Early discontinuation of empirical antibiotic treatment in neutropenic patients with acute myeloid leukaemia and high-risk myelodysplastic syndrome

Floor Annabel Niessen (f.a.niessen@umcutrecht.nl)
Universitair Medisch Centrum Utrecht https://orcid.org/0000-0001-6586-9776
Maaike S. M. van Mourik
Universitair Medisch Centrum Utrecht
Anke H. W. Bruns
Universitair Medisch Centrum Utrecht
Reinier A. P. Raijmakers
Universitair Medisch Centrum Utrecht
Mark C.H. de Groot
Universitair Medisch Centrum Utrecht
Tjomme van der Bruggen
Universitair Medisch Centrum Utrecht

Research

Keywords: Carbapenems, febrile neutropenia, acute myeloid leukaemia, antibiotic stewardship

Posted Date: November 9th, 2019

DOI: https://doi.org/10.21203/rs.2.17037/v1

Version of Record: A version of this preprint was published at Antimicrobial Resistance and Infection Control on May 27th, 2020. See the published version at https://doi.org/10.1186/s13756-020-00729-2.

Abstract

Introduction: Current guidelines advocate empirical antibiotic treatment (EAT) in haematological patients with febrile neutropenia. However, the optimal duration of EAT is unknown. In 2011, we have implemented a protocol advocating more restrictive use of EAT in patients with febrile neutropenia. This study assesses the effect of this protocol on carbapenem use in high risk haematological patients and its safety. Methods: A retrospective before-after study was performed comparing a cohort from 2007 to 2011 (period I, before restrictive EAT use) with a cohort from 2011-2014 (period II, restrictive EAT use). Neutropenic episodes related to chemotherapy or stem cell transplantation (SCT) in patients with acute myeloid leukaemia (AML) or high-risk myelodysplastic syndrome (MDS) were analysed. The primary outcome was the use of carbapenems as EAT during neutropenia, expressed as days on therapy (DOT). Also the use of other antibiotics was analysed. Safety measurements included 30-day mortality, ICU admittance within 30 days after start of EAT and blood cultures positive for microorganisms sensitive to a carbapenem. Results: 362 neutropenic episodes with a median duration of 18 days were analysed, involving 201 patients. DOT with carbapenems decreased from a median of eight days (period I) to a median of six days (period II), a reduction of 25%. Additionally, vancomycin use decreased with 55%. No deaths were directly related to early discontinuation of EAT, also no notable difference in ICU-admission and positive blood cultures was detected. Conclusion: Implementation of a protocol promoting restrictive use of EAT resulted in reduction of carbapemen use and appears to be safe in AML or high-risk MDS patients with febrile neutropenia during chemotherapy or SCT.

Introduction

Patients with acute myeloid leukaemia (AML) or high-risk myelodysplastic syndrome (MDS) are treated with intensive chemotherapy and, if indicated, an allogenic stem cell transplantation (SCT). This treatment results in periods of neutropenia with mucositis, making patients vulnerable to severe infections. Due to the mucosal barrier injury, microorganisms from the gastrointestinal tract can translocate to the bloodstream, including Gram-negative bacteria, viridans streptococci and *Candida* spp.. Therefore, patients receive antimicrobial prophylaxis during the period of neutropenia. Despite prophylaxis, more than 50% of these patients become febrile (1,2).

When a patient develops fever during neutropenia, broad spectrum empirical antibiotic treatment (EAT) is started immediately to rapidly and adequately treat a bacterial infection. Empirical antibiotic options all include coverage of *Pseudomonas aeruginosa*. Commonly used EAT regimes are a carbapenem, piperacillin/tazobactam or ceftazidime with or without an aminoglycoside (1).

Current guidelines advocate to continue EAT until the patient has been afebrile for ≥ 48 hours (3) or even as long as the duration of neutropenia (1). However, fever during neutropenia does not necessarily have a bacterial etiology. Viral and fungal infections are also frequently encountered. In addition, in 30-50% of cases no causative pathogen can be identified (4). The haematological malignancy, administration of blood products, or mucositis itself might also cause fever (5,6). Current protocols advocating continuous

EAT in neutropenic fever may therefore lead to overtreatment with broad-spectrum antibiotics and associated risks of side effects and antibiotic resistance.

Recent studies suggest that protocols with a more restrictive use of EAT can be safely implemented (7,8). A prospective study from Slobbe *et al*. (9) concluded that discontinuation of EAT after 3 days in febrile neutropenia is safe in a subset of hemodynamically stable patients without positive blood cultures. However, no control group was available in this study.

As of 2011, a new protocol promoting early discontinuation of EAT adapted from Slobbe *et al*. (9), has been implemented at the haematology department of the University Medical Centre Utrecht (UMCU). This offered the opportunity to assess with a historical control group the effect of this protocol on carbapenem use and its safety in AML and high-risk MDS patients with febrile neutropenia.

Methods

Patient population

This retrospective before-after study was performed with a cohort of haematological patients treated from 2007-2014 at the haematology department of the UMCU. A new local protocol, promoting early discontinuation of EAT with carbapenems, was compared with the earlier protocol for patients receiving intensive treatment for AML or high-risk MDS.

All adult patients (≥ 18 years) with the diagnoses AML or high risk MDS, treated between January 1st 2007 and December 31st2014 in the UMCU with at least one period of prolonged and profound neutropenia were included. Of these patients, only neutropenic episodes related to intensive chemotherapy (including one of the following cytostatic agents: idarubicin, cytarabine, daunorubicin, vincristine, adriamycin, mitoxantrone or etoposide) or allogenic SCT were included. Neutropenic episodes following other chemotherapeutic regimens or unrelated to chemotherapy or allogenic SCT were excluded. The new protocol on restrictive EAT use was implemented on January 1st 2011. The period from October 1st2010 to April 1st 2011 was considered as transition period, therefore neutropenic episodes occurring within this interval were excluded. Neutropenic episodes between January 1st 2007 and October 1st 2010 (period I) were compared to neutropenic episodes between April 1st 2011 and December 31st 2014 (period II).

Definition of profound and prolonged neutropenia

Neutropenia was defined as at least two consecutive neutrophil measurements of < $0.5x10^9$cells/L within 90 days. A single neutrophil count above $0.5x10^9$cells/L was ignored, if flanked by neutrophil counts

below < $0.5x10^9$ cells/L within one week. Only prolonged neutropenic episodes, with a duration of seven days or more, occurring within fourteen days after start of chemotherapy or conditioning for allogenic SCT were taken into account. These neutropenic episodes are frequently accompanied by mucositis. If chemotherapy or allogenic SCT was started during a period of pre-existing neutropenia, the neutropenic episode was considered to be (at least partially) treatment- related if the neutropenia continued for at least seven days after start of treatment.

Prophylaxis and antimicrobial treatment

An overview of the old and new protocols is shown in figure 1. See supplement for more details on antimicrobial prophylaxis and treatment.

Data sources

A primary database containing patient data extracted from hospital electronic patient record systems was set up using the Research Data Platform in the UMCU. This database consisted of all patients linked to the diagnosis or treatment of AML or MDS. Data of prescribed antibacterial therapy and cell-count data used to identify neutropenic episodes, were derived from the Utrecht Patient Oriented Database (UPOD) (10). Data of administered cytostatic agents and data concerning allogenic SCT in our patient selection was collected from the in-hospital pharmacy department of the UMCU and the treatment files of the haematology department, respectively. Data of positive blood cultures was derived from the General Laboratory Information Management System (GLIMS). This study was performed in accordance with the ethical standards of our centre.

Outcome measurements

The primary outcome was carbapenem use within neutropenic episodes following chemotherapy or conditioning for allogenic SCT in AML and high-risk MDS patients, expressed as total days on therapy (DOT). The median DOT with a carbapenem within neutropenia in period I was compared with the median DOT after implementation of the new protocol in period II. Carbapenem use in the transition period was not taken into account.

Antibiotic use was analysed for different antibiotics, expressed as DOT/100 neutropenic days. Antibiotics were grouped as prophylactic and therapeutic agents. Total antibiotic consumption consisted of the sum of DOT of the individual antibiotics, e.g. if a patient used 2 different antibiotics on a particular day this was counted as 2 DOT/neutropenic days. Cotrimoxazol was analysed when dosed in 960 mg BID, leaving out *Pneumocystis jirovecii/ Toxoplasma* prophylaxis after allogenic SCT (480 mg QD).

Secondary outcomes were 30-day mortality, ICU-admittance within 30 days after start EAT and blood cultures positive for microorganisms sensitive to imipenem. These outcomes were measured for the neutropenic episodes in which EAT was started. Cases of mortality within 30 days after start of EAT with a carbapenem were reviewed separately by three of the authors (AN, AB and TVDB). Overall mortality, infection-related mortality and carbapenem preventable mortality were distinguished. Carbapenem preventable mortality was defined as infection-related mortality where continuing EAT possibly could have prevented the adverse outcome, because of a suspected or proven etiologic agent that was carbapenem sensitive.

Positive blood cultures within neutropenia drawn after discontinuation of EAT were analysed, because the goal was to study the possible adverse consequences of early discontinuation of carbapenems (e.g. infection/bacteraemia with carbapenem sensitive microorganisms).

Data analysis

Analysis was conducted at the level of the neutropenic episodes. Data-analysis was performed using SAS enterprise Guide 7.1. A descriptive statistical analysis was done using SPSS statistics 21. Continuous data are expressed in median (IQR) or mean (SD) depending on distribution.

Results

Patients and neutropenic episodes

In total, 234 patients with AML or MDS and neutropenia were identified with a total number of 494 neutropenic episodes. After exclusion of episodes not related to chemotherapy or allogenic SCT and 20 neutropenic episodes during the transition period, 362 neutropenic episodes remained for further analysis (figure 2). These neutropenic episodes involved 201 individual patients, of which 184 were diagnosed with AML and 17 with high-risk MDS (table 1). In AML patients 267 neutropenic episodes were associated with intensive chemotherapy and 72 neutropenic episodes were associated with allogenic SCT (not shown). Further analysis of neutropenic episodes, primary and secondary outcomes, was performed on neutropenic episodes with AML and high-risk MDS patients grouped together. Characteristics of patients and the neutropenic episodes are shown in table 1. The median duration of neutropenia of all neutropenic episodes combined was 18 days in both period I and period II. (table 2)

Primary outcome

The median DOT with a carbapenem within neutropenia is shown in table 2. Carbapenem use within neutropenia decreased from a median of 8 DOT in period I to 6 DOT in period II, a reduction of 25%. A

slight difference was detected in the frequency of neutropenic episodes in which a carbapenem was started (72% in period I versus 76% in period II, Table 2).

Carbapenem therapy was restarted more often within the same neutropenic episode after initial discontinuation under the protocol on restrictive EAT use. Before 2011 this occurred in 24 of the 116 (21%) neutropenic episodes, whereas after 2011, a carbapenem was restarted in 56 of the 152 (37%) episodes. Despite the increased frequency of restarting EAT, the DOT within neutropenia remained shorter.

Secondary outcomes

The antibiotic consumption within neutropenic episodes (expressed as DOT/100 neutropenic days) of various antibiotics is shown in table 3. In addition to an 18% decrease in carbapenem use (from 33.6 to 27.7 DOT/100 neutropenic days), the administration of vancomycin decreased with 55% (from 26.7 DOT/100 neutropenic days in period I to 12.1 DOT/100 neutropenic days in period II). The results show no major differences in total consumption of prophylactic antibiotics between period I (82.2 DOT/100 neutropenic days) and period II (85.3 DOT/100 neutropenic days). Although the consumption of ciprofloxacin and clindamycin decreased, the prophylactic use of cotrimoxazole and cefazoline had increased. Overall, the total antibiotic consumption of period II was 9,9 % less than in period I (146.8 versus 132.3 DOT/100 neutropenic days).

No apparent difference in mortality related to an infection that could have been prevented with continued carbapenem treatment was identified. The overall mortality within 30 days after starting with EAT was 5.6% (in 15/268 neutropenic episodes). Eleven fatal cases were associated with infection: two in period I and nine in period II. However, these cases were all classified as unlikely to be preventable with continuation of carbapenem therapy for the following reasons. Firstly, a carbapenem was actually continued (n=5), according to the protocol in hemodynamically instable patients. Secondly, the pathogen was not susceptible to carbapenems (n=3), i.e. mucormycosis, pulmonary aspergillosis and invasive Candidiasis with *Candida glabrata.* Thirdly, appropriate targeted therapy was given, based on microbiological findings (n=1), i.e. a case of *Clostridium difficile* pseudomembranous colitis in combination with *Stenotrophomonas maltophilia* bacteraemia, treated with metronidazole and levofloxacin. Finally, presumed appropriate targeted therapy was given based on a clinical diagnosis (n=2), i.e. a patient with cellulitis treated with cefuroxim and a patient with neutropenic enterocolitis treated with a carbapenem which was interrupted for one day. Twelve days after interruption of EAT this last patient died of a bleeding in the liver, which was considered not to be related to colitis. For all cases in which EAT was discontinued, ciprofloxacin prophylaxis was administered according to the protocol.

No notable difference between the number of ICU-admissions within 30 days after starting EAT was observed, 9/116 neutropenic episodes in period I (7.8%) and 9/152 neutropenic episodes in period II (5.9%).

During the study period, blood cultures obtained after discontinuation of EAT were positive in 56 of 362 neutropenic episodes (15%). In six of these neutropenic episodes blood cultures were positive for microorganisms sensitive to imipenem, i.e. *Streptococcus mitis* (n=1), *Escherichia coli* (n=1), *Clostridium perfringens* (n=1), *Pseudomonas aeruginosa* (n=1) and *Enterococcus* spp. (n=2). Four of these positive blood cultures were obtained in period I and two in period II. One blood culture in period II was positive for *Enterococcus* spp. and one for *Pseudomonas aeruginosa*. In all cases adequate therapy was started when blood culture results became available. No fatal outcomes were recorded within 30 days after early discontinuation of EAT. More details are shown in table 4.

Discussion

This study shows a reduction in carbapenem use after implementation of a protocol promoting early discontinuation of EAT in high risk haematology patients with febrile neutropenia. According to this protocol, EAT is discontinued after three days (with bacterial prophylaxis restarted), regardless of fever, provided blood cultures remain negative, patients are hemodynamically stable and do not have a pulmonary infection with unknown etiology. As expected EAT was re-administered within the same neutropenic episode more often after initial discontinuation, since according to the new protocol restarting EAT for a second time was allowed (see supplement). This also explains, at least partly, that in period II the median DOT with EAT was six days, rather than three days. In period II, carbapenems were started slightly more often compared to period I (76% vs. 72%), but also when this fact was taken into account overall carbapenem use in neutropenia was reduced by 18% (table 3). Beside the reduction of EAT with carbapenems, there was a 55% reduction of vancomycin use, most likely because the new protocol did not advocate addition of empirical vancomycin when fever persisted. Analysis of administration of other antibiotics did not show striking increases, indicating that the restrictive use of carbapenems was not compensated by replacement with other broad-spectrum antibiotics.

Moreover, the reduction of EAT after protocol implementation did not lead to an increase in adverse events. Although all-cause mortality was higher in period II, detailed analysis did not reveal causality between early discontinuation of EAT and fatal outcomes. Secondly, there was no notable difference in ICU admittance within 30 days after discontinuing EAT between the two periods. Thirdly, in both periods there were some episodes of bacteraemia with a carbapenem-susceptible microorganism within 30 days after stopping EAT. However, all these episodes of bacteraemia were treated adequately and no mortality within 30 days after early discontinuation of EAT was observed in these cases.

Shortening the course of EAT in haematological patients with febrile neutropenia remains a subject of debate (11) while there is increasing evidence supporting a shorter course of EAT in these high risk haematology patients (7–9,12). Many of these studies focus on the safety of the Fourth European Conference on Infections in Leukaemia (ECIL-4) recommendation to discontinue EAT after 48 hours of apyrexia (3,7,8,13). This policy reduces EAT in comparison to previous recommendations (7,8,13). However, broad-spectrum antibiotic use may be reduced even further, because febrile neutropenia is frequently unrelated to infection (4–6). In this respect, the prospective study of Slobbe *et al*. is interesting,

describing a protocol to discontinue EAT after three days, regardless of persisting fever (9). The authors did not document any mortality related to an untreated bacterial infection and concluded early discontinuation of EAT is safe, although the study lacked a control group. We compared mortality and other measures of safety before and after implementation of a similar protocol, thereby providing a historical control group.

This study has limitations. Most important, the retrospective design of this before-after study makes it impossible to take into account all time-related factors that could have influenced the outcome measures. Therefore, the results can only be interpreted as descriptive. Two potential time-related factors, i.e. changes in patient population and treatment intensity, may influence the outcomes. More vulnerable patients (e.g. more serious comorbidities) have become eligible for haematological treatment regimens and conditioning regimens for allogenic SCT have become more intense. This may have led to more severe morbidity in the second (intervention) cohort. Despite these changes, potentially leading to an overestimation of adverse events, this study shows a decrease in consumption of EAT and other antibiotics and no increased infection-related morbidity and mortality. No data on temperature was available. However, patients were considered febrile when carbapenems were started because febrile neutropenia was an almost exclusive indication for administering carbapenems.

In conclusion, this study shows that a protocol advocating early discontinuation of EAT in AML and high-risk MDS patients with febrile neutropenia during chemotherapy or conditioning for allogenic SCT, was successfully implemented and resulted in decreased use of carbapenems, without compromising patient safety. In addition to current recommendations, early discontinuation of EAT without the explicit need for apyrexia is worth further exploration in stable haematological patients with febrile neutropenia.

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the ethical standards of our centre and approved by the ethics committee medical research (METC Utrecht).

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to confidentiality, but are available from the corresponding author on reasonable request for researchers who meet the criteria for access.

Funding

Not applicable

Author's contribution

T designed and supervised the study, MS developed the methodology and made substantial contributions to the design of the work, MC provided data, FA analysed the data, FA, T, AH and RA interpreted patient data, T and FA wrote the manuscript, the manuscript was revised by all authors. All authors have approved the submitted version.

Acknowledgements

We thank Pieter-Jan Haas, Francis Verweij, Julia Velikopolskaia, Danny Broekhuizen for providing, clinical, laboratory and pharmacy data and valuable help with SAS Enterprise.

Competing interests

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors declare that they have no competing interests.

References

1. Freifeld A, Bow E, Sepkowitz K, Boeckh M, Ito J, Mullen C, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2011;52(4):e93.
2. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med [Internet]. 2005;142(12 Pt 1):979–95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15968013
3. Averbuch D, Orasch C, Cordonnier C, Livermore D, Mikulska M, Viscoli C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica. 2013;98(12):1826–35.
4. Pagano L, Caira M, Nosari A, Rossi G, Viale P, Aversa F, et al. Etiology of febrile episodes in patients with acute myeloid leukemia: results from the Hema e-Chart Registry. Vol. 171, Archives of internal medicine. United States; 2011. p. 1502–3.
5. van der Velden WJFM, Herbers AHE, Netea M, Blijlevens NMA. Mucosal barrier injury, fever and infection in neutropenic patients with cancer: introducing the paradigm febrile mucositis. Br J Haematol. 2014;167(4):441–52.
6. Wenneras C, Hagberg L, Andersson R, Hynsjo L, Lindahl A, Okroj M, et al. Distinct inflammatory mediator patterns characterize infectious and sterile systemic inflammation in febrile neutropenic hematology patients. PLoS One. 2014;9(3):e92319.

7. Clech L Le, Talarmin J-P, Couturier M-A, Ianotto J-C, Nicol C, Calloch R Le, et al. Early discontinuation of empirical antibacterial therapy in febrile neutropenia: the ANTIBIOSTOP study. Infect Dis (Auckl). 2018;50(7):539–49.
8. Guisado MA, Espigado I, Peña AM, Gudiol C, Cebrecos CR, Falantes J, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. Lancet Haematol. 2017;4(12):e583.
9. Slobbe L. Three-day treatment with imipenem for unexplained fever during prolonged neutropaenia in haematology patients receiving fluoroquinolone and fluconazole prophylaxis: A prospective observational safety study. Eur J Cancer. 2009;45(16):2810–7.
10. ten Berg MJ, Huisman A, van den Bemt PMLA, Schobben AFAM, Egberts ACG, van Solinge WW. Linking laboratory and medication data: new opportunities for pharmacoepidemiological research. Clin Chem Lab Med. 2007;45(1):13–9.
11. Micol J-B, Chahine C, Woerther P-L, Ghez D, Netzer F, Dufour C, et al. Discontinuation of empirical antibiotic therapy in neutropenic acute myeloid leukaemia patients with fever of unknown origin: is it ethical? Clin Microbiol Infect. 2014 Jul;20(7):O453-5.
12. Orasch C, Averbuch D, Mikulska M, Cordonnier C, Livermore DM, Gyssens IC, et al. Discontinuation of empirical antibiotic therapy in neutropenic leukaemia patients with fever of unknown origin is ethical. Vol. 21, Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. England; 2015. p. e25-7.
13. la Martire G, Robin C, Oubaya N, Lepeule R, Beckerich F, Leclerc M, et al. De-escalation and discontinuation strategies in high-risk neutropenic patients: an interrupted time series analyses of antimicrobial consumption and impact on outcome. Eur J Clin Microbiol Infect Dis. 2018 Oct;37(10):1931–40.
14. Norrby SR. Neurotoxicity of carbapenem antibacterials. Drug Saf. 1996 Aug;15(2):87–90.

Tables

Table 1: Characteristics of patients and neutropenic episodes

			Period I	Period II
			n=97	n=104
Patients	Diagnosis	AML	90 (93%)	94 (90%)
		High-risk MDS	7 (7%)	10 (10%)
	Sex	Male	46 (47%)	48 (46%)
	Age	Years ± SD	50.7 ± 14.7	53.4 ±15.1
			n=162	n=200
Duration of neutropenic episodes in days (IQR)	Total		18 (12-25)	18 (12-26)
			n=128	n=153
	Chemotherapy		19 (14-26)	18 (13-25)
			n=34	n=47
	SCT		11 (8-17)	12 (9-26)

Abbreviations: AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; SCT, allogenic stem cell transplant

Table 2: Carbapenem use

	Period I				Period II			
	Neutropenic episodes			Days on therapy	Neutropenic episodes			Days on therapy
	Total	*With carbapenem use*			*Total*	*With carbapenem use*		
	n	n	%	Median (IQR)	n	n	%	Median (IQR)
Chemotherapy	128	105	(82)	8 (6 - 11)	153	123	(80)	6 (4 - 10)
Stem cell transplant	34	11	(32)	7 (4 - 10)	47	29	(62)	4 (3 - 8)
Total	162	116	(72)	8 (6-11)	200	152	(76)	6 (4 – 9)

Table 3: Antibiotic consumption within neutropenia

		Days on therapy/100 neutropenic days	
		Period I	**Period II**
Therapy	Carbapenems	33,6	27,7
	Ceftazidime	0,13	0,31
	Piperacillin/tazobactam	0,19	1,05
	Aminoglycosides	0,54	0,64
	Ceftriaxone	0,80	0,82
	Penicillin	2,6	4,4
	Vancomycin	26,7	12,1
Prophylaxis	Clindamycin	10,9	7,0
	Ciprofloxacin	64,1	58,6
	Cotrimoxazole*	3,2	5,6
	Cefazolin	4,0	14,1
Total		146.8	132.3

***dose > 960 mg BID*

Table 4: Positive blood cultures with carbapenem sensitive microorganisms within 30 days after discontinuation of EAT

	Patient (sex, age, diagnosis)	Duration of initial EAT	Micro-organism in blood culture	Days between discontinuation of EAT and positive blood culture	Focus of infection	Treatment
Period I	F 51, AML	11	*Enterococcus* species	4	Central venous catheter	Vancomycin, followed by amoxicillin
	F 44, AML	7	*Streptococcus mitis*	6	Sinusitis	Restart EAT with a carbapenem
	F 65, MDS	7	*Escherichia coli*	11	Urosepsis	Restart EAT with a carbapenem, followed by ceftriaxone
	M 59, AML	16	*Clostridium perfringens*	7	Translocation of infected trombus	Restart EAT with a carbapenem + vancomycin
Period II	M 49, AML	4	*Pseudomonas aeruginosa*	6	Dental focus	Piperacillin/tazobactam + tobramycin
	M 42, AML	5	Enterococcus species	17	Unknown	Vancomycin

Abbreviations: F, female; M, male; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; EAT, empirical antibiotic treatment

Figures

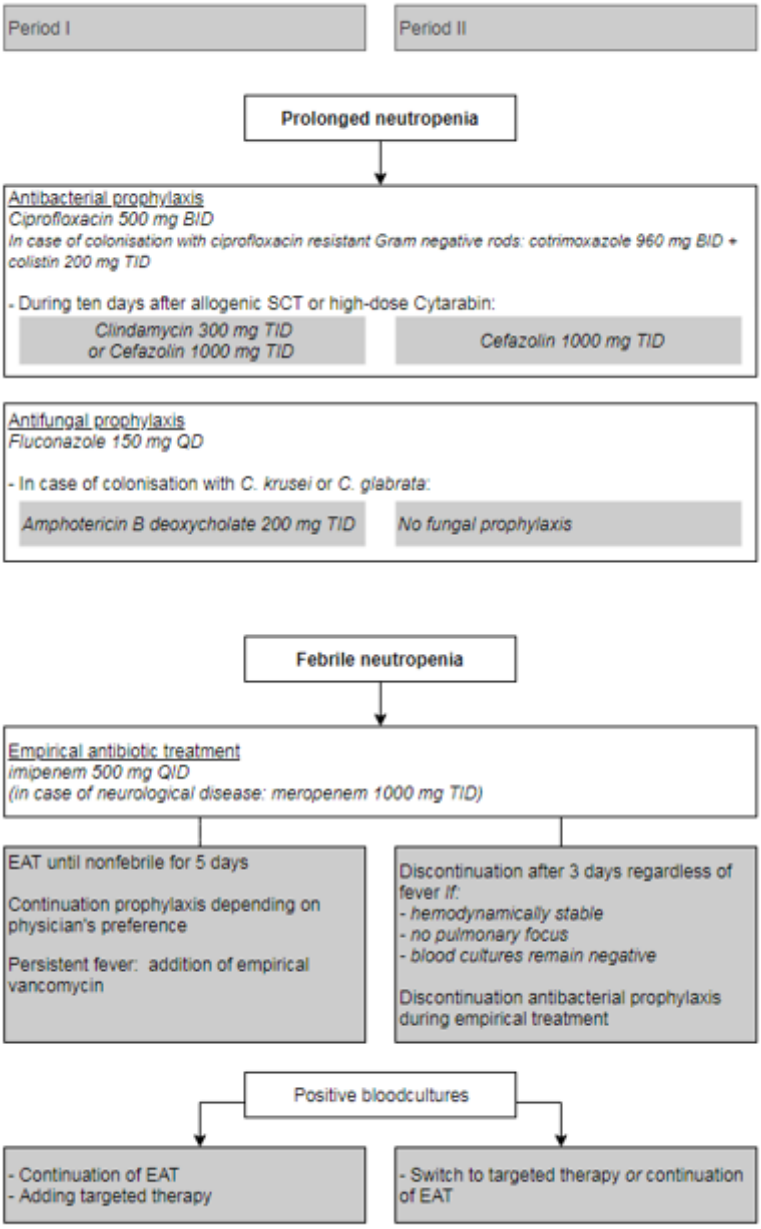

Figure 1

Prophylaxis and antibiotic treatment protocol

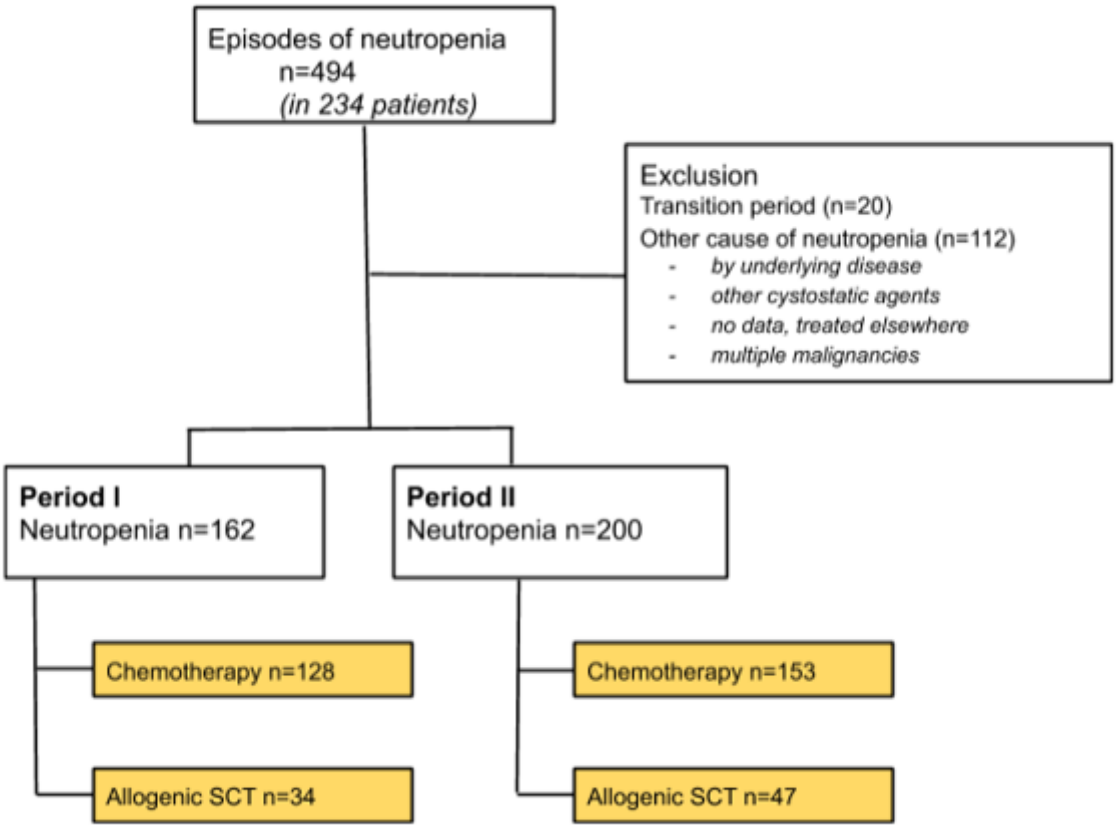

Figure 2

Selection of neutropenic episodes

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFile.pdf