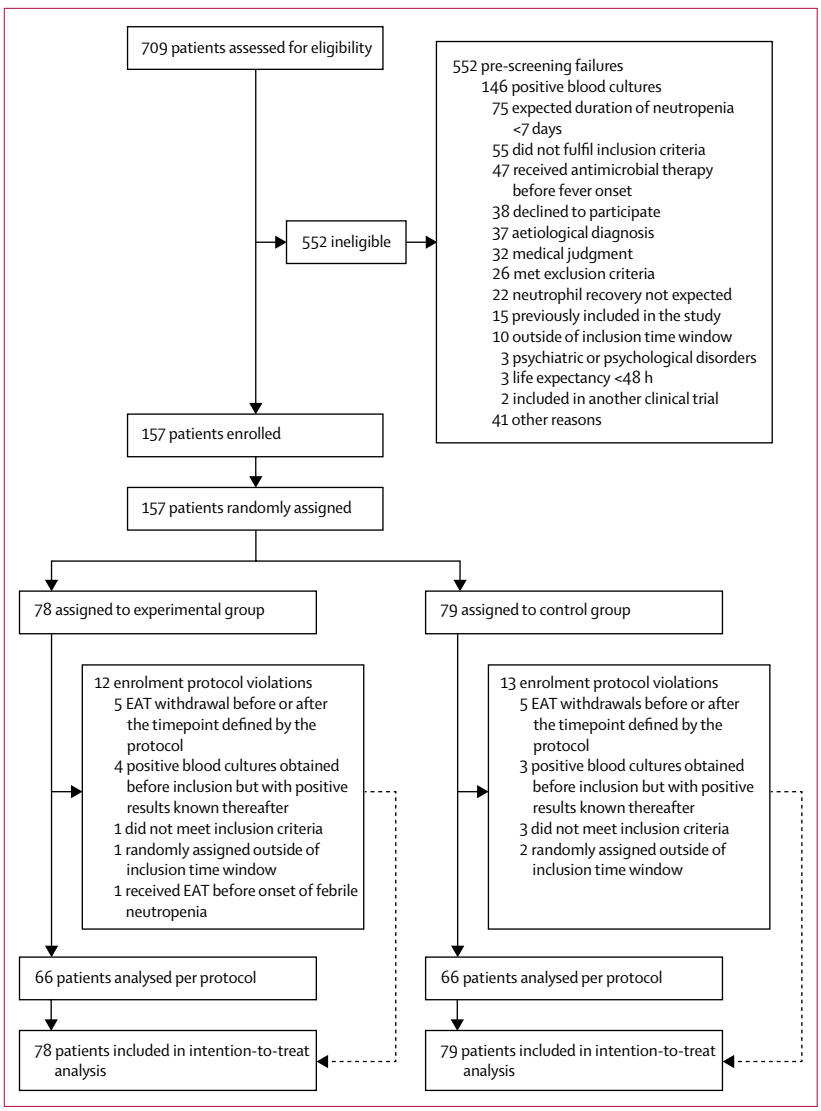

Figure: **Trial profile**
EAT=empirical antimicrobial therapy.

antimicrobial therapy was clinically driven. Universal antibacterial prophylaxis other than co-trimoxazole was not routinely used in the participating centres. Only data on antimicrobial drugs used during the study period were collected in the study case report form as concomitant medication.

Four planned follow-up visits were organised: the first visit was 72 h after apyrexia, the second was 72 h after clinical recovery, the third when neutrophil count was greater than $0{\cdot}5\times10^9$ cells per L, and the final visit was 28 (±2) days from the beginning of EAT. Additionally, data from unplanned visits were collected with special consideration given to any episode of recurrent fever (the fourth visit) and any episode of fever or infection following recovery from neutropenia until the end of the follow-up. Procedures done during the pre-selection, inclusion, and follow-up visits are specified in the appendix (p 9). Patients included in the study were monitored by physicians in the research teams for up to 28 (±2) days from the beginning of EAT or until death. For patients who were discharged before the end of the planned follow-up, pending visits were carried out as outpatients. The flowchart of the study is provided in the appendix (p 10).

Outcomes

The primary efficacy endpoint was the number of EAT-free days. This variable was calculated as the difference between the number of follow-up days (28 days) and the number of days of antibacterial treatment received by each patient. The secondary (safety) endpoints were crude (all-cause) mortality and total number of days of fever. Every recurrent fever episode during neutropenia and all infections or fever episodes developed during the follow-up were also recorded. Outcome definitions and timeframes in which they were measured are described in the appendix (p 11).

Any adverse event occurring from receipt of the informed consent form signature up to the final visit was recorded according to guidelines on good clinical pharmacovigilance practice of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[19]

The results on the secondary objective of establishing the procalcitonin cutoff for prediction of recurrent fever are not included in this report. These data will be published separately at a later date.

Statistical analysis

The primary analyses were done on an intention-to-treat basis (all randomised patients). Efficacy and safety analyses were done in the intention-to-treat population and in the entire per-protocol population (those patients who completed EAT in the assigned study group without protocol deviation during the follow-up). We also analysed those patients who remained neutropenic after apyrexia and clinical recovery as a modified per-protocol population. Data were censored at the end of the 28-day follow-up period or at death.

The efficacy analysis was designed to show whether a clinical approach was superior to the standard approach for optimising the duration of EAT, as assessed by the number of EAT-free days. Assuming a mean number of 12 EAT-free days in the control group[3] and 18 days in the experimental group (SD 6 in both groups), we calculated that 140 patients would provide 90% power at a one-sided alpha of 0·05 to detect a difference of three EAT-free days. Accounting for a 10% rate of dropouts, the estimated sample size was 156 patients (78 patients in each group). A safety evaluation was included in a non-inferiority assumption with an inferiority margin of 10%. Although not specified in the protocol, to further establish the effect of the experimental approach on the number of EAT-free days, a linear regression analysis

was applied, adjusting for age, gender, allogeneic or autologous haemopoietic stem-cell transplantation, neutropenia duration, and underlying haematological disease.

A prespecified interim analysis was done once 50% of the patients had been recruited, to assess the safety of the study. Although not specified in the protocol, a worst-case imputation method was used for missing data as an exploratory sensitivity analysis.

Secondary outcomes were compared between the groups with the χ^2 or Fisher's exact test as appropriate for proportions and with the *t* test or Mann-Whitney *U* test for continuous outcomes. All tests were two-sided, with p values of 0·05 considered significant. Analysis were done with the Statistical Package for Social Sciences, version 19.0.

This trial is registered with ClinicalTrials.gov, number NCT01581333.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 10, 2012, and May 31, 2016, 709 patients with febrile neutropenia episodes from the six participating centres were assessed for eligibility (figure). 157 patients were enrolled and randomly assigned to the experimental (n=78) or control group (n=79). The median time from onset of fever to randomisation was 72 h in both groups (IQR 48–96 in the experimental group and 72–96 in the control group). Median follow-up was 30·0 days (IQR 27·3–32·0).

Baseline characteristics are described in table 1. The most frequent underlying disease was acute leukaemia (71 [45%] of 157 patients), and 86 (55%) occurrences of febrile neutropenia were in haemopoietic stem-cell transplantation recipients (both autologous and allogeneic).

Most episodes were fevers of unknown origin (63 [40%] of 157), followed by fevers due to oral mucositis (31 [20%]), and of abdominal origin (30 [19%]; table 2). Median duration of neutropenia was 14·0 days (IQR 9·5–24·0) in the experimental group versus 11·0 days (8·0–21·3) in the control group (p=0·13). In eight patients in the control group, withdrawal of EAT occurred during neutropenia, in six of these patients because neutrophil recovery was not expected because of a refractory underlying disease and in the remaining two patients because of a suspected adverse event attributable to antibiotics. These last two patients had signs of initial neutrophil recovery when EAT was stopped; one reached a neutrophil count of $0·5 \times 10^9$ cells per L within the following 24 h and the other within the following 48 h.

	Experimental group (n=78)	Control group (n=79)
Sex		
Male	36 (46%)	43 (54%)
Female	42 (54%)	36 (46%)
Age, years	52 (42–61)	54 (39–63)
Haematological disease and treatment		
Acute leukaemia	40 (51%)	31 (39%)
Induction or reinduction	24 (31%)	18 (23%)
Other chemotherapy	8 (10%)	6 (8%)
Autologous HSCT	3 (4%)	3 (4%)
Allogeneic HSCT	5 (6%)	4 (5%)
Lymphoma	23 (29%)	29 (37%)
Chemotherapy	5 (6%)	5 (6%)
Autologous HSCT	17 (22%)	23 (29%)
Allogeneic HSCT	1 (2%)	1 (1%)
Chronic lymphocytic leukaemia	2 (3%)	0
Chemotherapy	2 (3%)	0
Multiple myeloma	7 (9%)	14 (18%)
Chemotherapy	0	1 (1%)
Autologous HSCT	6 (8%)	13 (16%)
Allogeneic HSCT	1 (1%)	0
Myelodysplastic syndrome	2 (3%)	0
Allogeneic HSCT	2 (3%)	0
Severe aplastic anaemia	0	1 (1%)
Immunosuppressive treatment	0	1 (1%)
Other diagnosis	4 (5%)	4 (5%)
Chemotherapy	1 (1%)	..
Autologous HSCT	3 (4%)	4 (5%)
Summary of treatments		
Chemotherapy or immunosuppressive therapy	39 (50%)	31 (39%)
Autologous HSCT	29 (37%)	43 (54%)
Allogeneic HSCT	9 (12%)	5 (6%)
G-CSF treatment	29 (37%)	29 (37%)
Days of neutropenia before fever onset	2·5 (1–7)	2 (1–4)

Data are n (%) or median (IQR). HSCT=haemopoietic stem-cell transplantation. G-CSF=granulocyte colony-stimulating factor.

Table 1: **Baseline characteristics of the intention-to-treat population**

In the intention-to-treat analyses (table 3), the mean number of EAT-free days was 16·1 (SD 6·3) in the experimental group and 13·6 (7·2) in the control group with an absolute difference of –2·4 (95% CI –4·6 to –0·3; p=0·026). The mean number of EAT-free days in the per-protocol population (n=66 in each group) was also higher in the experimental group than in the control group (16·9 [SD 5·8] *vs* 13·0 [7·2]) with an absolute difference of –3·8 (95% CI –6·1 to –1·6; p=0·0010). The last follow-up was done 24–72 h before the final visit date that was established by the protocol (28 days from the beginning of EAT) in 13 patients (eight in the control group and five in the experimental group); none of these patients were receiving antibiotic treatment at the time of the last

	Experimental group (n=78)	Control group (n=79)	Between-group absolute difference (95% CI)	p value
Source of fever				
Unknown	31 (40%)	32 (41%)	0·8% (–14·6 to 16·1)	0·92
Oral mucositis	14 (18%)	17 (22%)	3·5% (–8·9 to 16·0)	0·57
Abdominal	15 (19%)	15 (19%)	0·3% (–12·1 to 12·6)	0·97
Pulmonary	7 (9%)	2 (3%)	6·4% (–0·8 to 13·7)	0·10
Perianal	2 (3%)	5 (6%)	3·7% (–2·7 to 10·2)	0·44
Other	11 (14%)	6 (8%)	6·5% (–3·2 to 16·2)	0·19
Median neutropenia duration, days	14 (9·5–24·0)	11 (8·0–21·3)	–1·6 (–4·1 to 1·0)	0·13
Neutropenia at EAT withdrawal	41 (53%)	8 (10·1%)	42·5% (28 to 57)	<0·0001
Recurrent fever (at least one episode)	11 (14%)	14 (18%)	3·6% (–7·8 to 15·1)	0·54
Infections per 1000 patient-days* (N)	16·8 (36)	16·4 (35)	0·4 (–7·3 to 8·1)	0·17
Bacteraemia	4·2 (9)	6·6 (14)	2·5 (–2 to 6·8)	0·29
Invasive fungal infection	1·9 (4)	4·7 (10)	2·8 (–0·4 to 6·2)	0·12
Adverse events per 1000 patient-days* (N)	158·9 (341)	138·2 (295)	20·7 (–0·6 to 42)	0·057
Serious adverse events per 1000 patient-days* (N)	5·1 (11)	12·7 (27)	7·6 (1·9 to 13·2)	0·0087

Data are n (%), median (IQR), or mean (95% CI), unless otherwise stated. Between-group absolute differences were calculated with mean values, percentage differences, and 95% CI. EAT=empirical antimicrobial therapy. *During the follow-up period.

Table 2: **Febrile neutropenia episodes in the intention-to-treat population**

	Experimental group (n=78)	Control group (n=79)	Between-group absolute difference (95% CI)	p value
Intention-to-treat population				
Number of patients (%)	78 (100%)	79 (100%)	..	..
Efficacy variable				
EAT-free days	16·1 (6·3)	13·6 (7·2)	–2·4 (–4·6 to –0·3)	0·026
Safety variables				
Crude mortality	1 (1·3)	3 (3·8)	NA	0·62
Days of fever	5·7 (5·0)	6·3 (5·9)	0·5 (–1·2 to 2·3)	0·53
Per-protocol population				
Number of patients (%)	66 (85%)	66 (84%)	..	..
Efficacy variable				
EAT-free days	16·9 (5·8)	13·0 (7·2)	–3·8 (–6·1 to –1·6)	0·0010
Safety variables				
Crude mortality	0 (0)	2 (3)	NA	0·49
Days of fever	5·9 (5·1)	6·7 (6·1)	0·86 (–1·1 to 2·8)	0·38
Modified per-protocol population				
Number of patients (%)	36 (46%)	30 (38%)	..	..
Efficacy variable				
EAT-free days	17·5 (6·4)	11·3 (7·0)	–6·4 (–9·7 to –3·0)	0·0003
Safety variables				
Crude mortality	0 (0)	0 (0)	NA	1·00
Days of fever	4·9 (5·4)	5·4 (6·3)	0·5 (–2·4 to 3·4)	0·72

Data are n (%) or mean (SD), unless otherwise stated. EAT=empirical antimicrobial therapy. NA=not applicable.

Table 3: **Efficacy and safety endpoints**

follow-up. A worst-case imputation was done as an exploratory sensitivity analysis. In this approach, all patients in the experimental group were considered to have received antibiotics until the expected date, whereas none of the control group was considered to have received antibiotics until the expected date. Even in this scenario, the differences in the number of EAT-free days remained significant (–2·3 days, 95% CI –4·4 to –0·1; p=0·040).

In both the intention-to-treat and per-protocol analyses, the mean number of total days of fever during the follow-up did not differ significantly between the experimental group and the control group (table 3). At the end of the follow-up, four patients had died, one (1%) in the experimental group and three (4%) in the control group (p=0·62). In the per-protocol population, crude mortality was 0% in the experimental group and 3% in the control group (p=0·49). Two patients in the control group died from persistent profound neutropenia due to uncontrolled haematological malignancies that were non-responsive to chemotherapy: one died from multiorgan failure and the other from invasive pulmonary aspergillosis. One patient in the experimental group died after an allogeneic haemopoietic stem-cell transplantation because of hepatic veno-occlusive disease and one patient in the control group diagnosed with advanced non-Hodgkin lymphoma died because of a post-chemotherapy intestinal perforation. All of these patients were receiving antibacterial therapy during the follow-up, until death.

In the modified per-protocol analysis, the mean number of EAT-free days was 17·5 (SD 6·4) in the experimental group versus 11·3 (7·0) in the control group, with an absolute difference of –6·4 (95% CI –9·7 to –3·0; p=0·0003; table 3). In this population, no patient died in either group, and the mean days of fever did not differ significantly between the experimental and control groups (p=0·72; table 3).

In the multivariate regression analysis, the experimental group was an independent predictor of the efficacy primary endpoint (p=0·00019; appendix p 12).

	Experimental group (n=78)	Control group (n=79)
All infections	36 (100%)	35 (100%)
Bacterial infections		
All bacterial infections	14 (39%)	16 (46%)
Bacteraemia	9 (25%)	14 (40%)
Escherichia coli	4 (11%)	1 (3%)
Enterococcus faecium	1 (3%)	4 (11%)
Pseudomonas aeruginosa	..	3 (9%)
Klebsiella pneumoniae	1 (3%)	2 (6%)
Staphylococcus epidermidis	1 (3%)	1 (3%)
Coagulase-negative Staphylococci	..	1 (3%)
Streptococcus viridans	..	1 (3%)
Bacteroides vulgatus	..	1 (3%)
Capnocytophaga sputigena	2 (6%)	..
Other bacterial infections	5 (14%)	2 (6%)
Salmonella typhimurium diarrhoea	..	1 (3%)
P aeruginosa tracheobronchitis	..	1 (3%)
Clostridium difficile colitis	1 (3%)	..
Campylobacter coli colitis	1 (3%)	..
Campylobacter jejuni colitis	1 (3%)	..
E coli and *Proteus mirabilis* perianal infection	1 (3%)	..
E coli urinary tract infection	1 (3%)	..
Multidrug-resistant bacteria*	3 (8%)	4 (11%)
Viral infections		
All viral infections	6 (17%)	4 (11%)
Oronasal herpes simplex virus	4 (11%)	4 (11%)
Herpes zoster	1 (3%)	..
Respiratory syncytial virus	1 (3%)	..
(Table 4 continues in next column)		

	Experimental group (n=78)	Control group (n=79)
(Continued from previous column)		
Fungal infections		
All fungal infections	8 (22%)	13 (37%)
Invasive infection	4 (11%)	10 (29%)
Proven invasive candidiasis	..	1 (3%)
Proven invasive trichosporonosis	..	1 (3%)
Probable disseminated candidiasis	..	2 (6%)
Probable pulmonary aspergillosis	3 (8%)	3 (9%)
Possible disseminated candidiasis	..	1 (3%)
Possible pulmonary aspergillosis	1 (3%)	2 (6%)
Mucocutaneous infection	4 (11%)	3 (9%)
Genital candidiasis	3 (8%)	1 (3%)
Oropharyngeal candidiasis	..	2 (6%)
Tinea cruris	1 (3%)	..
Non-aetiological diagnoses		
All non-aetiological diagnoses	8 (22%)	3 (9%)
Severe sepsis or septic shock	1 (3%)	2 (6%)
Cystitis	1 (3%)	1 (3%)
Pneumonia	3 (8%)	..
Upper respiratory tract infection	1 (3%)	..
Odontogenic infection	2 (6%)	..

*Not susceptible to at least one agent in three or more antimicrobial categories.[20]

Table 4: **Episodes of infection during the follow-up period**

25 patients had at least one episode of recurrent fever during the follow-up, 11 (14%) in the experimental group and 14 (18%) in the control group (p=0·54; table 2). In three patients, two episodes of recurrent fever were reported (two in the experimental group and one in the control group). The median duration of recurrent fever episodes was 2 days (IQR 1–5) in the experimental group and 3 days (1–6) in the control group (p=0·52). The cause of the recurrent fever was identified in 12 (48%) of 25 patients, six (54·5%) of 11 patients in the experimental group and six (42·8%) of 14 in the control group (p=1·00). In the experimental group, one patient had two infections (*Escherichia coli* bacteraemia and possible invasive pulmonary aspergillosis) and five patients had one infection each: bacteraemia due to *E coli* (n=2), *Klebsiella pneumoniae* (n=1), and *Enterococcus faecium* (n=1), and invasive pulmonary aspergillosis (n=1). None of the infections was severe nor the cause of the patient's death. In the control group, three patients had one infection each (one proven disseminated trichosporonosis, one bacteraemia due to *E coli*, and one probable invasive pulmonary aspergillosis) and the other three patients had two infections each (one *K pneumoniae* and *E faecium* bacteraemia, one severe sepsis due to *Pseudomonas aeruginosa* and possible disseminated candidiasis, and one *E faecium* bacteraemia and candidaemia). None of the 11 patients who had recurrent fever in the experimental group died, whereas two of 14 patients in the control group died from uncontrolled haematological disease during treatment of the recurrent fever (p=0·19).

In 31 episodes of infection in the experimental group and 23 in the control group, at least one was reported during the follow-up (p=0·17). 71 infection episodes were reported during the follow-up, and most (n=60 [85%]) had an aetiological diagnosis (table 4). 23 bacteraemia episodes (nine episodes in nine patients in the experimental group *vs* 14 episodes in 12 patients in the control group; p=0·29) and 14 invasive fungal infections (four in the experimental group *vs* ten in the control group; p=0·12) were reported.

636 adverse events were reported (341 for the experimental group *vs* 295 for the control group; p=0·057) and most (580 [91%]; 323 *vs* 257) were considered mild or moderate (grade 1–2). The most common adverse events in the experimental versus control groups were mucositis (28 [36%] of 78 patients *vs* 20 [25%] of 79 patients), diarrhoea (23 [29%] of 78 *vs* 24 [30%] of 79), and nausea and vomiting (20 [26%] of 78 *vs* 22 [28%] of 79). 56 adverse events (18 in the experimental group and 38 in the control group) were reported as severe (grade 3–5), affecting 13 patients (17%) in the experimental group and

	Experimental group (n=78)	Control group (n=79)
All serious adverse events (%)	11 (14%)	27 (34%)
Non-infectious aetiology		
Number of patients (%)	4 (5%)	11 (14%)
Renal failure	..	2 (3%)
Respiratory failure	..	1 (1%)
Neutropenic enterocolitis	2 (3%)	2 (3%)
Multiorgan failure	1 (1%)	1 (1%)
Possible veno-occlusive disease	1 (1%)	..
Liver failure	..	1 (1%)
Cholestasis	..	2 (3%)
Epileptic seizures	..	1 (1%)
Paralytic ileus	..	1 (1%)
Infectious aetiology		
Number of patients (%)	7 (9%)	16 (20%)
Acute peritonitis	..	1 (1%)
Septic shock	1 (1%)	2 (3%)
Escherichia coli bacteraemia	1 (1%)	..
Pseudomonas aeruginosa bacteraemia	..	2 (3%)
Klebsiella pneumoniae bacteraemia	..	1 (1%)
Clostridium difficile colitis	1 (1%)	..
Probable pulmonary aspergillosis	3 (4%)	3 (4%)
Possible pulmonary aspergillosis	1 (8%)	2 (3%)
Probable disseminated candidiasis	..	2 (3%)
Possible disseminated candidiasis	..	1 (1%)
Proven invasive trichosporonosis	..	1 (1%)
Proven candidiasis	..	1 (1%)

Table 5: **Serious adverse events during follow-up**

20 (25%) in the control group, corresponding to an incidence of 8·4 per 1000 patient-days in the experimental group versus 17·8 per 1000 patient-days in the control group (p=0·0062). 38 adverse events were reported as serious, 11 in the control group and 27 in the experimental group (table 5), corresponding to an incidence of 5·1 per 1000 patient-days in the experimental group versus 12·7 per 1000 patient-days in the control group (p=0·0087; table 2). Table 6 shows adverse events recorded in 10% or more of patients, and all grade 3–5 adverse events.

Discussion

The results of the How Long clinical trial suggest that, in patients with haematological malignancies and high-risk febrile neutropenia without microbiological documentation, withdrawal of EAT in afebrile and stable patients with clinical recovery is better than the standard recommendation of waiting for neutrophil recovery.[1] This insight could contribute to changes in clinical practice, resulting in a reduction in antibiotic pressure in this vulnerable population.

The clinical approach significantly reduced the number of days of antimicrobial therapy compared with the classic approach. This difference was even higher when we considered only those patients who remained neutropenic after apyrexia and clinical recovery, showing that patients with prolonged neutropenia benefit the most from this clinical approach, with antibiotic overexposure reduced when compared with the classic approach of maintaining antibiotics until neutrophil recovery.

Discontinuation of EAT in persistently neutropenic patients remains an issue of debate.[9,18] Our study provides evidence on the optimal duration of EAT in patients with haematological malignancies and supports the ECIL-4 recommendation[17] stating that EAT can be discontinued in haemodynamically stable patients after apyrexia, irrespective of their neutrophil count. Discontinuation of EAT when a patient is afebrile for at least 2 days and has a neutrophil count of more than $0·5\times10^9$ cells per L has been accepted as the standard approach for three decades in patients without an identifiable source of fever and with negative cultures.[1] This approach is based on the increased frequency of recurrent fever and mortality that was observed following discontinuation of EAT in an open-label clinical trial done in 33 patients in 1979.[2] However, the alternative approach of EAT withdrawal without waiting for neutrophil recovery is now increasingly being implemented.[17] Most important studies of EAT discontinuation in patients with neutropenia, including two clinical trials,[8,10] have been done in paediatric populations[8,10,14–16] and include mainly low-risk patients with febrile neutropenia.[10] In adults, a few studies—which also have several limitations—have explored the feasibility of antibiotic discontinuation in patients with neutropenia.[11–13,21,22] Most of these studies had an observational, non-comparative, and prospective design, the criteria for EAT discontinuation were variable, and three studies included low numbers of patients.[13,18,22,23] Switching from intravenous broad-spectrum antibiotics to an oral fluoroquinolone sequential treatment until marrow recovery is an alternative approach that has not been shown to reduce the frequency of recurrent fever in some of these studies[12,22,23] and would only be feasible in centres with low rates of fluoroquinolone resistance.[9,22]

The reduction in the total number of days of antimicrobial therapy by reducing unnecessary antimicrobial exposure is an additional benefit for patients with haematological malignancies that has not been previously described in this vulnerable population. This finding could also contribute to the development of antimicrobial stewardship programmes, which are relevant in patients with haematological malignancies who are repeatedly exposed to broad-spectrum antimicrobials for prevention and treatment of infections.[7] Our results contrast with those reported by Micol and colleagues,[18] who applied both clinical and biochemical EAT discontinuation criteria and reported a median reduction of 3 days of antimicrobial therapy but considered this a modest reduction that was not worth the risk of recurrent fever and secondary infections. However, in our opinion, the benefit of such a reduction would be

greater than the above mentioned risks, since unnecessarily prolonged antimicrobial therapy is known to be associated with increasing selective pressure on colonising microbial flora that might lead to subsequent difficult-to-treat breakthrough infections, the incidence of which has in fact increased in haematology wards in the past years.[24–27] Nevertheless, further studies are required to explore the ecological effect of this important reduction of antibiotic pressure.

The clinical approach of the How Long study is also safe for two reasons: first, no patient died after withdrawal of antimicrobial therapy, despite having persistent neutropenia. Second, the frequency of recurrent fever and the number of infections during the follow-up were similar in both groups. This observation is especially relevant because recurrent fever and secondary infections have been one of the main concerns when deciding to discontinue antimicrobial therapy in patients with neutropenia.[1,18] The frequency of recurrent fever in adults with haematological malignancies after EAT discontinuation is variable in different studies, oscillating between 8% and 50%.[2,11–13,18,22] The only comparative study on EAT discontinuation, by Cherif and colleagues,[11] found a similar proportion of patients with recurrent fever and mortality in patients with haematological malignancies who discontinued EAT after 48 h of defervescence (n=31) versus patients who continued antimicrobial therapy (n=29). In another study in high-risk patients with haematological malignancies,[18] fever recurred in three of seven patients after discontinuation of antibiotics during neutropenia. Although none of the patients with recurrent fever died, the authors concluded that discontinuation of EAT in high-risk patients with haematological malignancies might not be safe. In our study, the frequency of recurrent fever and its duration were similar in both groups. The cause of recurrent fever was identified in nearly half of patients in both groups. Notably, only one of these infections was severe and no patient with recurrent fever died in the experimental group. Our results support the view that recurrence of fever is not a marker for mortality or severe infections and that it occurs regardless of continuation or discontinuation of EAT. Additionally, our findings provide no evidence for a worse outcome related to recurrence of fever if antimicrobial therapy is immediately restarted when fever recurs.

The frequency of infections recorded during the whole follow-up, and specifically the incidence of bacteraemia, was similar in both groups. The frequency of bacterial infections due to multidrug-resistant strains did not differ, although the study was not designed to detect the ecological effect of the treatment, and a larger sample size and longer follow-up might have been needed to assess this outcome. Four invasive fungal infections occurred in the experimental group compared with ten in the control group. Although this difference was not significant, invasive fungal infection is known to be another collateral effect of antibiotic pressure,[28] and this finding might be influenced by the different loads of antimicrobial therapy in each group.

	Experimental group (n=78)				Control group (n=79)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Abdominal distension	0	0	0	0	0	1 (1%)	0	0
Abdominal pain	9 (12%)	0	0	0	11 (14%)	0	0	0
Acute kidney injury	3 (4%)	0	0	0	3 (4%)	3 (4%)	0	0
Acute peritonitis	0	0	0	0	0	0	0	1 (1%)
Atrial fibrillation	1 (1%)	0	0	0	0	1 (1%)	0	0
Bacteraemia	0	7 (9%)	1 (1%)	0	0	5 (6%)	3 (4%)	0
Bone pain or myalgia	15 (19%)	2	0	0	8 (%)	2 (3%)	0	0
Cholestasis	4 (5%)	0	0	0	3 (4%)	2 (3%)	0	0
Clostridium difficile colitis	0	0	1 (1%)	0	0	0	0	0
Cough	11 (14%)	0	0	0	6 (8%)	1 (1%)	0	0
Diarrhoea	23 (29%)	0	0	0	23 (29%)	1 (1%)	0	0
Fatigue	17 (22%)	1 (1%)	0	0	12 (15%)	0	0	0
Invasive fungal infection	0	0	4 (5%)	0	0	0	10 (13%)	0
Liver dysfunction	0	1 (1%)	0	0	0	0	1 (1%)	0
Mucositis	24 (31%)	4 (5%)	0	0	19 (24%)	1 (1%)	0	0
Multiorgan failure	0	0	1 (1%)	0	0	0	1 (1%)	0
Nausea and vomiting	20 (26%)	0	0	0	22 (28%)	0	0	0
Neutropenic enterocolitis	0	3 (4%)	2 (3%)	0	0	0	2 (3%)	0
Perianal disease	7 (9%)	0	0	0	7 (9%)	0	0	0
Pleural effusion	1 (1%)	0	0	0	0	1 (1%)	0	0
Rash	11 (14%)	1 (1%)	0	0	15 (19%)	0	0	0
Respiratory failure	0	0	1 (1%)	0	0	0	0	0
Seizures	0	0	0	0	0	1 (1%)	0	0
Septic shock	0	0	1 (1%)	0	0	0	2 (3%)	0
Veno-occlusive disease	0	0	0	1 (1%)	0	0	0	0

Table 6: **Description of adverse events recorded in more than 10% of patients, and all grade 3–5 adverse events**

Notably, the incidence of total adverse effects was higher in the experimental group than in the control group; most adverse events were considered non-severe. Conversely, the incidence of adverse events defined as severe was significantly higher in the control group than in the experimental group. Taking into account that most of these adverse events were secondary infections and events potentially due to pharmacological toxicity, we hypothesise that prolonged exposure to antimicrobial therapy could be the cause of the increased incidence of severe adverse events observed in the control group.

Our study has some limitations. The most important limitation is the possible centre effect, because most patients were enrolled in the promoter centre. The later incorporation of the rest of the centres, along with the complexity of this kind of intervention, which requires substantial effort to carry out in a clinical trial setting,

might have contributed to this limitation. However, when comparing the efficacy and safety endpoints in the patients included in the two main recruiting centres, accounting for 83% (131 of 157) of the entire intention-to-treat population and 92% (122 of 132) of the per-protocol population, the results were similar (data not shown), suggesting that if a centre effect had occurred its influence on the overall results would have been minor. The total number of patients randomised might seem small, but this was the calculated sample size needed to show the superiority of the experimental approach over the standard approach. With regard to the design of the trial, no agreement has been reached on how the optimal duration of antibiotic treatment should be assessed in clinical trials, and this issue is particularly prominent in patients with febrile neutropenia without a microbiological diagnosis. We chose the endpoint of EAT-free days in this study because this outcome was an objective measurement, estimation of the sample size is feasible with this endpoint, and this endpoint has already been used in other trials that assessed the optimal treatment duration. Importantly, ascertaining the optimal duration of antimicrobial treatment in the different clinical syndromes is essential in the era of antimicrobial resistance. The open-label design is an unavoidable limitation of the study, since knowing whether the patient is receiving antimicrobial therapy or not is necessary for clinical management of febrile neutropenia. To minimise selection bias, the investigator did not know the study group allocation until the study consent form was signed and patients had been randomised. Another limitation of this study is that the number of allogeneic haemopoietic stem-cell transplantation recipients included was small. However, 63 patients with profound prolonged neutropenia (40% of the study population) were included in the study.

In summary, the findings of this trial indicate that, in high-risk patients with neutropenia, the clinical approach is better than the standard approach of waiting for neutrophil recovery to initiate withdrawal of antimicrobial therapy in otherwise afebrile and stable patients, and that the fear of recurrent fever, secondary infections, and increased mortality is not justified. These results support the application of this clinical approach into clinical practice, even in high-risk patients. Furthermore, these findings could contribute to the development and implementation of strategies for antimicrobial stewardship to improve the use of antimicrobials and restrict bacterial resistance in this vulnerable population.

Contributors

JMC and IE were responsible for formulating the overall research questions and the methodological design of the study. JMC was responsible for obtaining public funding from the Spanish Ministry of Economy, Industry and Competitiveness. AM-P, MA-G, EM-M, and CR-F collaborated in the methodological aspects and organisation of the study. AM-P and MA-G wrote the draft of the manuscript and JMC and IE revised it. JMC was the coordinating investigator and leader of the coordination team. MA-G was the responsible physician of the coordination team. CR-F was responsible for the clinical trial unit and the pharmacovigilance monitor. MA-G, JF, MLM, RP, MIM, JG-C, CC-C, NR, JC, JAP-S, IE, CG, CR-C, LV-L, SG-L, PB, and MR were responsible for inclusion and follow-up of patients. All authors read and approved the final manuscript.

Declaration of interests

JMC has received travel grants and honoraria as a speaker from Astellas, Novartis, Pfizer, MSD, and AstraZeneca. IE has received travel grants or honoraria as a speaker or advisory board member from Astellas, Novartis, Pfizer, MSD, Janssen, and Jazz Pharmaceutical. MA-G has received honoraria as a speaker from MSD. LV-L has received travel grants and honoraria as a speaker from Astellas, MSD, Gilead, and Pfizer. SG-L has received travel grants or honoraria as a speaker or advisory board member from Jansen, Celgene, and Amgen. PB has received travel grants or honoraria as a speaker or advisory board member from Astellas, Pfizer, MSD, and Jazz Pharmaceutical. MA-G, IE, AM-P, CG, CR-C, CR-F, EM-M, JC, and JMC report grants from the Spanish Goverment during the conduct of this study. JF, MIM, MLM, RP, JG-C, CC-C, NR, MR, and JAP-S declare no competing interests.

Acknowledgments

The How Long study was a non-commercial, investigator-driven clinical study funded by the Instituto de Salud Carlos III, Spanish Ministry of Economy (PI11/02674). The study was supported by Plan Nacional de I+D+i 2013–2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Economía, Industria y Competitividad, Spanish Network for Research in Infectious Diseases (REIPI RD12/0015/0015), co-financed by the European Development Regional Fund "A way to achieve Europe", Operative program Intelligent Growth 2014–2020, and supported by the Spanish Clinical Research Network Spanish Government, co-financed by the Plan Nacional de I+D+i and Instituto de Salud Carlos III, Subdirección General de Evaluación y Fomento de la Investigación (PT13/0002/0010), and CIBER-ONC CB16/12/00480. We acknowledge the invaluable contribution of Patricia Fernández-del Valle from the Unit of Clinical Research and Clinical Trials of the Andalusian Public Foundation for Health Research Management in Seville for her contribution in the statistical analyses.

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