Nötropenik Hastada Antibiyotik Tedavi Süreleri

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İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı

Febril Nötropeni (FEN)

- Mikrobiyolojik olarak belgelenmiş infeksiyon: Klinik bir infeksiyon odağı ve ilişkili bir patojen ile nötropenik ateş

- Klinik olarak belgelenmiş infeksiyon: Klinik odaklı (örn. selülit, pnömoni) ancak ilişkili bir patojen izolasyonu olmayan nötropenik ateş

- Açıklanamayan ateş: Ne klinik bir infeksiyon odağı ne de tanımlanmış bir patojen olmayan nötropenik ateş

- Bakteriler, nötropenik ateşin en sık infeksiyöz nedenleridir.

- Gram-negatif basiller, özellikle *Pseudomonas aeruginosa*, 1980'lere kadar nötropenik hastalarda en sık tanımlanan patojenlerdi.

- Daha sonra, gram-pozitif bakteriler en yaygın patojenler haline geldi.
- Yaygın gram-pozitif koklar arasında *Staphylococcus epidermidis* (açık farkla en yaygın olan), *Staphylococcus aureus* ve streptokoklar

- Son zamanlarda, belgelenmiş infeksiyonlarda antibiyotiğe dirençli gram-negatiflerin ortaya çıkmasıyla birlikte, gram-negatif bakterilere doğru bir eğilim

- Gram negatif bakteriler genellikle en ciddi infeksiyonlarla ilişkilendirilir.

Gudiol C, Bodro M, Simonetti A, et al. Changing aetiology, clinical features, antimicrobial resistance, and outcomes of bloodstream infection in neutropenic cancer patients. Clin Microbiol Infect 2013; 19:474.

Montassier E, Batard E, Gastinne T, et al. Recent changes in bacteremia in patients with cancer: a systematic review of epidemiology and antibiotic resistance. Eur J Clin Microbiol Infect Dis 2013; 32:841.

Trecarichi EM, Tumbarello M. Antimicrobial-resistant Gram-negative bacteria in febrile neutropenic patients with cancer: current epidemiology and clinical impact. Curr Opin Infect Dis 2014; 27:200.

Perez F, Adachi J, Bonomo RA. Antibiotic-resistant gram-negative bacterial infections in patients with cancer. Clin Infect Dis 2014; 59 Suppl 5:S335.

Mikulska M, Viscoli C, Orasch C, et al. Aetiology and resistance in bacteraemias among adult and paediatric haematology and cancer patients. J Infect 2014; 68:321.

ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

DOI: 10.4274/atfm.galenos.2022.58070
Ankara Üniversitesi Tıp Fakültesi Mecmuası 2022;75(3):373-378

DAHİLİ TIP BİLİMLERİ / MEDICAL SCIENCES

Hematolojik Febril Nötropeni Ataklarında Kan Kültürlerinden İzole Edilen Gram-negatif Bakterilerin Dağılımı ve Antimikrobiyal Duyarlılıklarının Değerlendirilmesi

Evaluation of the Distribution and Antimicrobial Susceptibility of Gram-negative Bacteria Isolated from Blood Cultures in Heamatologic Febrile Neutropenia Attacks

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Tablo 1: Kan kültürlerinden izole edilen gram-negatif bakteriler (n=388)

Etken	Sayı (%)
Klebsiella spp.	162 (%41,7)
Klebsiella pneumoniae	130
Klebsiella oxytoca	32
E. coli	98 (%25,2)
Acinetobacter spp.	67 (17,2)
Acinetobacter baumannii	59
Acinetobacter pittii	8
Pseudomonas spp.	37 (9,5)
Pseudomonas aeruginosa	33
Diğer	24 (%6,1)
Enterobacter spp.	13
Proteus spp.	6
Citrobacter spp.	5

Tablo 2: Kan kültürlerinden izole edilen gram-negatif bakterilerin antibiyotik direnç oranları

	Klebsiella spp. Dirençli/Toplam (%)	*E. coli* Dirençli/Toplam (%)	*Acinetobacter* spp. Dirençli/Toplam (%)	*Pseudomonas* spp. Dirençli/Toplam (%) 37
Amikasin	100/162 (%61,7)	50/98 (%51)	48/67 (%71,6)	7/37 (%18,9)
Gentamisin	90/162 (%55,5)	44/98 (%44,8)	44/67 (%65,6)	7/37 (%18,9)
Sefepim	116/162 (%71,6)	51/98 (%52)	59/67 (%88)	26/37 (%70,2)
Seftazidim	118/162 (%72,8)	51/98 (%52)	62/67 (%92,5)	26/37 (%70,2)
Siprofloksasin	124/162 (%76,5)	64/98 (%65)	52/67 (%77,6)	27/37 (%40,2)
Levofloksasin	124/162 (%76,5)	64/98 (%65)	52/67 (%77,6)	27/37 (%40,2)
Piperasilin-tazobaktam	116/162 (%70,6)	37/98 (%37,7)	58/67 (%86)	25/37 (%67,5)
Meropenem	78/162 (%48,1)	29/98 (%29,5)	53/67 (%79,1)	17/37 (%45,9)
İmipenem	78/162 (%48,1)	29/98 (%29,5)	53/67 (%79,1)	17/37 (%45,9)
Trimetoprim-sulfametoksazol	42/162 (%25,9)	48/98 (%40,7)	29/67 (%43,2)	-
Kolistin	48/162 (%29,6)	*12/38 *(%31,5)	41/67 (%61,1)	9/37 (%24,3)

*Sadece çoklu ilaca dirençli suşlarda kolistin duyarlılığına bakılmıştır

Tablo 3: Etkenlerin genişlemiş spektrumlu β-laktamaz ve karbapenemaz üretimi açısından dağılımı

	K. pneumoniae n=130 Pozitif/Toplam (%)	*K. oxytoca* n=32 Pozitif/Toplam (%)	*E. coli* n=98 Pozitif/Toplam (%)	*A. baumannii* n=59 Pozitif/Toplam (%)	*A. pittii* n=8 Pozitif/Toplam (%)	*P. aeruginosa* n=33 Pozitif/Toplam (%)
Genişlemiş spektrumlu β-laktamaz	108/130 (%83)	10/32 (%31,25)	51/98 (%52)	-	-	-
Karbapenemaz	73/130 (%56,1)	5/32 (%15,6)	25/98 (%25,5)	51/59 (%86,4)	-	17/33 (%51,5)

Nötropenik ateşi olan hastalarda zararı önlemek için ampirik antibakteriyel tedavisi başlanmalıdır.

Nötropenik ateşi olan hastalarla ilgili çalışmalar, antibiyotik başlanması geciktiği takdirde 70%'e varan ölüm oranlarını belgelemiştir.

Bir kohort çalışmasında, febril nötropenik hastalarda ampirik antibakteriyel uygulama süresindeki her bir saatlik gecikmenin 28 günlük mortaliteyi 18% artırdığı gözlemlenmiş.

Komplikasyon oranlarını ve mortaliteyi azaltmak için erken ve uygun ampirik antibiyotik tedavisi de dahil olmak üzere protokol uyumu çok önemli

Rosa RG, Goldani LZ. Cohort study of the impact of time to antibiotic administration on mortality in patients with febrile neutropenia. Antimicrob Agents Chemother 2014; 58:3799.

Gaieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med 2010; 38:1045.

Zuckermann J, Moreira LB, Stoll P, et al. Compliance with a critical pathway for the management of febrile neutropenia and impact on clinical outcomes. Ann Hematol 2008; 87:139.

Lynn JJ, Chen KF, Weng YM, Chiu TF. Risk factors associated with complications in patients with chemotherapy-induced febrile neutropenia in emergency department. Hematol Oncol 2013; 31:189.

- Uygun risk değerlendirmesi, ampirik tedavinin tipini (oral/IV), antibiyotik tedavisinin süresini ve yatarak veya ayaktan hasta yönetimini belirleyebilir.

- Hastalar yüksek riskli ve düşük riskli gruplara ayrılır.
- Yüksek riskli hastalar:

Sitotoksik kemoterapiyi takiben beklenen, uzun süreli (>7 günlük süre) ve derin nötropeni (MNS < 100/µL)

Hipotansiyon, pnömoni, yeni başlayan karın ağrısı veya nörolojik değişiklikler dahil olmak üzere önemli tıbbi komorbiditeler

- Düşük riskli hastalar:

Beklenen kısa (< 7 günlük süre) nötropeni süresi

MNS>100/µL

Akciğer grafisinde normal bulgular

Ateş başlangıcında ayaktan tedavi durumu

İlişkili akut komorbid hastalık yok

Karaciğer veya böbrek yetmezliği yok

Kemik iliği iyileşmesinin erken kanıtı

TABLE 1. The Multinational Association for Supportive Care in Cancer (MASCC) Score

Characteristic	Weight
Burden of febrile neutropenia	
No or mild symptoms	5
Moderate symptoms	3
No hypotension (SBP > 90 mm Hg)	5
No active COPD	4
Solid tumor or no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Outpatient status	3
Age < 60 years	2

NOTE. Applicable points are added to create a cumulative score. The maximum score is 26, and a score of greater than 20 has a predicted low risk (< 10%) for serious medical complications during the course of the febrile neutropenia.[13]

Abbreviations: COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure.

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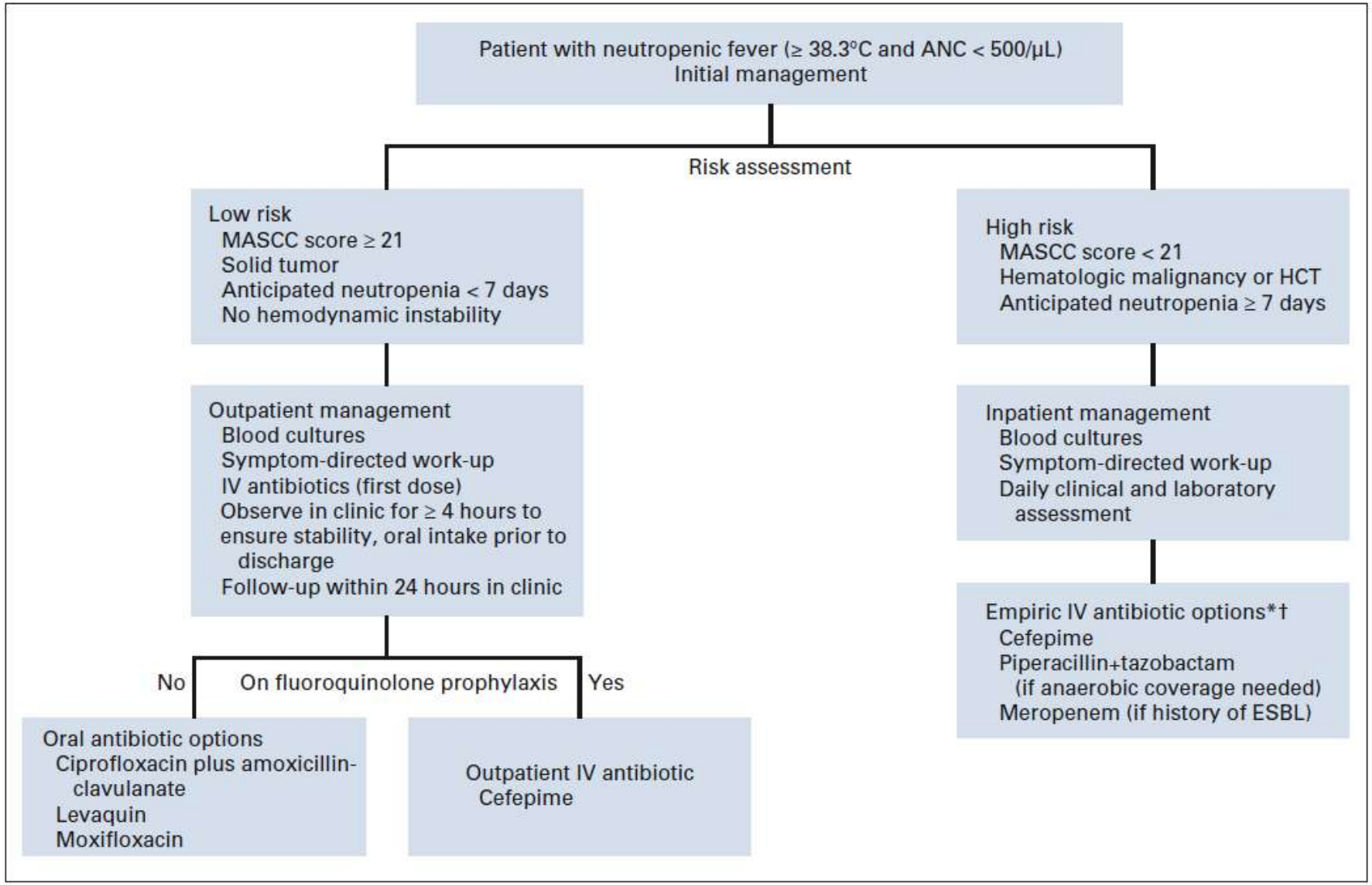

FIG 1. Flowchart of patient with neutropenic fever.[2] (*) Based on institutional antibiogram. (†) Indications to add vancomycin include hemodynamic instability, skin or catheter site infection, concern for methicillin-resistant *Staphylococcus aureus* pneumonia, and blood cultures with gram-positive bacteria before final identification and susceptibilities. ANC, absolute neutrophil count; ESBL, extended-spectrum β-lactamase; HCT, hematopoietic cell transplantation; IV, intravenous; MASCC, Multinational Association for Supportive Care in Cancer.

Nötropeninin şiddetiyle ilişkili infeksiyon riski
Olası infeksiyon odağı
Klinik belirtiler
Önceki antibiyotik kullanımı
Alerjiler

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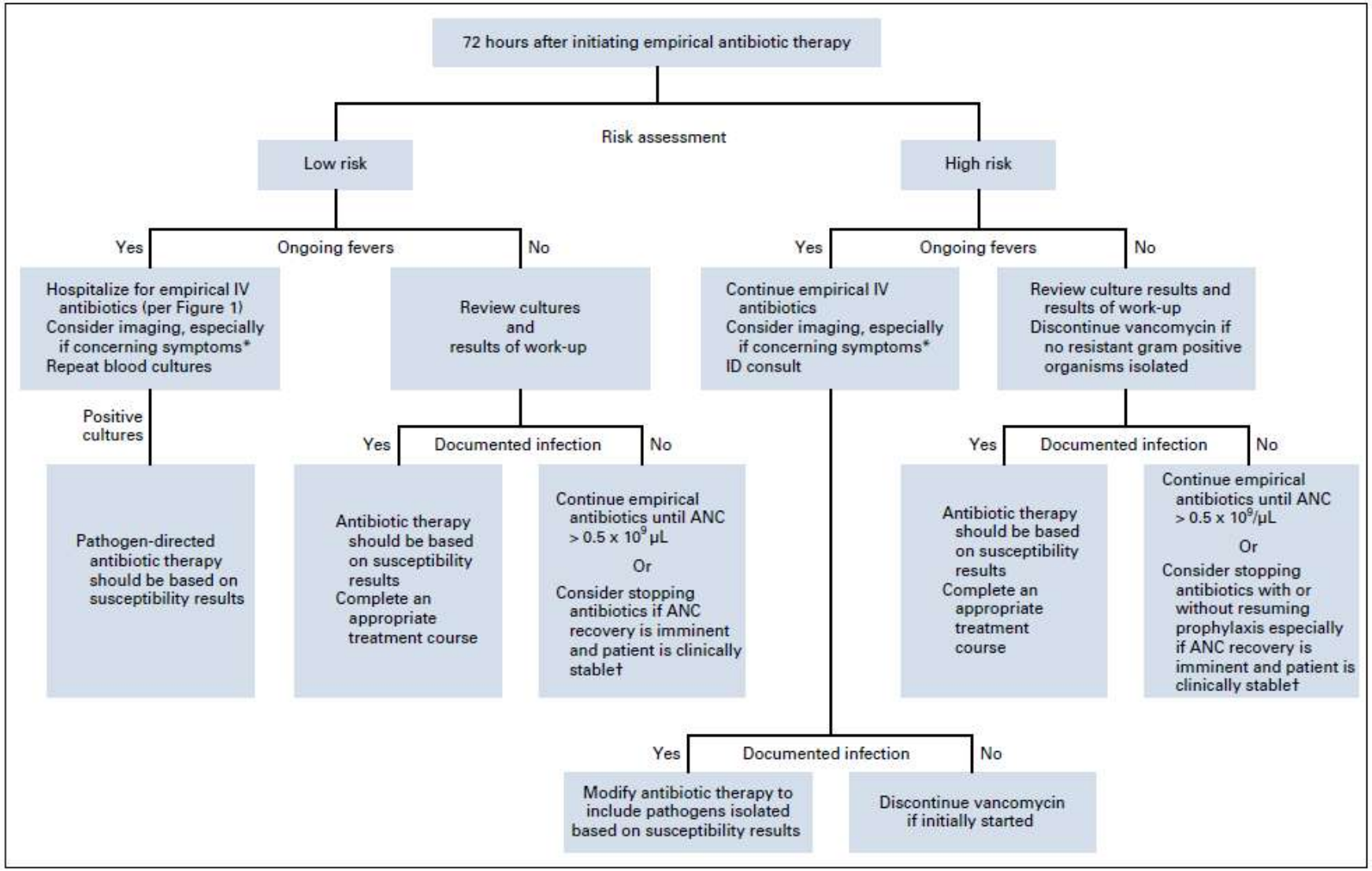

FIG 2. Flowchart of risk assessment 72 hours after initiating empirical antibiotic therapy.[2,17] (*) Imaging may include computed tomography of the sinuses, chest, abdomen, and/or pelvis depending on symptoms and severity of illness. (†) This practice is controversial, and more clinical trial data are needed, but European Conference on Infections in Leukaemia guidelines support this option. ANC, absolute neutrophil count; ID, infectious disease; IV, intravenous.

Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

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Table 1. Guideline recommendations regarding antibiotic usage duration in febrile neutropenia

Guidelines	Recommendation for documented infection	Recommendation for unexplained fever
The Infectious Diseases Society of America (IDSA) clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer (Freifeld 2011)	Duration of antibiotic therapy dictated by the particular organism and site; appropriate antibiotics should continue for at least the duration of neutropenia (until absolute neutrophil count is > 500 cells/mm^3), or longer if clinically necessary.	Initial regimen continued until clear signs of marrow recovery. An option is given, if an appropriate treatment course has been completed and all signs and symptoms of a documented infection have resolved, to resume oral fluoroquinolone prophylaxis until marrow recovery.

GUIDELINE ARTICLE

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

Diana Averbuch,[1] Christina Orasch,[2] Catherine Cordonnier,[3] David M. Livermore,[4] Małgorzata Mikulska,[5] Claudio Viscoli,[5] Inge C. Gyssens,[6,7,8] Winfried V. Kern,[9] Galina Klyasova,[10] Oscar Marchetti,[2] Dan Engelhard,[1] and Murat Akova;[11] on behalf of ECIL4, a joint venture of EBMT, EORTC, ICHS, ESGICH/ESCMID and ELN

Table 1. Guideline recommendations regarding antibiotic usage duration in febrile neutropenia

Guidelines	Recommendation for documented infection	Recommendation for unexplained fever
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 (ECIL-4) (Averbuch 2013a; Averbuch 2013b)	Targeted antibiotics should be continued until infection is microbiologically eradicated and all clinical signs of infection are resolved for at least 7 days, of which at least 4 days are afebrile.	Intravenous empirical antibacterial therapy may be discontinued after ≥ 72 h in patients who have been afebrile ≥ 48 h and are stable, irrespective of neutrophil count or expected duration of neutropenia.

Table 1. Guideline recommendations regarding antibiotic usage duration in febrile neutropenia *(Continued)*

The European Society for Medical Oncology (ESMO) guidelines for the management of febrile neutropenia, 2010 (de Naurois 2010)	Antibacterial therapy may be stopped in patients who suffered no complications and have been afebrile for at least 5 to 7 days, except in certain high-risk cases such as patients with acute leukaemia or following high-dose chemotherapy, in which longer courses of antibiotics or continuation until marrow recovery is recommended.	Antibacterial therapy may be stopped in patients who suffered no complications and have been afebrile for at least 5 to 7 days, except in certain high-risk cases such as patients with acute leukaemia or following high-dose chemotherapy, in which longer courses of antibiotics or continuation until marrow recovery is recommended.
Evidence-Based Recommendations for Antimicrobial Use in Febrile Neutropenia in Japan, 2004 (Masaoka 2004)	In low-risk patients who remain neutropenic, antibiotic therapy may be withheld after a minimum of 15 days without fever. High-risk patients should receive antibiotic therapy until there is neutrophil recovery.	In low-risk patients who remain neutropenic, antibiotic therapy may be withheld after a minimum of 15 days without fever. High-risk patients should receive antibiotic therapy until there is neutrophil recovery.
Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO) for the management of sepsis in neutropenic patients, updated in 2014 (Penack 2014)	Not addressed	Not addressed
Australian consensus guidelines for the management of neutropenic fever in adult cancer patients 2010/2011 (Lingaratnam 2011)	Not addressed	Not addressed
The United Kingdom National Institute for Health and Care Excellence (NICE) guidelines for prevention and management of neutropenic sepsis in cancer patients (Phillips 2012)	Discontinue empiric antibiotic therapy in patients whose neutropenic sepsis has responded to treatment, irrespective of neutrophil count.	Discontinue empiric antibiotic therapy in patients whose neutropenic sepsis has responded to treatment, irrespective of neutrophil count.

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

Manuela Aguilar-Guisado, Ildefonso Espigado, Almudena Martín-Peña, Carlota Gudiol, Cristina Royo-Cebrecos, José Falantes, Lourdes Vázquez-López, María Isabel Montero, Clara Rosso-Fernández, María de la Luz Martino, Rocío Parody, José González-Campos, Sebastián Garzón-López, Cristina Calderón-Cabrera, Pere Barba, Nancy Rodríguez, Montserrat Rovira, Enrique Montero-Mateos, Jordi Carratalá, José Antonio Pérez-Simón, José Miguel Cisneros

Lancet Haematol 2017; 4: e573–583

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

- Açık etiketli, randomize kontrollü faz 4 çalışması
- 2012-2016, 709 hasta, 157 epizod
- Etiyolojik tanısı olmayan yüksek riskli febril nötropenisi olan hematolojik maligniteli hastalar veya hemopoietik kök hücre nakli alıcıları
- Monoterapi (seftazidim/sefepim, meropenem/imipenem/piperasilin-tazobaktam)
- Kombinasyon tedavisi antipsödomonal β-laktam ile aminoglikozit, florokinolon veya glikopeptid ile
- Deney grubu için AAT, ≥ 72 saat apireksi artı klinik iyileşmeden sonra kesilmiş
- Kontrol grubu için, nötrofil sayısı ≥ 0.5 x 10^9/L hücre veya daha yüksek olduğunda kesilmiş
- Birincil sonlanım, AAT'siz günlerin sayısı

	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**

	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**

	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.[25]

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

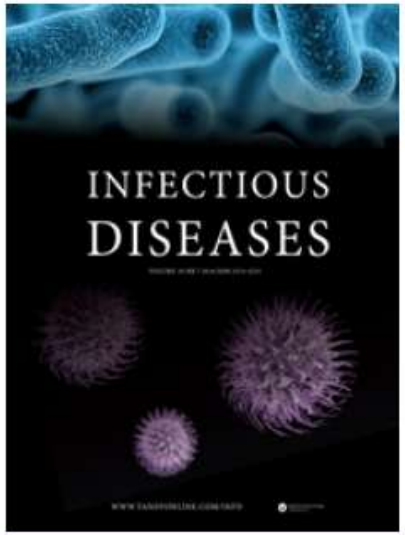
	Experimental group (n=78)				Control group (n=79)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Abdominal distension	0	0	0	0	0	1 (1%)	0	0
Abdominal pain	9 (12%)	0	0	0	11 (14%)	0	0	0
Acute kidney injury	3 (4%)	0	0	0	3 (4%)	3 (4%)	0	0
Acute peritonitis	0	0	0	0	0	0	0	1 (1%)
Atrial 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

	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

Deney grubunda bir hasta ex (allojeneik hemopoietik kök hücre transplantasyonundan sonra hepatik veno-tıkayıcı hastalıktan)
Kontrol grubunda 3 hasta ex (biri çoklu organ yetmezliğinden, biri invaziv pulmoner aspergillozdan ve biri kemoterapi sonrası intestinal perforasyon)



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Infectious Diseases

ISSN: 2374-4235 (Print) 2374-4243 (Online) Journal homepage: https://www.tandfonline.com/loi/infd20

INFECTIOUS DISEASES,
2018; VOL. 50,
NO. 7, 539–549

https://doi.org/10.1080/23744235.2018.1438649

ORIGINAL ARTICLE

Check for updates

Early discontinuation of empirical antibacterial therapy in febrile neutropenia: the ANTIBIOSTOP study

Lenaïg Le Clech[a,b], Jean-Philippe Talarmin[b], Marie-Anne Couturier[a], Jean-Christophe Ianotto[a], Christophe Nicol[a], Ronan Le Calloch[a], Stéphanie Dos Santos[a], Pascal Hutin[b], Didier Tandé[c], Virginie Cogulet[d], Christian Berthou[a] and Gaëlle Guillerm[a]

123 hastada 238 FEN atağı
Prospektif gözlemsel çalışma

Table 1. Characteristics of included patients.

Number of patients	123	
Mean age (± standard deviation)	54.5 years (±12.9)	
Minimum–maximum	18–76 years	
Male to female ratio	64/59 = 1.1	
Haematological malignancies (number and percentage)		
Acute myeloid leukaemia	54	44%
Multiple myeloma	19	16%
Acute lymphoblastic leukaemia	16	13%
Diffuse large B-cell lymphoma	14	11%
Others haemopathy	20	16%
Chemotherapy (number and percentage)		
Autologous stem cell transplant	38	31%
Induction	35	29%
Allogeneic stem cell transplant	19	15%
Consolidation	16	13%
Salvage	14	11%
Other	1	1%
Median duration of neutropenia (PMN $\leq 0.5 \times 10^9$/L) (in days and quartiles)	16 (10; 23)	
Febrile neutropenia	238	
FUO	82	34.5%
MDI	114	47.9%
Bacteraemia	85	74.6%
CDI	42	17.6%

Çalışmanın ilk aşamasında, ECIL-4 kılavuzuna uygun olarak, ampirik antibiyotik tedavisi apireksiden 48 saat sonra durdurulmuş.

Çalışmanın ikinci fazında, vücut ısısı veya lökosit sayısına bakılmaksızın antibiyotikler en geç 5. günde durdurulmuş.

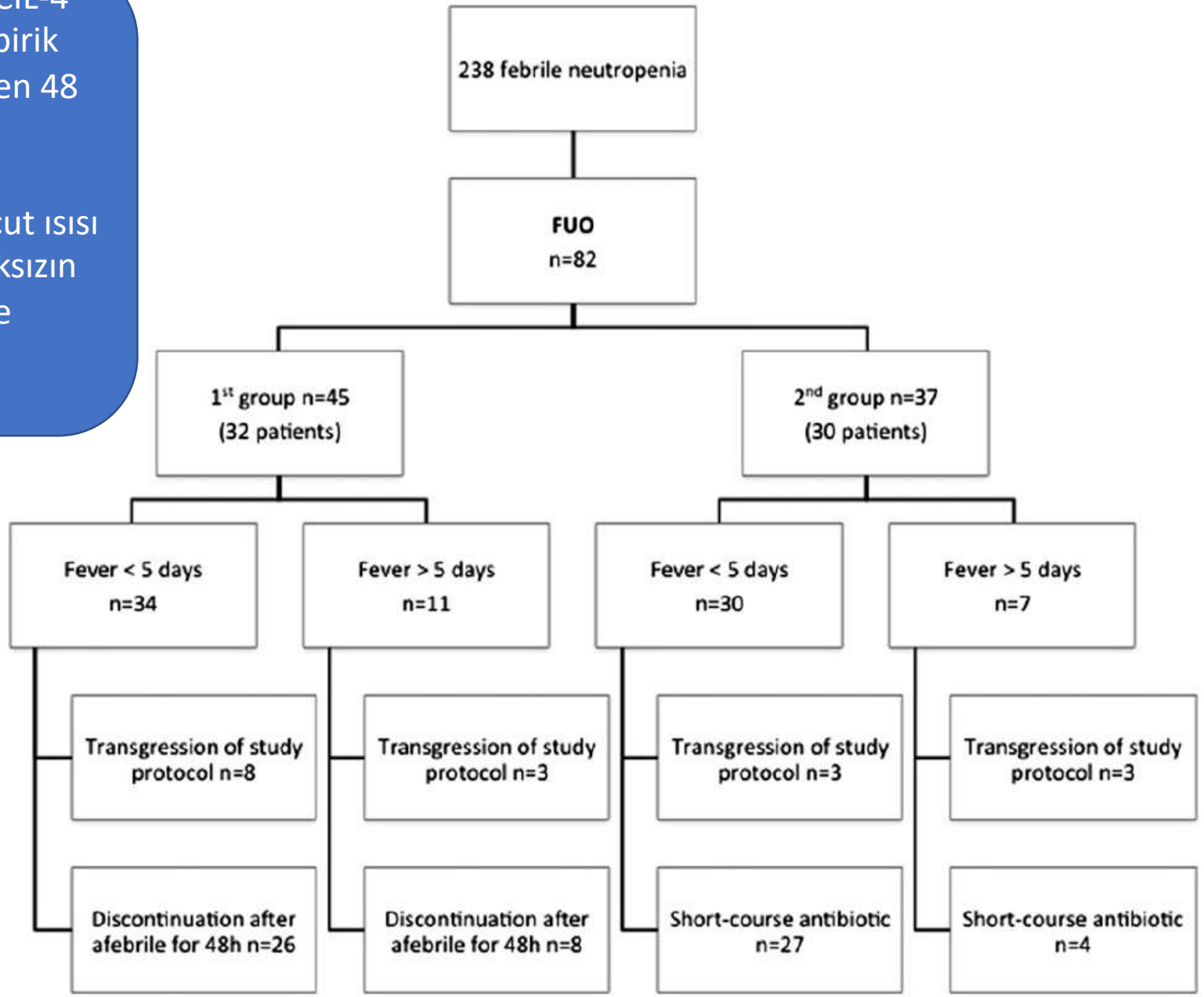


Figure 2. Flow chart of FUO patients. FUO: fever of unknown origin

Table 2. Characteristic of patients with fever of unknown origin.

	1th group $n = 45$ FUO (32 patients)	2nd group $n = 37$ FUO (30 patients)	p value
Age (mean ± standard deviation)	49.6 ± 16.2	54.3 ± 12.8	*.14*
Male to female ratio	1.4	1.5	*1.00*
Haematological malignancies, *n* (%)			*.09*
AML	26 (57.8%)	25 (67.6%)	
ALL	6 (13.3%)	0	
MM	4 (8.9%)	6 (16.2%)	
DLBCL	3 (6.7%)	4 (10.8%)	
Others	6 (13.3%)	2 (5.4%)	
Chemotherapy, *n* (%)			***.03***
Induction	16 (35.6%)	10 (27%)	*.40*
Consolidation	4 (8.9%)	7 (18.9%)	*.18*
Salvage	3 (6.7%)	7 (18.9%)	*.09*
Allogeneic stem cell transplant	14 (31.1%)	3 (8.2%)	*.01*
Autologous stem cell transplant	7 (15.5%)	10 (27%)	*.20*
Other	1 (2.2%)	0	*.36*
Duration of neutropenia (median and quartiles)	20 (13; 27)	12 (9; 19)	***.01***
Duration of empirical antibiotics (median and quartiles)	7 (5; 12)	5 (4; 5.5)	***.0002***
Duration of fever (median and quartiles)	3 (2; 4)	3 (2; 4)	*.49*
Duration of apyrexia before 2nd FN (median and quartiles)	8 (5; 15)	4 (3; 11)	*.099*
Intervals between neutropenia and FUO (median and quartiles)	4 (2; 9)	4 (2; 5)	*.63*
Recurrence of fever (*n*)	19	15	*1*
Recurrence with CDI or MDI	10	10	*.79*

AML: acute myeloid leukaemia; MM: multiple myeloma; ALL: acute lymphoblastic leukaemia; DLBCL: diffuse large B-cell lymphoma; CDI: clinically documented infection; MDI: microbiologically documented infection; FN: febrile neutropenia. Statistic test: Fisher's exact test, Student's *t* test and Mann–Whitney *U* test for mean and median.

	Number of FUO episodes with an event (%)		Event free survival (median in days)	
	1st phase of the study (n=45 FUO)	2nd phase of the study (n=37 FUO)	1st phase of the study	2nd phase of the study
Primary endpoint	10 (22.2%)	12 (32.4%)	1.5	2
In-hospital mortality	1 (2.2%)	2 (5.4%)	20	28
Intensive care admission	1 (2.2%)	5 (13.5%)	9	10
Relapse of fever ≤48 hours after antbiotics discontinuation	9 (20%)	8 (21.6%)	1	1.5

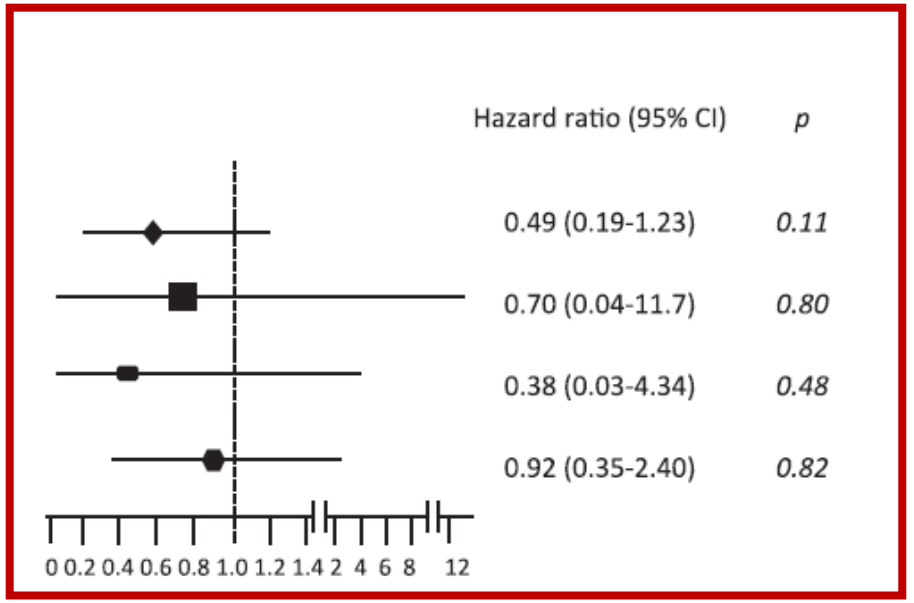
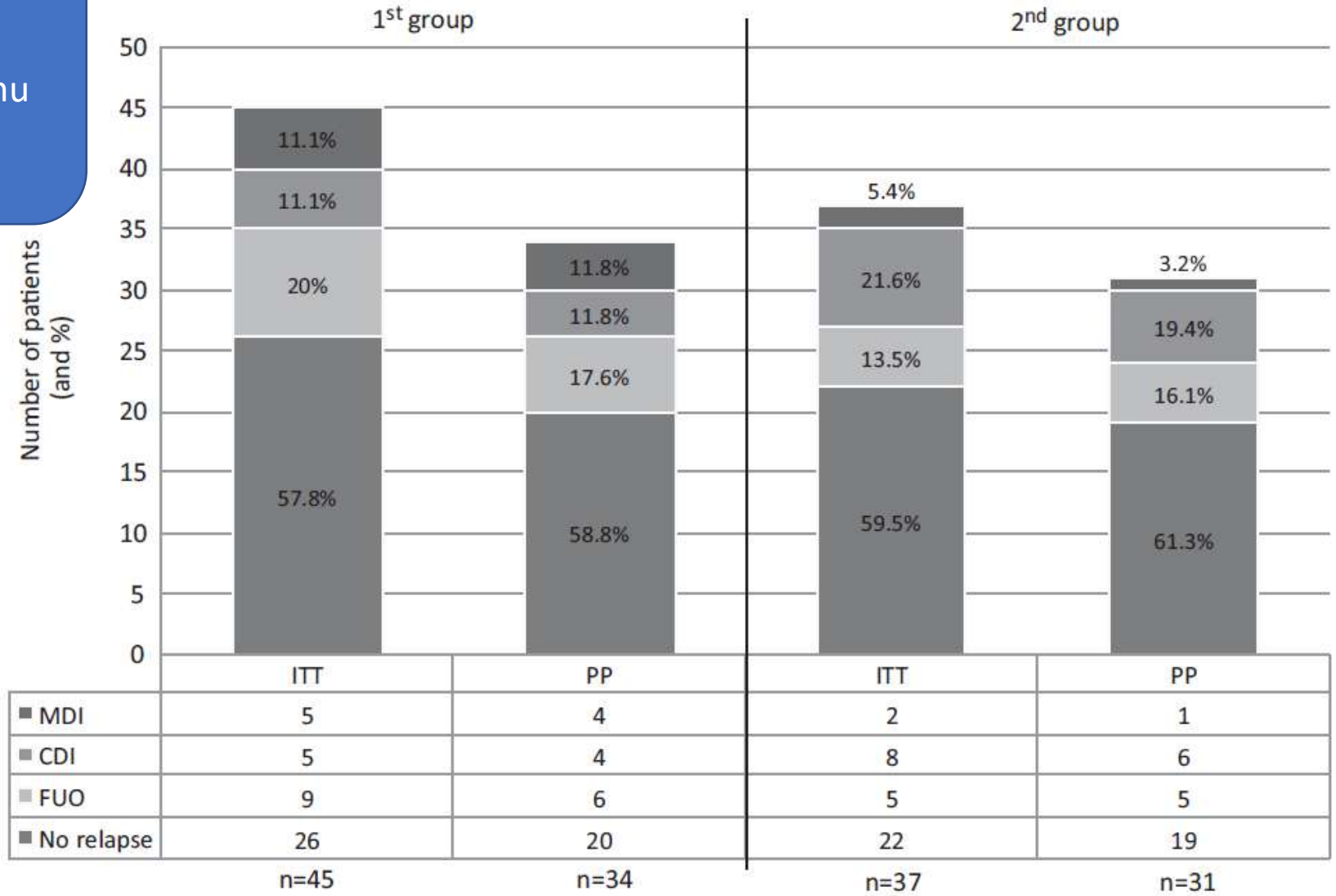


Figure 3. Effect of antibiotic protocol on primary endpoint. During the 1st phase of the study (from 1 February 2014 to 30 November 2014), antibiotics were stopped when patients had been afebrile for more than 48 h, as recommended by the ECIL-4 guidelines [2]. During the 2nd phase of the study (from 1 December 2014 to 30 September 2015), antibiotics were stopped no later than day 5 in febrile or afebrile patients (short-course antibiotic therapy). Event free survival represents t… the onset of one event (mortality, intensive care unit admission or relapse … FUO episodes in denominator.

Hastane içi mortalite
Yoğun bakım ünitesine kabul
Ateşli hastalarda antibiyotiklerin kesilmesinden 48 saat sonra ateş tekrarlaması
İnatçı ateşi olan hastalarda klinik veya mikrobiyolojik olarak belgelenmiş yeni bir infeksiyon.

Antibiyotik tedavisinin süresi
Ateşin süresi
Komplike infeksiyon
İnvaziv mantar infeksiyonu
C. Difficile koliti
Ateşsiz gün sayısı



	ITT	PP	ITT	PP
MDI	5	4	2	1
CDI	5	4	8	6
FUO	9	6	5	5
No relapse	26	20	22	19
	n=45	n=34	n=37	n=31

Figure 4. Outcome of FUO patients after antibiotics discontinuation. In ITT analysis, fever relapsed in 19 and 15 patients ($p = 1$) and among recurrences, 10 patients in each group exhibited a MDI or a CDI ($p = .79$). No difference was noted in PP analysis. FUO: fever of unknown origin; CDI: clinically documented infection; MDI: microbiologically documented infection; ITT: intention-to-treat; PP: per protocol

Annals of Hematology (2020) 99:1917–1924
https://doi.org/10.1007/s00277-020-04132-0

ORIGINAL ARTICLE

De-escalation of empiric broad spectrum antibiotics in hematopoietic stem cell transplant recipients with febrile neutropenia

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Received: 10 April 2020 / Accepted: 5 June 2020 / Published online: 17 June 2020

Fig. 1 Flow diagram. HSCT: hematopoietic stem cell transplantation; FN: febrile neutropenia

2012-2018
Allojenik-otolog HKHN hastalarında FEN atakları
Retrospektif

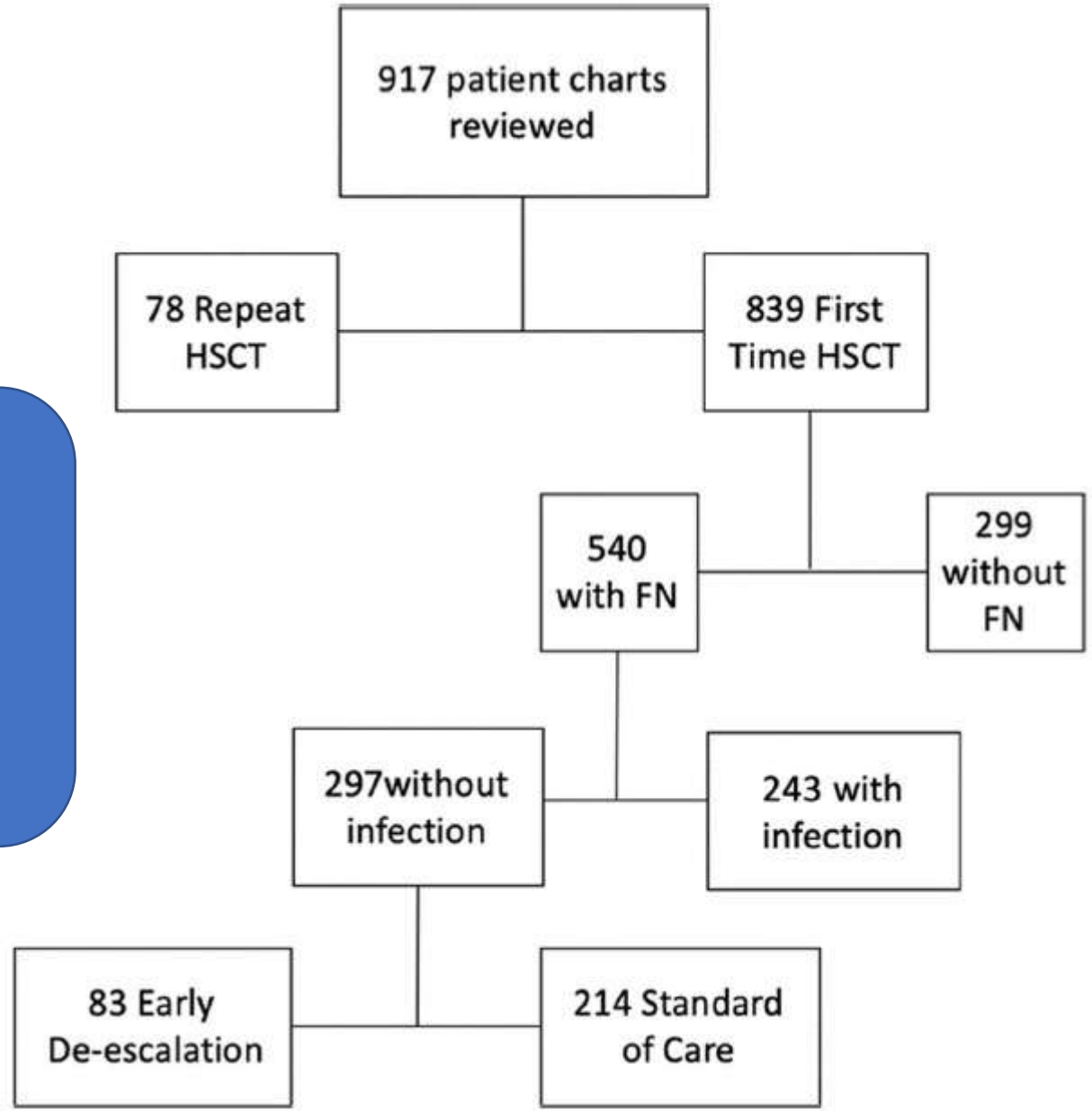


Table 1 Baseline characteristics

	Early de-escalation group	Standard of care group	*P* value
Age (years)	53.7	56.8	0.01
Sex			
Male	59/83 (71%)	130/214 (61%)	0.11
Type of HSCT			
Autologous	47/83 (57%)	183/214 (86%)	
Allogeneic	36/83 (43%)	31/214 (14%)	< 0.001
Type of allogeneic			
Matched	31/36(86%)	31/31 (100%)	
Unmatched	5/36 (14%)	0/31 (0%)	0.06
Underlying malignancy			
AML	13/83 (16%)	11/214 (5%)	0.01
ALL	9/83 (11%)	3/214 (1%)	< 0.001
MDS	7/83 (8%)	8/214 (4%)	0.14
HL	13/83 (16%)	16/214 (7%)	0.05
NHL	27/83 (32%)	86/214 (40%)	0.23
MM	8/83 (10%)	80/214 (38%)	< 0.001
CML	1/83 (1%)	3/214 (1%)	1.00
CLL	2/83 (2%)	0/214 (0%)	0.08
Other	3/83 (4%)	7/214 (3%)	1.00
Conditioning regimen			
Myeloablative	72/83 (87%)	200/214 (93%)	
Reduced intensity	11/83 (13%)	14/200 (7%)	0.1
Duration of neutropenia (days)	9.1	8	< 0.001
Duration of initial fever (days)	2.7	3.5	< 0.001

HSCT hematopoietic stem cell transplantation, *AML* acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *MDS* myelodysplastic syndrome, *HL* Hodgkin's lymphoma, *NHL* non-Hodgkin's lymphoma, *MM* multiple myeloma, *CML* chronic myeloid leukemia, *CLL* chronic lymphoblastic leukemia. Statistical methods included medians, minimums, and maximums for continuous data and counts and percentages for categorical data. The Mann-Whitney test was used to compare the median values between the groups and the Fisher's exact test was used to compare categorical data with de-escalation group; a p value < 0.05 was considered statistically significant

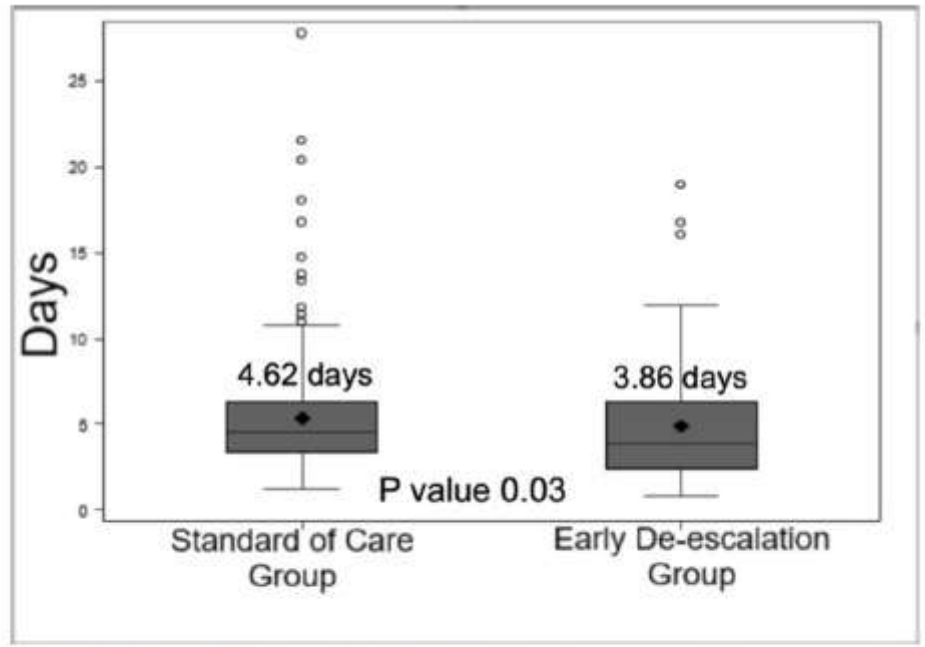


Fig. 2 Median duration of BSA use. Primary endpoint demonstrating median duration of BSA utilization was significantly less in the EDG compared to the SCG

Table 2 Primary and secondary outcomes at 30 days

	Early de-escalation group	Standard of care group	*P* value
Total duration of BSA	3.86	4.62	0.03
LOS from initial FN episode	6.96	6.4	0.048
New infection identified	11 (13.2%)	18 (8.4%)	0.27
Fever recurrences	15 (18%)	18 (8%)	0.02
Clinical de-compensation			
ICU transfer	0	3 (1.4%)	0.56
Pressor use	0	2 (0.9%)	1.00
Re-hospitalization	6 (7.2%)	23 (10.7%)	0.51
Mortality	0	1 (0.4%)	1.00

Niessen *et al. Antimicrobial Resistance and Infection Control* (2020) 9:74
https://doi.org/10.1186/s13756-020-00729-2

Antimicrobial Resistance
and Infection Control

RESEARCH Open Access

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

F. A. Niessen[1*], M. S. M. van Mourik[1], A. H. W. Bruns[1,2], R. A. P. Raijmakers[2], M. C. H. de Groot[3] and T. van der Bruggen[1]

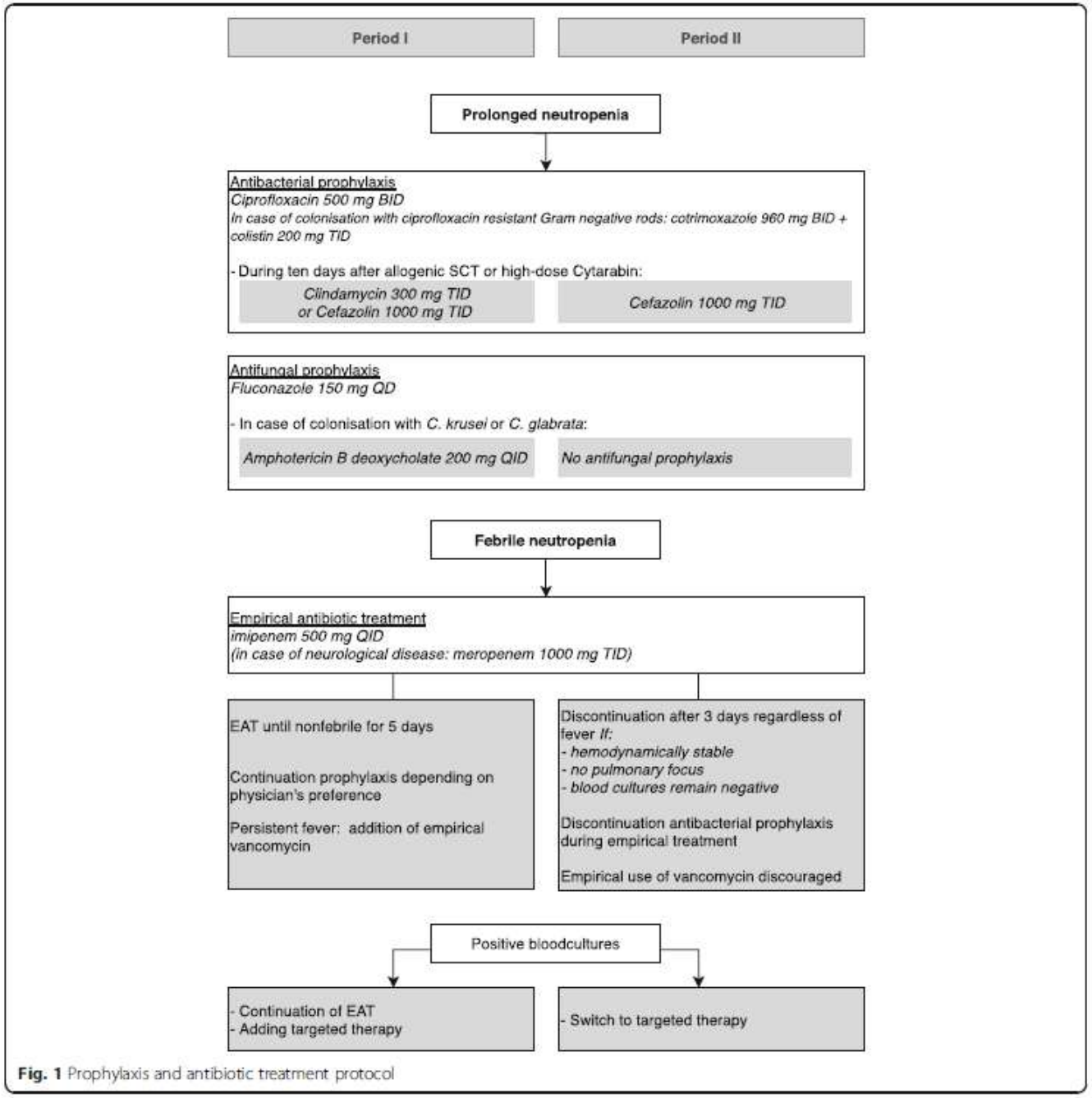


Fig. 1 Prophylaxis and antibiotic treatment protocol

2007'den 2011'e
(Dönem I, kısıtlayıcı AAT kullanımından önceki dönem)
2011'den 2014'e
(Dönem II, kısıtlayıcı AAT kullanımından sonraki dönem)
Retrospektif öncesi-sonrası çalışması

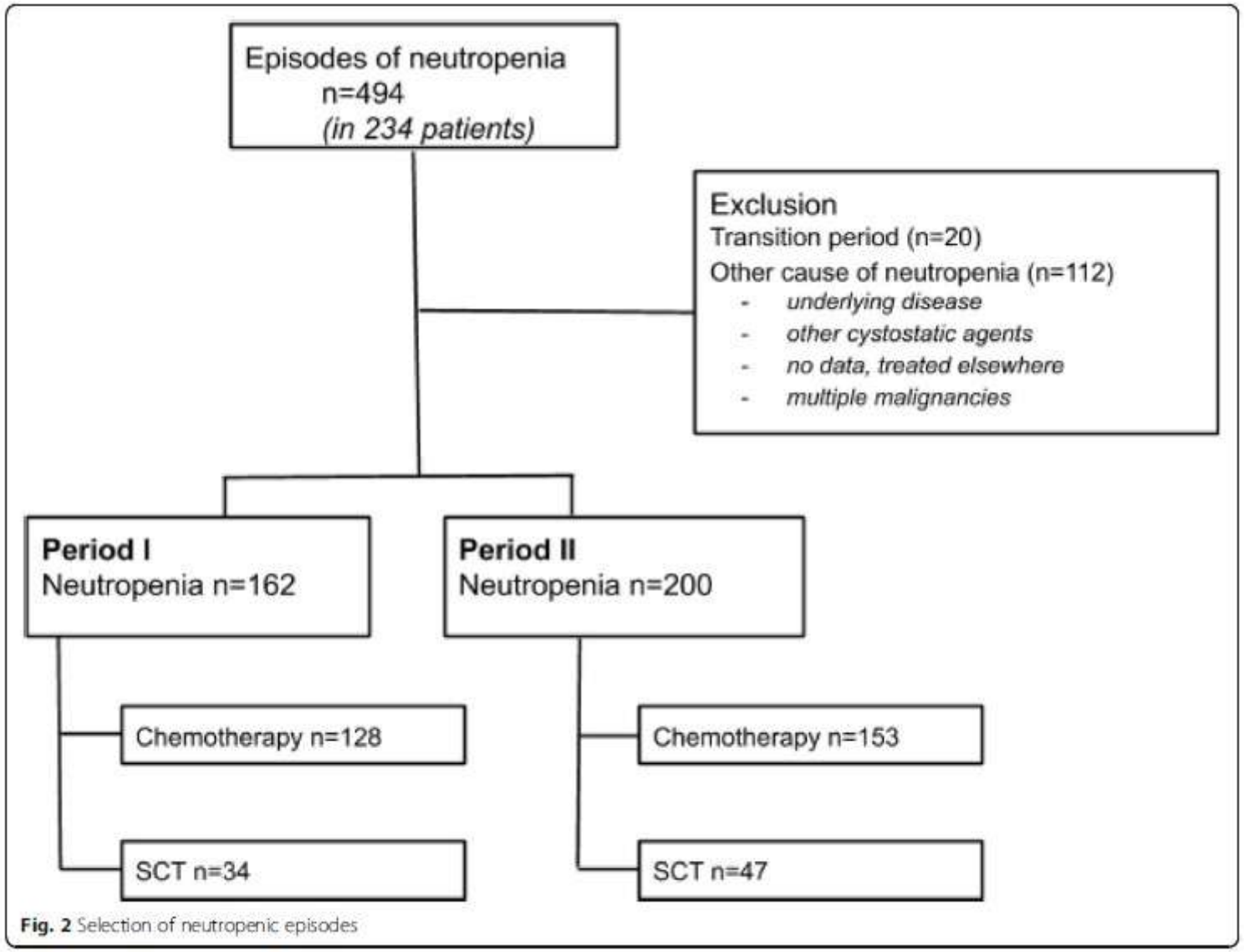


Fig. 2 Selection of neutropenic episodes

Table 1 Patient characteristics

		Period I	Period II
Total	n	97	104
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

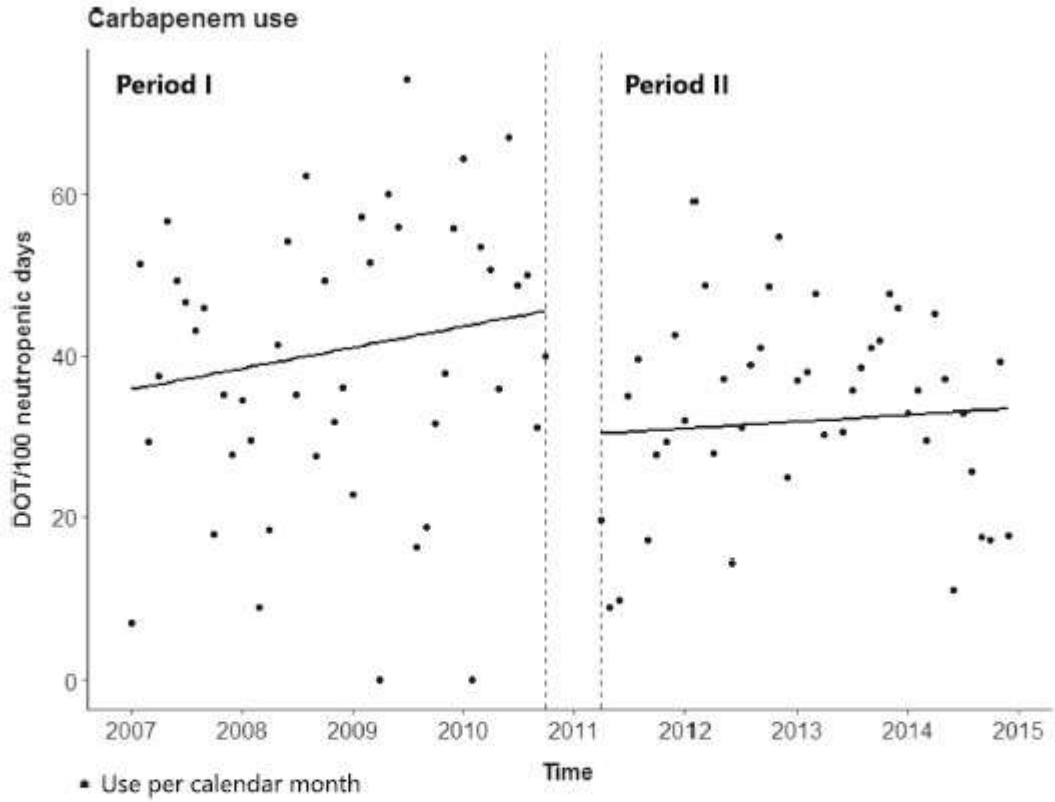
Abbreviations: AML acute myeloid leukaemia; MDS myelodysplastic syndrome

Table 2 Characteristics of neutropenic episodes

	Neutropenic episodes in period I					**Neutropenic episodes in period II**				
	Total	Duration in days		Carbapenem started		Total	Duration in days		Carbapenem started	
	n	*median (IQR)*		*n*	%	*n*	*median (IQR)*		*n*	%
Chemotherapy	128	19	(14–26)	105	(82)	153	18	(13–25)	123	(80)
Allogenic SCT	34	11	(8–17)	11	(32)	47	12	(9–26)	29	(62)
Total	162	18	(12–25)	116	(72)	200	18	(12–26)	152	(76)

Primer sonuç, nötropeni sırasında AAT olarak karbapenemlerin ve vankomisinin kullanılması Tedavi günleri (DOT)/100 nötropenik gün olarak ifade edildi ve kesintili zaman serileri (ITS) ile analiz edilmiş.

İmipenem ITS analizi
-16,1 DOT/100 nötropenik gün değişikliği (%95 GA - 26,77 - - 1,39)
Genel olarak %21,6 azalma (8,7 DOT/100 nötropenik gün)

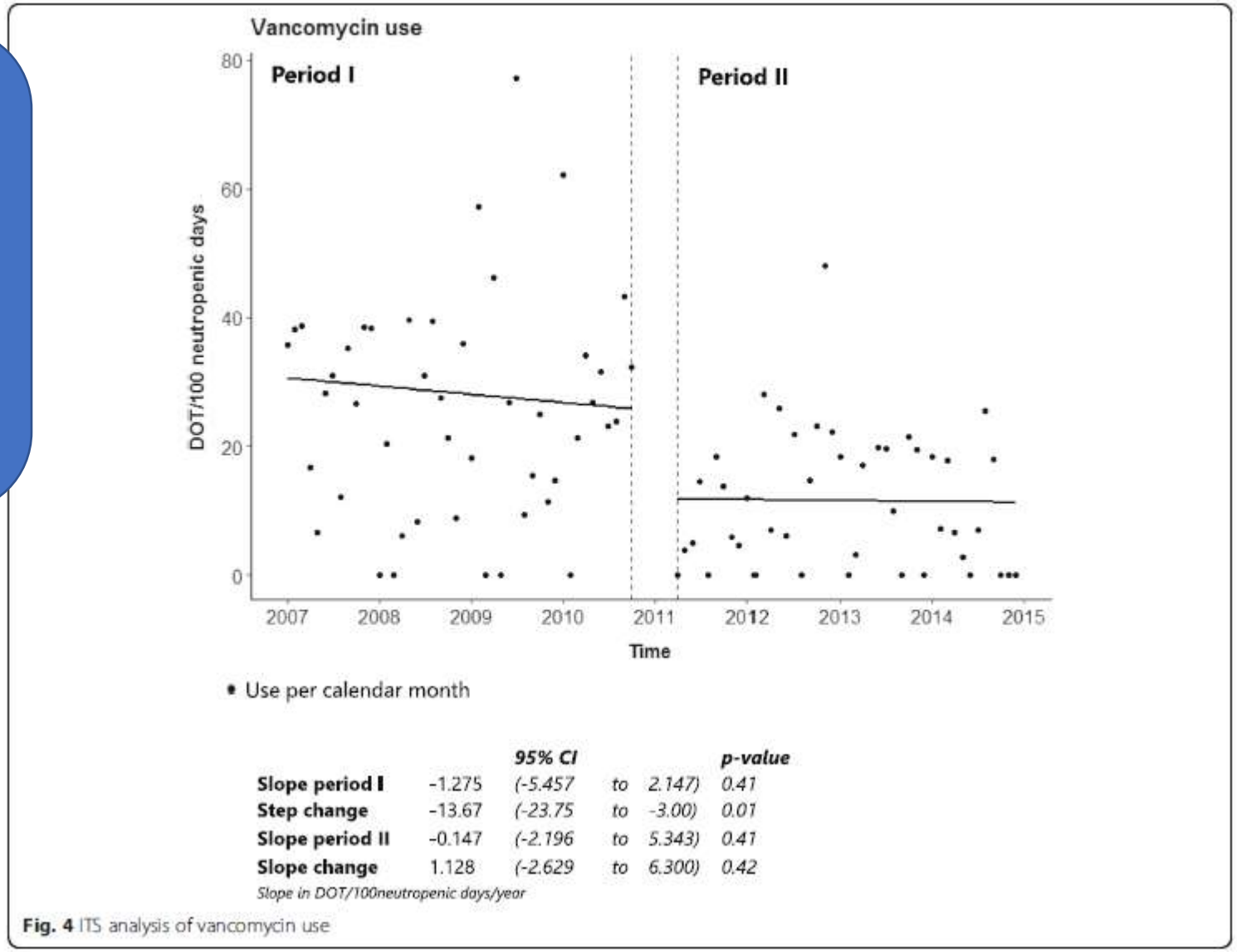


		95% CI			p-value
Slope period I	2.604	*(-2.161*	*to*	*5.495)*	*0.40*
Step change	-16.10	*(-26.77*	*to*	*-1.39)*	*0.03*
Slope period II	0.847	*(-1.821*	*to*	*6.036)*	*0.37*
Slope change	-1.757	*(-5.933*	*to*	*3.462)*	*0.64*

Slope in DOT/100neutropenic days/year

Fig. 3 ITS analysis of carbapenem use

Vankomisin kullanımı
- 13,7 DOT/100 nötropenik gün (%95 GA -23,75 ila - 3,0) değişikliği
%54,7'lik (14,6 DOT/100 nötropenik gün) toplam azalma



		95% CI			p-value
Slope period I	-1.275	*(-5.457*	*to*	*2.147)*	*0.41*
Step change	-13.67	*(-23.75*	*to*	*-3.00)*	*0.01*
Slope period II	-0.147	*(-2.196*	*to*	*5.343)*	*0.41*
Slope change	1.128	*(-2.629*	*to*	*6.300)*	*0.42*

Slope in DOT/100neutropenic days/year

Fig. 4 ITS analysis of vancomycin use

Tüm antibiyotiklerin birlikte kullanımı %11,3'lük bir azalmayla 155,6'dan 138 DOT/100 nötropenik güne düşmüş.

Table 3 Overall antibiotic use

		Days of therapy/100 neutropenic days	
		Period I	Period II
Therapeutical agents	Carbapenems	40.3	31.6
	Vancomycin	26.7	12.1
	Ceftazidime	0.1	0.3
	Ceftriaxone	0.8	0.8
	Piperacillin/tazobactam	0.2	1.1
	Penicillin	3.1	3.8
	Aminoglycosides	0.5	0.6
Prophylactic agents	Clindamycin	10.9	7.0
	Ciprofloxacin	65.8	60.1
	Cotrimoxazole *	3.1	5.6
	Cefazolin	4.1	15.0
Total		155.6	138.0

**dose > 960 mg BID*

Güvenlik ölçümleri arasında 30 günlük mortalite, AAT başladıktan sonraki 30 gün içinde yoğun bakıma yatış ve karbapenemlere duyarlı mikroorganizmaları içeren pozitif kan kültürleri yer almış.

AAT'nin erken kesilmesiyle doğrudan ilişkili ölüm yok
YBÜ'ne yatışta (dönem I'de 9/116, dönem II'de 9/152)
Pozitif kan kültürlerinde (dönem I'de 4/116, dönem II'de 2/152) kayda değer bir fark yok

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

Enferm Infecc Microbiol Clin. 2020;38(4):174–181

Enfermedades Infecciosas y Microbiología Clínica

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Consensus statement

Executive summary of the consensus document of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Network for Research in Infectious Diseases (REIPI) and the Spanish Society of Haematology and Haemotherapy (SEHH) on the management of febrile neutropenia in patients with hematological malignancies☆

Carlota Gudiol[a,*], Manuela Aguilar-Guisado[b], José Ramón Azanza[c], Francisco Javier Candel[d], Rafael Cantón[e], Jordi Carratalà[a], Carolina Garcia-Vidal[f], Isidro Jarque[g], Manuel Lizasoain[h], José Molina Gil-Bermejo[b], Isabel Ruiz-Camps[i], Isabel Sánchez-Ortega[j], Carlos Solano[k], María Suárez-Lledó[l], Lourdes Vázquez[m], Rafael de la Cámara[n]

Klinik veya mikrobiyolojik olarak belgelenmiş enfeksiyonu olmayan FEN'li hastalarda antibiyotik tedavisinin süresi ne kadardır?

1. Klinik veya mikrobiyolojik olarak belgelenmiş infeksiyonu olmayan FEN'li hematolojik hastalarda ampirik antibiyotik tedavisi, en az 72 saattir ateşsiz ve hemodinamik olarak stabil ve başlangıçtan beri nötrofil sayısı veya beklenen nötropeni süresinden bağımsız olarak asemptomatikse kesilebilir (AII).

2. Tedavi kesildikten sonra hasta en az 24-48 saat yakın klinik gözlem altında tutulmalı, böylece ateş tekrar ederse antibiyotik tedavisine erken başlanabilir (B-II).

3. Antibakteriyel profilaksi uygulayan merkezler, nötropeni devam ettiği sürece ampirik antimikrobiyal tedaviyi kestikten sonra profilaksiyi yeniden başlamayı düşünmelidir (C-III).

FEN'li ve klinik veya mikrobiyolojik olarak belgelenmiş infeksiyonu olan hastalarda antibiyotik tedavisinin süresi ne kadardır?

1. FEN'li ve klinik olarak belgelenmiş infeksiyonu olan hematolojik hastalarda, infeksiyonun klinik belirtileri ve semptomları düzeldiğinde ve hasta en az 72 saattir ateşsiz olduğunda antibiyotik tedavisi kesilebilir (B-II).

2. FEN'li ve mikrobiyolojik olarak belgelenmiş infeksiyonu olan hematolojik hastalarda, tedavi, infeksiyonun klinik ve mikrobiyolojik iyileşmesine kadar (infeksiyonun belirti ve semptomlarının ortadan kalkması ve mikrobiyolojik eradikasyon) ve en az 4 günlük apireksi ve en az 7 günlük antibiyotik tedavisi tamamlanana kadar sürdürülmelidir (BIII).

3. Her iki durumda da, tedavi kesildikten sonra nötropeni devam ederse hasta en az 24-48 saat yakın klinik gözlem altında tutulmalıdır, böylece ateş tekrarlarsa antibiyotik tedavisi hemen yeniden başlatılabilir (B-II).

4. Profilaktik antibakteriyel ajanlar veren merkezler, nötropeni devam ettiği sürece ampirik antibiyotikler kesildiğinde bu rejimi yenilemeyi düşünmelidir (C-III).

EClinicalMedicine 35 (2021) 100855

Contents lists available at ScienceDirect

EClinicalMedicine

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Research paper

Stopping antibiotic therapy after 72 h in patients with febrile neutropenia following intensive chemotherapy for AML/MDS (safe study): A retrospective comparative cohort study

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Fig. 1. the different strategies in both centers for empirical antibiotic treatment.

2011'den 2019'a kadar remisyon indüksiyon kemoterapisi alan AML veya MDS hastaları

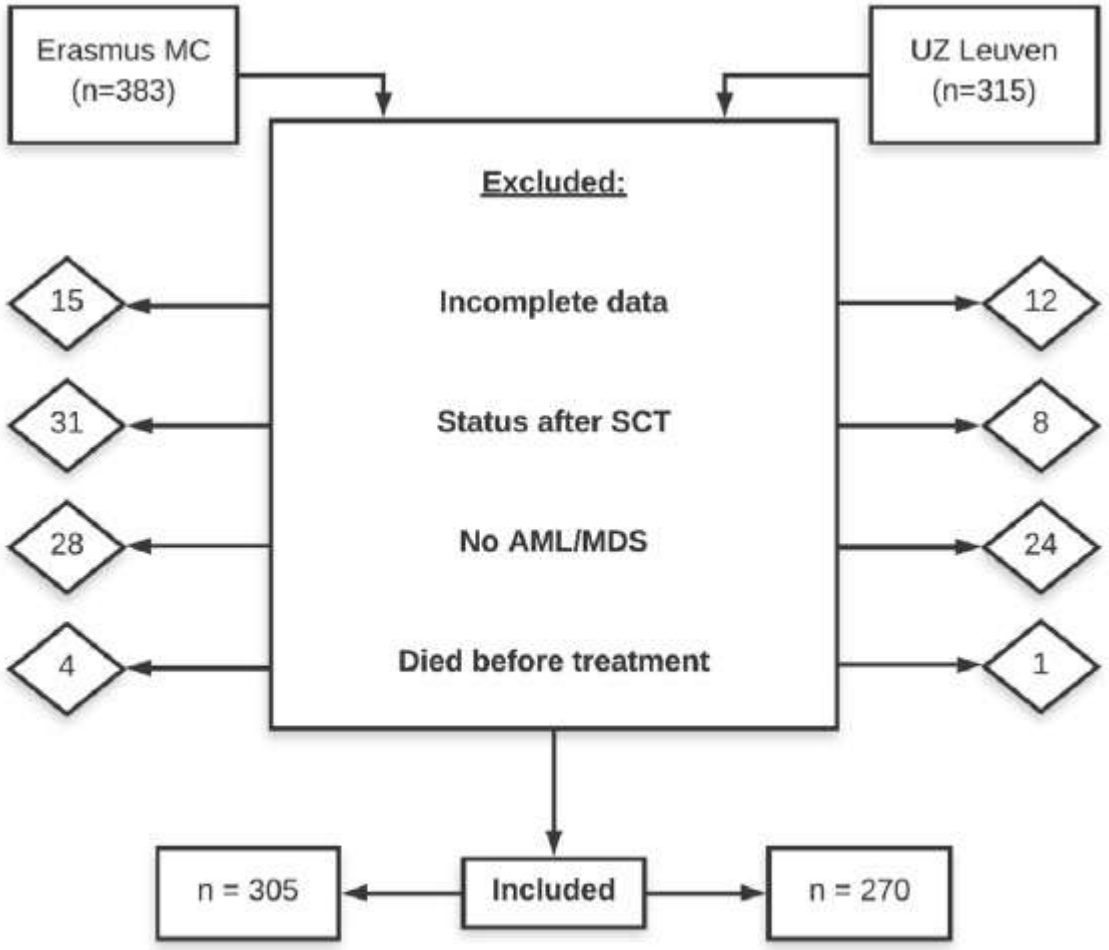

Fig. 2. inclusion and exclusion of patients.

Table 1.
Patient characteristics. For age and HCT-CI score, the median with interquartile ranges are reported.

	EMC(n = 305)	UZL(n = 270)	p value
Sex			1·000
Male	177 (58%)	150 (55·6%)	
Female	128 (42%)	120 (44.4%)	
Age (years)	62 (53–69)	61 (49–66)	**0·024**
HCT-CI	2 (1–4)	3 (2–4)	**<0·001**
HCT-CI (excl pulmonary)	1 (0–3)	1 (0–3)	0·248
Cardiovascular disease	41 (13·4%)	44 (16·3%)	1·000
Diabetes Mellitus	26 (8·5%)	18 (6·7%)	1·000
Obesity (BMI>30 kg/m2)	16 (5·2%)	17 (6·3%)	1·000
Moderate/severe hepatic disease	32 (10·5%)	7 (2·6%)	**0·002**
Moderate/severe renal disease	11 (3·6%)	4 (1·5%)	0.884
Infection at admission	71 (23·3%)	36 (13·3%)	**0·024**
Colonization by a resistant pathogen	15 (4·9%)	9 (3·3%)	1.000
AML Type			1.000
Favorable	81 (26.6%)	60 (22.2%)	
Intermediate	72 (23.6%)	82 (30.4%)	
Adverse	124 (40.7%)	99 (36.7%)	
Unclassifiable	28 (9.2%)	29 (10.7%)	
Year of admission			**< 0·001**
2011–2013	0	102 (37·8%)	
2014–2016	161 (52·8%)	80 (29·6%)	
2017–2019	144 (42·7%)	88 (32·6%)	
MDS	27 (8.9%)	17 (6.3%)	1.000

Primer sonlanım noktası, kemoterapinin başlamasından sonraki 30 gün içinde ölüm veya YBÜ kabulü olarak tanımlanan ciddi bir tıbbi komplikasyon

Table S1: Distribution of SMCs and its components in both centers.

	EMC	UZL	Univariate p-value
Death within 30 days	26 (8·5%)	12 (4·4%)	0·049
ICU admissions within 30 days	28 (9·2%)	19 (7%)	0·27
Total SMCs	38 (12·5%)	24 (8·9%)	0·17
Male	23	14	0·30
Female	15	10	0·38

Table S2: Hazard ratios for experiencing an SMC in Erasmus MC compared to UZL, adjusted for age at inclusion, AML risk, HCT-CI score (excluding pulmonary values) and year of admission.

	Hazard ratio for an SMC (95% CI)
Medical center	1.458 (0.802 – 2.652)
Age at inclusion	1.025 (0.999 – 1.050)
AML risk classification	
Favorable	1
Intermediate	0.779 (0.374 – 1.621)
Adverse	0.654 (0.331 – 1.295)
Unclassifiable	0.940 (0.363 – 2.434)
HCT-CI without pulmonary score	1.194 (1.042 – 1.369)
Year of admission	0.935 (0.820 – 1.066)

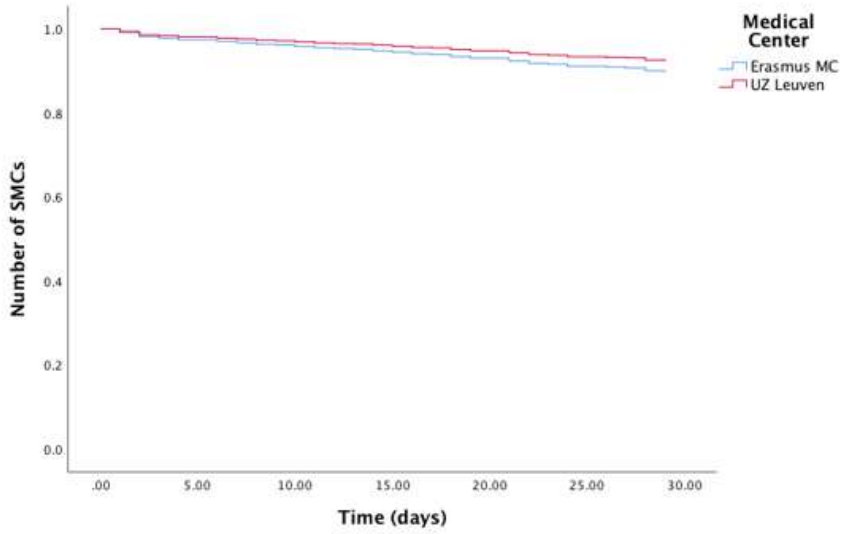

Figure S3: Cox regression of the number of SMCs in both centers, adjusted for age, non-pulmonary HCT-CI score and year of admission.

3 günlük tedavi ile %12.5 oranında bir ciddi komplikasyon gözlenirken, uzatılmış strateji ile %8.9 (p = 0.17).
Ciddi komplikasyon için HR, 3 günlük stratejiyle yüksek değil
(HR 1.357,95%CI 0.765 2.409)

Journal of Infection 84 (2022) 1–7

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Efficacy of antibiotic short course for bloodstream infections in acute myeloid leukemia patients with febrile neutropenia: A retrospective comparative study

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- Tek merkez, retrospektif çalışma
- 2017-2019 FEN'li AML hastalarında ardışık tüm KDİ epizodları
- Epizodlar antibiyotik tedavisinin uzunluğuna göre sınıflandırılmış
- Tedavi ≤7 gün sürdüyse kısa süreli olarak kabul edilmiş
  (≤10 gün NF bakteriler / ≤14 gün Staphylococcus aureus veya lugdunensis)
- Birincil sonuç, her iki grupta da antibiyotiğin kesilmesinden sonraki 30 gün içinde KDİ nükslerinin sayısı
- 71 AML hastası
- 104 KDİ

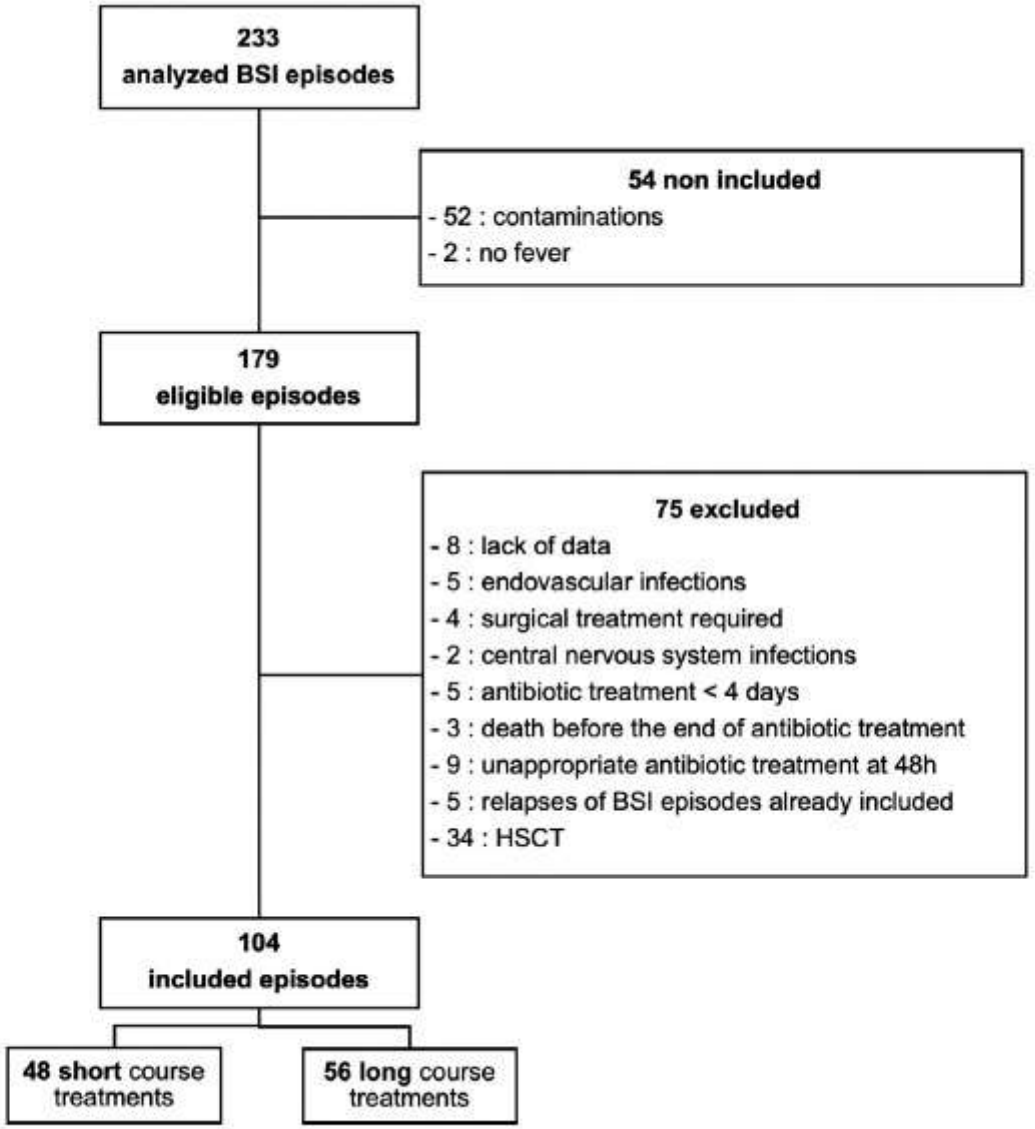

Fig. 1. Flowchart of bloodstream infection (BSI) episodes among acute leukemia patients (AML) hospitalized for febrile neutropenia.

2017 %29
2018%50
2019 %55

Table 2
Initial characteristics of BSI episodes among 104 AML patients with chemo-induced FN.

	Short treatment ($n = 48$)	Long treatment ($n = 56$)	p
Chronic kidney disease (n, %)			1
No	45 (93.8)	53 (94.6)	
Stage 1	1 (2.1)	0	
Stage 2	0	0	
Stage 3	2 (4.2)	3 (5.4)	
Corticosteroid treatment (n, %)	1 (2.1)	1 (1.8)	0.67
Treatment phase (n, %)			0.88
Induction	21 (43.8)	22 (37.9)	
Consolidation	13 (27.0)	15 (26.8)	
SalvageNon intensive chemotherapy	11 (22.9)3 (6.3)	15 (26.8)3 (5.4)	
History of MDR bacteria infection (n, %)	3 (6.3)	5 (8.9)	0.89
Severity (n, %)			
No	45 (93.8)	39 (69.6)	**0.008**
Transfer to intensive care unit	3 (6.3)	9 (16.1)	
Duration of neutropenia (median in days, IQR)	23.5 (15–29)	24 (14–32)	0.28
Duration of fever (median in days, IQR)	3 (2–7)	7.5(3–14)	**0.02**
Duration of antibiotic treatment (median in days, IQR)	6 (6–7)	11 (9.5–14)	< **0.001**

BSI: bloodstream infection; AML: acute myeloid leukemia; FN: febrile neutropenia; MDR: multi-drug resistant; IQR: inter-quartile range

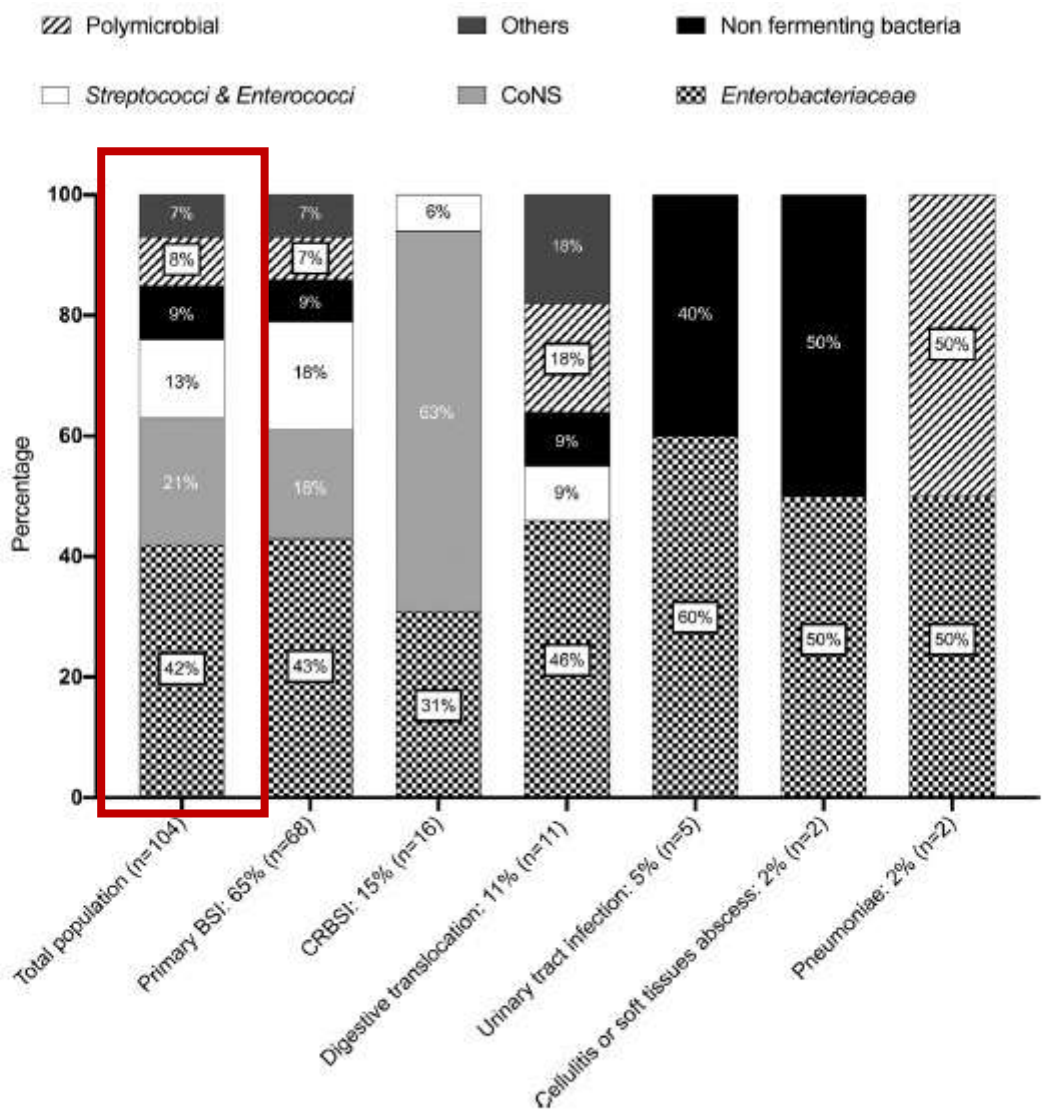

Fig. 2. Distribution of bacteria responsible for bloodstream infection (BSI) episodes among acute leukemia patients (AML) hospitalized for febrile neutropenia. CoNS: coagulase-negative staphylococci; CRBSI: catheter-related bloodstream infection.

7 hasta, 8 tekrarlayan KDİ
5 hasta kısa süreli tedavi
7 Enterobacteriacea
1 KNS

Tekrarlayan KDi'nin %88'i (n = 7/8) refrakter/tekrarlayan (R/R) AML'si olan hastalarda
%38'i remisyonda (n = 36/96)
(çok değişkenli analiz, p = 0.05)

Assessment of risk factors for BSI relapses among AML patients in FN, univariate and multivariate analysis.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*	OR	95% CI	*p*
Short treatment	6.96	0.94–512.70	0.37	4.57	0.68 – 30.70	0.11
Chronic kidney disease	0.92	0.78–1.07	0.28			
Duration of neutropenia	1.03	1.01–1.05	**0.005**	1.04	1.01–1.06	**0.003**
Remaining fever when stopping AT	0.43	0.008–24.4	0.68	0.48	0.05–4.83	0.53
Use of GCSF	0.096	0.0035–26.5	0.42			
Duration of fever	0.98	0.81–1.18	0.81			
Primary BSI	1.31	4.32 _ 3.99	0.63			

BSI: bloodstream infection; AML: acute myeloid leukemia; FN: febrile neutropenia; GCSF: Granulocyte colony-stimulating factor; AT: antibiotic treatment; OR: odds ratio; CI: confidence interval

AT kesilirken 17 hasta hala ateşli (kısa süreli 8, uzun süreli 9)
Bunların arasında 11'inde inatçı ateş için başka bir etiyoloji:
5'inde invaziv mantar hastalığından şüphelenilmiş
5'inde eş zamanlı başka bir klinik neden, 1'inde tromboz
Uzun tedavi grubundan sadece bir tanesinde KDİ relapsı görüldü (p = 0.53).

Nötropeni süresi
Tekrarlayan epizotlar 45 gün
(IQR = 28-92)
Tekrarlamayan KDİ 22.5 gün
(IQR = 14-30)
(p = 0.005)

Open Forum Infectious Diseases

MAJOR ARTICLE

Safety and Efficacy of Antibiotic De-escalation and Discontinuation in High-Risk Hematological Patients With Febrile Neutropenia: A Single-Center Experience

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Open Forum Infectious Diseases®2022

Table 1. Admission Characteristics

Characteristic	Control Group (n = 512)	ECIL-4 Group (n = 446)	*P* Value
Age, y, median (range)	58 (16–84)	59 (17–81)	
Sex, male/female	329/183	249/197	.005
Hematologic disease			
Acute myeloid leukemia	223 (43.5)	217 (48.7)	
Multiple myeloma	96 (18.7)	82 (18.4)	
Non-Hodgkin lymphoma	51 (10.0)	41 (9.2)	
Myelodysplastic syndrome	50 (9.8)	31 (6.9)	
Acute lymphoblastic leukemia	42 (8.2)	31 (6.9)	
Other (Hodgkin, PMF, CMML, CML, SAA)	50 (9.8)	44 (9.9)	
Treatment			
Chemotherapy	232 (45.3)	189 (42.4)	
Acute myeloid leukemia	167/232 (72.0)	152/189 (80.4)	
Acute lymphoblastic leukemia	28/232 (12.1)	18/189 (9.5)	
Myelodysplastic syndrome	28/232 (12.1)	10/189 (5.3)	
Autologous transplant	143 (27.9)	134 (30.0)	
Multiple myeloma	85/143 (59.4)	79/134 (59.0)	
Non-Hodgkin lymphoma	43/143 (30.1)	40/134 (29.9)	
Hodgkin lymphoma	15/143 (10.5)	9/134 (6.7)	
Allogeneic transplant	137 (26.8)	123 (27.6)	
Acute myeloid leukemia	56/137 (40.9)	64/123 (52.0)	
Myelodysplastic syndrome	22/137 (16.1)	21/123 (17.1)	
Acute lymphoblastic leukemia	14/137 (10.2)	13/123 (10.6)	
Duration of hospitalization, d, median (range)	27 (10–101)	27 (12–79)	
Duration of profound neutropenia, d, median (range)	15 (2–78)	15 (3–45)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; ECIL-4, Fourth European Conference on Infections in Leukaemia; PMF, primary myelofibrosis; SAA, severe aplastic anemia.

Table 2. Clinical Impact (Admission Periods)

Characteristic	Control Group (n = 512)	ECIL-4 Group (n = 446)	*P* Value
Febrile neutropenia	441 (86.1)	406 (91.0)	.020
No. of fever episodes, median (range)	1 (0–4)	1 (0–4)	<.001
0	71 (13.9)	40 (9.0)	
1	250 (48.8)	193 (43.3)	
2	156 (30.5)	145 (32.5)	
3	31 (6.1)	60 (13.5)	
4	4 (0.8)	8 (1.8)	
Bacteremia	156 (30.5)	209 (46.9)	<.001
Severe sepsis	51 (10.0)	48 (10.8)	
Septic shock	23 (4.5)	21 (4.7)	
Infection-related ICU admission	21 (4.1)	22 (4.9)	
Mortality during hospitalization			
Overall mortality	14 (2.7)	3 (0.7)	.016
Infection-related mortality	9 (1.8)	2 (0.4)	.058

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ECIL-4, Fourth European Conference on Infections in Leukaemia; ICU, intensive care unit.

Table 3. Clinical Impact (Fever Episodes)

Characteristic	Control Group (n = 672)	ECIL-4 Group (n = 695)	*P* Value
Type of fever			
Microbiologically documented infection	174 (25.9)	245 (35.3)	<.001
Bacteremia gram-negative	78/174 (44.8)	135/245 (55.1)	.038
Bacteremia gram-positive	59/174 (33.9)	75/245 (30.6)	
Bacteremia coagulase-negative staphylococci	14/174 (8.0)	24/245 (9.8)	
Fungal sepsis	9/174 (5.2)	1/245 (0.4)	.002
Pneumonia	6/174 (3.4)	8/245 (3.3)	
Proven invasive pulmonary aspergillosis	1/174 (0.1)	1/245 (0.1)	
Urinary tract infection	6/174 (3.4)	2/245 (0.8)	
Clinically documented infection	168 (25.0)	161 (23.2)	
Pneumonia	104/168 (61.9)	88/161 (54.7)	
Possible invasive pulmonary aspergillosis	24/168 (14.3)	21/161 (13.0)	
Probable invasive pulmonary aspergillosis	25/168 (14.9)	20/161 (12.4)	
(Entero)colitis	26/168 (15.5)	36/161 (22.4)	
Skin/soft tissue infection	18/168 (10.7)	7/161 (4.3)	
Oral cavity/dental abscess	6/168 (3.6)	10/161 (6.2)	
Sinusitis	6/168 (3.6)	3/161 (1.9)	
Fever of unknown origin	330 (49.1)	289 (41.6)	.005
Time to defervescence, d, median (range)	2 (1–23)	2 (1–20)	.001
Severe sepsis	51 (7.6)	51 (7.3)	
Septic shock	25 (3.7)	21 (3.0)	
Infection-related ICU admission	21 (3.1)	23 (3.3)	
Compliance with stewardship SOP flowchart (when applicable)			
Microbiologically documented infection	…	179/195 (91.8)	
Clinically documented infection	…	120/127 (94.5)	
Fever of unknown origin	…	215/260 (82.7)	
Antibiotic discontinuation prior to neutrophil recovery	91 (13.5)	289 (41.6)	<.001
Microbiologically documented infection	14/174 (18.9)	75/245 (30.6)	
Duration of antibiotic therapy, d, median (range)	9.5 (5–14)	7 (5–21)	
Antibiotic days saved, d, median (range)	1 (0–8)	4 (0–22)	
Clinically documented infection	15/168 (8.9)	54/161 (33.5)	
Duration of antibiotic therapy, d, median (range)	10 (6–17)	8 (4–15)	
Antibiotic days saved, d, median (range)	4 (3–7)	3.5 (1–10)	
Fever of unknown origin	62/330 (18.8)	160/289 (55.4)	
Duration of antibiotic therapy, d, median (range)	9 (3–17)	5 (0–19)	
Antibiotic days saved, d, median (range)	3 (0–12)	5 (0–19)	
Recurrent fever			
Overall	233/672 (34.7)	289/695 (41.6)	.009
After discontinuation prior to neutrophil recovery	49/91 (53.8)	153/289 (52.9)	
While still on antibiotics prior to neutrophil recovery	184/589 (31.7)	136/406 (33.5)	
Cause of recurrent fever after discontinuation			
Microbiologically documented infection—same as before	1/49 (2.0)	6/153 (3.9)	
Microbiologically documented infection—different	20/49 (40.8)	67/153 (43.8)	
Clinically documented infection—same as before	2/49 (4.1)	6/153 (3.9)	
Clinically documented infection—different	11/49 (22.4)	27/153 (17.6)	
Fever of unknown origin	15/49 (30.6)	47/153 (30.7)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ECIL-4, Fourth European Conference on Infections in Leukaemia; ICU, intensive care unit; SOP, standard operating procedure.

Table 4. Antibiotic Consumption

Characteristic	Control Group (n = 512)	ECIL-4 Group (n = 446)	*P* Value
Days of antibiotic therapy, median (range)	14 (0–69)	12 (0–60)	.001
Total antibiotic exposure, median (range of daily doses)	24 (0–129)	17 (0–82)	<.001
Amikacin			
Used (yes/no)	444 (86.7)	395 (88.6)	
Duration of treatment, d, median (range)	5 (1–23)	4 (1–20)	<.001
Meropenem			
Used (yes/no)	455 (88.9)	407 (91.3)	
Duration of treatment, d, median (range)	12 (1–53)	10 (1–46)	.002
Piperacillin-tazobactam			
Used (yes/no)	9 (1.8)	12 (2.7)	
Duration of treatment, d, median (range)	6 (2–10)	3.5 (3–18)	
Cefipime			
Used (yes/no)	57 (11.1)	9 (2.0)	<.001
Duration of treatment, d, median (range)	7 (1–25)	10 (4–19)	
Aztreonam			
Used (yes/no)	23 (4.5)	16 (3.6)	
Duration of treatment, d, median (range)	7 (2–31)	8.5 (1–38)	
Temocillin			
Used (yes/no)	7 (1.4)	38 (8.5)	<.001
Duration of treatment, d, median (range)	5 (1–8)	4 (1–7)	
Vancomycin			
Used (yes/no)	282 (55.1)	173 (38.8)	<.001
Duration of treatment, d, median (range)	10 (1–38)	8 (1–35)	.011
Teicoplanin			
Used (yes/no)	82 (16.0)	10 (2.2)	<.001
Duration of treatment, d, median (range)	9 (1–32)	12.5 (2–26)	
Amoxicillin-clavulanic acid			
Used (yes/no)	28 (5.5)	42 (9.4)	.019
Duration of treatment, d, median (range)	6 (1–20)	3 (1–16)	.004
Flucloxacillin			
Used (yes/no)	6 (1.2)	14 (3.1)	.034
Duration of treatment, d, median (range)	5 (2–8)	4 (1–12)	
Total glycopeptide			
Used (yes/no)	314 (61.3)	177 (39.7)	<.001
Compliance with start rules	143/314 (45.5)	146/177 (82.5)	<.001
Rationale for association of glycopeptide			
Prophylaxis	10/314 (3.2)	0/177 (0.0)	
Persisting fever	135/314 (43.0)	14/177 (7.9)	<.001
Rising inflammatory parameters	9/314 (2.9)	3/177 (1.7)	
MDI ≥2 sets gram positive	89/314 (28.3)	109/177 (61.6)	<.001
MDI 1 set pathogenic gram positive	10/314 (3.2)	10/177 (5.6)	
MDI 1 set contaminant gram positive	17/314 (5.4)	14/177 (7.9)	
MDI pneumonia	2/314 (0.6)	2/177 (1.1)	
CDI central line	7/314 (2.2)	4/177 (2.3)	
CDI skin/soft tissue/oral cavity/dental	27/314 (8.6)	14/177 (7.9)	
Septic shock	8/314 (2.5)	7/177 (4.0)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CDI, clinically documented infection; ECIL-4, Fourth European Conference on Infections in Leukaemia; MDI, microbiologically documented infection.

Table 5. Microbiological Impact

Type of Culture	Control Group (n = 149)	ECIL-4 Group (n = 233)	*P* Value
Blood cultures			
Gram-positive	73/149 (49.0)	98/233 (42.1)	.184
Streptococcus viridans	26/73 (35.6)	28/98 (28.6)	
CoNS	20/73 (27.4)	27/98 (27.6)	
Enterococcus faecium	10/73 (13.7)	19/98 (19.4)	
Staphylococcus aureus	7/73 (9.6)	14/98 (14.3)	
Other gram-positive	10/73 (13.7)	10/98 (10.2)	
Quinolone resistant	12/73 (16.4)	29/98 (29.6)	
MRSA	1/7 (14.3)	1/14 (7.1)	
Methicillin-resistant CoNS	11/20 (55.0)	21/27 (77.8)	.098
Vancomycin-resistant enterococci	1/10 (10.0)	0/19 (0.0)	
Gram-negative	76/149 (51.0)	135/233 (57.9)	.184
Escherichia coli	47/76 (61.8)	71/135 (52.6)	
Klebsiella species	7/76 (9.2)	28/135 (20.7)	
Pseudomonas species	7/76 (9.2)	12/135 (8.9)	
Other gram-negative	15/76 (19.7)	24/135 (17.8)	
Multidrug susceptible	51/76 (67.1)	93/135 (68.9)	
Quinolone resistant	9/76 (11.8)	11/135 (8.1)	
Multidrug resistant	5/76 (6.6)	4/135 (3.0)	
Stool cultures	Control group (n = 512)	ECIL-4 group (n = 446)	
CPE	1 (0.2)	4 (0.9)	
Vancomycin-resistant enterococci	16 (3.1)	1 (0.2)	<.001
Clostridioides	15 (2.9)	12 (2.7)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CoNS, coagulase-negative staphylococci; CPE, carbapenemase-producing Enterobacteriaceae; ECIL-4, Fourth European Conference on Infections in Leukaemia; MRSA, methicillin-resistant *Staphylococcus aureus*.

Infect Dis Ther (2022) 11:2063–2098
https://doi.org/10.1007/s40121-022-00700-1

GUIDELINES

The Dutch Working Party on Antibiotic Policy (SWAB) Recommendations for the Diagnosis and Management of Febrile Neutropenia in Patients with Cancer

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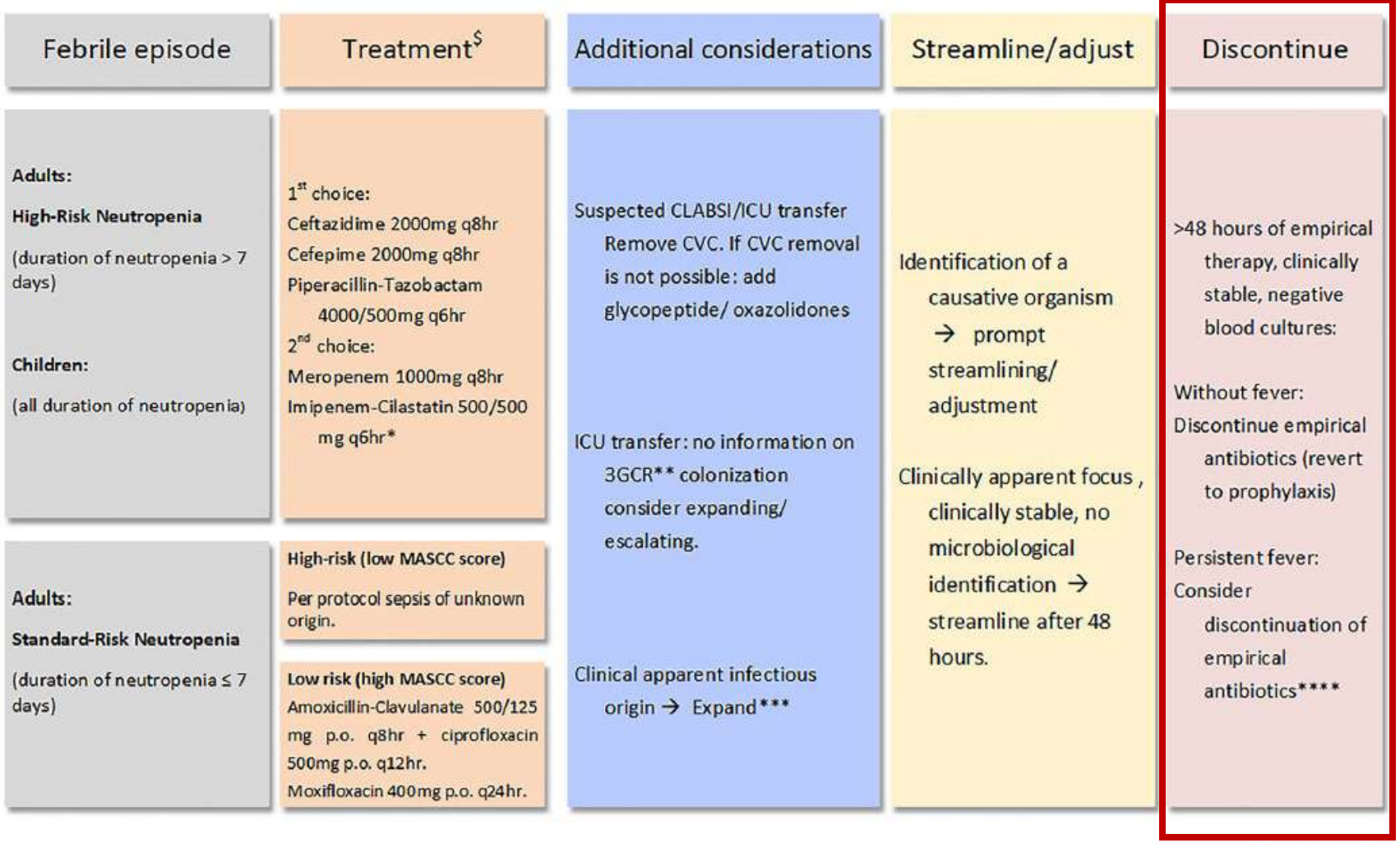

Fig. 1 Flowchart for treatment. $For dosages in children, see www.kinderformularium.nl. *This dose differs from the EUCAST recommended therapeutic dose for treatment of invasive *P. aeruginosa* infection, for rationale see 'Choice of Initial Empirical Antimicrobial Therapy/What is the Most Suitable Empirical Treatment for Febrile Neutropenia?' **3GCR: third-generation-cephalosporin resistance (e.g., due to production of AmpC or extended-spectrum beta-lactamases, ESBL). This is only relevant in case a cephalosporin is used. ***Skin: Gram-positive coverage (e.g., flucloxacillin); CVC: Gram-positive coverage including coagulase-negative staphylococci (CNS) (e.g., glycopeptide or oxazolidinones such as vancomycin or linezolid); neutropenic enterocolitis: anaerobic coverage (e.g., metronidazole). ****In case of neutropenic enterocolitis, no streamlining or discontinuation is advised except for addition of gram-positive coverage based on blood cultures. Reprinted with permission from Ned Tijdschr Hematol 2022;19(4):171–8

Table 8 Synopsis of recommendation: question 5

Recommendation	Strength	Quality of evidence
1. If no fever persists, blood cultures are negative, and the patient is clinically stable, empiric therapy should be discontinued after a total treatment duration of 48 h (and revert to prophylaxis)	Strong	Low
2. In patients that remain hospitalized and are clinically stable with negative blood cultures but with persisting fever, consider discontinuation of antibiotic treatment (revert to prophylaxis) and expand the search to find the source of infection	Weak	Very low

- 2019’da FENli klinik iyileşme belirtileri olan ve infeksiyon kanıtı olmayan hastalarda 7 günlük intravenöz anti-psödomonal tedaviden sonra deeskalasyon
- Retrospektif, tek merkezli, gözlemsel kohort bir çalışma
- AML veya ALL indüksiyon kemoterapisi alan ve belgelenmiş infeksiyonu olmadan FEN’li yetişkinler
- Ampirik antibiyotik tedavisi ≤ 9 gün ve > 9 gün
- Birincil sonuç, antibiyotiksiz günlerin sayısındaki fark
- İkincil sonuçlar ateş nüksü, yoğun bakım yatışları, ateş süresi, *Clostridioides difficile* infeksiyonu (CDI)
- AAT kesildikten sonra ateş (p=0.335), yoğun bakım ünitesine yatış (p=0.498) veya CDI (p=0.498) sonrası ateş açısından gruplar arasında fark saptanmadı.
- 9 günden fazla AAT alan daha fazla hastada AML tanısı vardı (p=0.001).

JOURNAL OF ONCOLOGY PHARMACY PRACTICE

J Oncol Pharm Practice
2023, Vol. 29(2) 305–310

DOI: 10.1177/10781552211067776
journals.sagepub.com/home/opp
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Original Article

Evaluation of early de-escalation of empiric antimicrobial therapy in acute leukemia patients with febrile neutropenia at a large academic medical center

Whitney J Ly[1], Erin E Brown[1], Zachary Pedretti[1], Jessica Auten[1] and William S Wilson[1]

Table 2. Comparison of outcomes based on EAT duration.

	EAT ≤9 days (n = 19)	EAT >9 days (n = 25)	All Patients	p-value
Length of Stay, days (median; IQR)	30 (18–34)	32 (28–36)	31.5 (27–35)	0.047
Duration of neutropenia, days (median; IQR)	23 (12–30.5)	25 (17–30)	24.5 (14.75–30.25)	0.776
Duration of EAT, days (median; IQR)	6 (4–7)	15 (13–23)	10.5 (6.75–16.5)	<0.001
Addition of Gram-positive EAT, n(%)	7 (36.8)	19 (76)	18 (40.9)	0.014
Duration of restarted EAT, days (median; IQR)	12.5 (5–20.75)	7 (6–11)	7 (6–19)	0.600
Time until recurrence of fever, days (median; IQR)	10 (3–18.25)	3 (2–4)	3 (3–6)	0.123
Recurrence of fever after discontinuation of EAT, n(%)	4 (21.1)	9 (36)	13 (29.5)	0.335

AAT ≤ 9 gün grubu
AAT > 9 gün grubuna kıyasla
En az 7 gün ve daha fazla
AT'siz gün (p < 0.001)

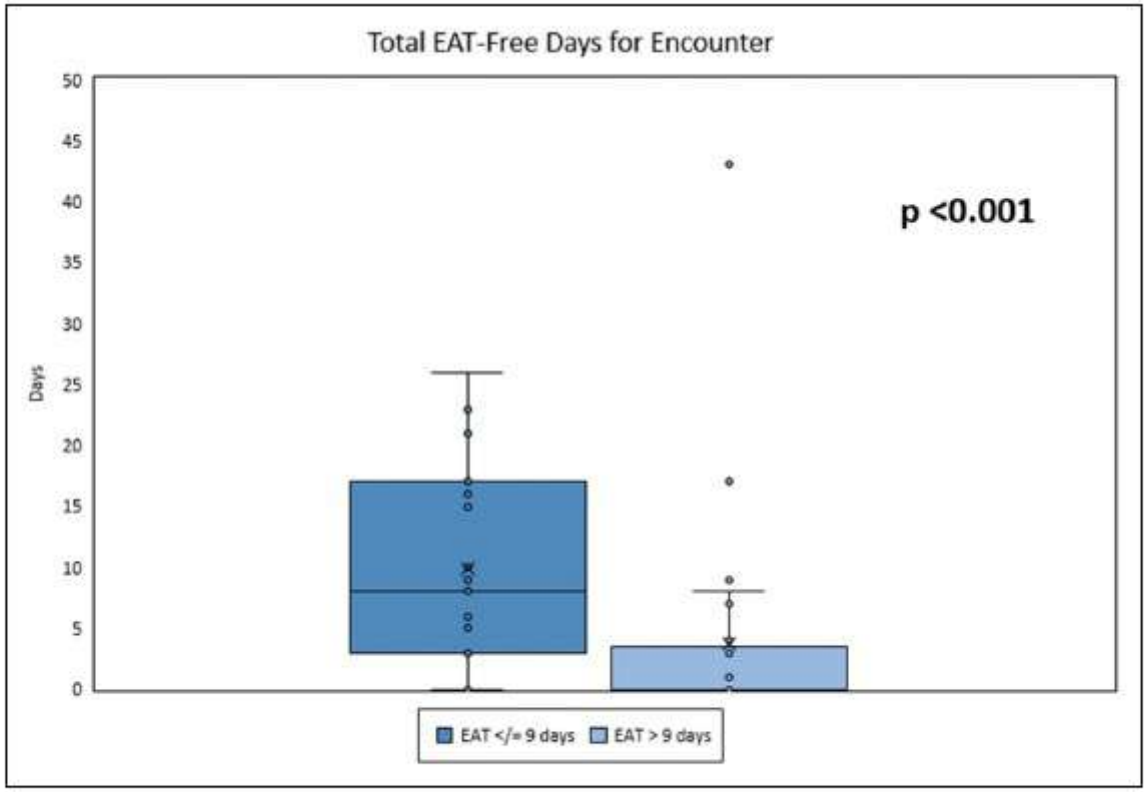

Figure 1. Total EAT-free days for encounter based on EAT duration.

AAT > 9 gün grubunda daha uzun başlangıç ateşi görüldü (p < 0.001) ve dirençli Gram-pozitifleri kapsayan antibiyotikler daha fazla (p=0.014).

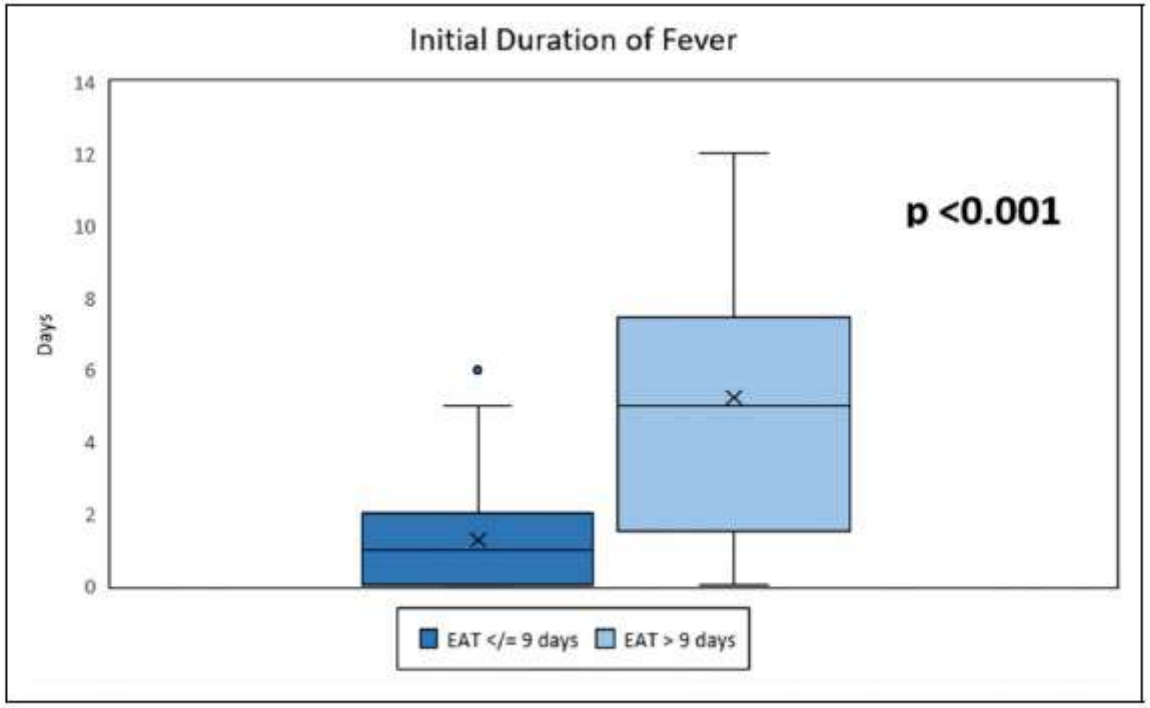

Figure 2. Duration of initial fever based on EAT duration.

Ankara Üniversitesi Tıp Fakültesi

- 1992 yılında Türkiye'de ilk ***Otolog Periferik Kök Hücre Transplantasyonu***
- 1993 yılında Türkiye'de ilk, Dünyada üçüncü ***Allojeneik Periferik Kök Hücre Transplantasyonu***
- Hematoloji servisinde 45, hematopoietik kök hücre nakli servisinde 12 olmak üzere hematoloji hastaları için toplam 57 yatak kapasitesi mevcuttur.
- ECIL-4 (48 saat ateşsiz, 72. saatten sonra antibiyotik kesmeyi düşün….)
- 2022 yılı 72 Allojenik HKHN, 106 Otolog HKHN
- 178 hastada 66 FEN atağı
- 66 FEN atağı→ 22 hastada klinik odak+mikrobiyolojik etken
  16 hastada klinik odak
  28 hastada hiçbir odak yok

- 6 hastada ateş tekrarı; 2'sinde tiflit, 1 hastada PJP, 1 hastada kandidemi,1 hastada mukor, 1 hastada odak yok
- 2 ex

- Febril nötropeni hematolojik malignansilerin önemli bir komplikasyonu
- %40 klinik ve mikrobiyolojik odak yok
- Kısa ve uzun süreli antibiyotik tedavisi→ Önemli fark yok
- Klinik başarısızlık ve bakteriyemi açısından nötropeni düzelene kadar antibiyotiklerin uzun süreli kullanımına kıyasla, nötrofil sayısından bağımsız olarak kısa süreli kullanım güvenli
- Hematolojik kanserli hastalar için antimikrobiyal yönetişim programlarının geliştirilmesi


İyileşeceğiz ama
unutmadan..