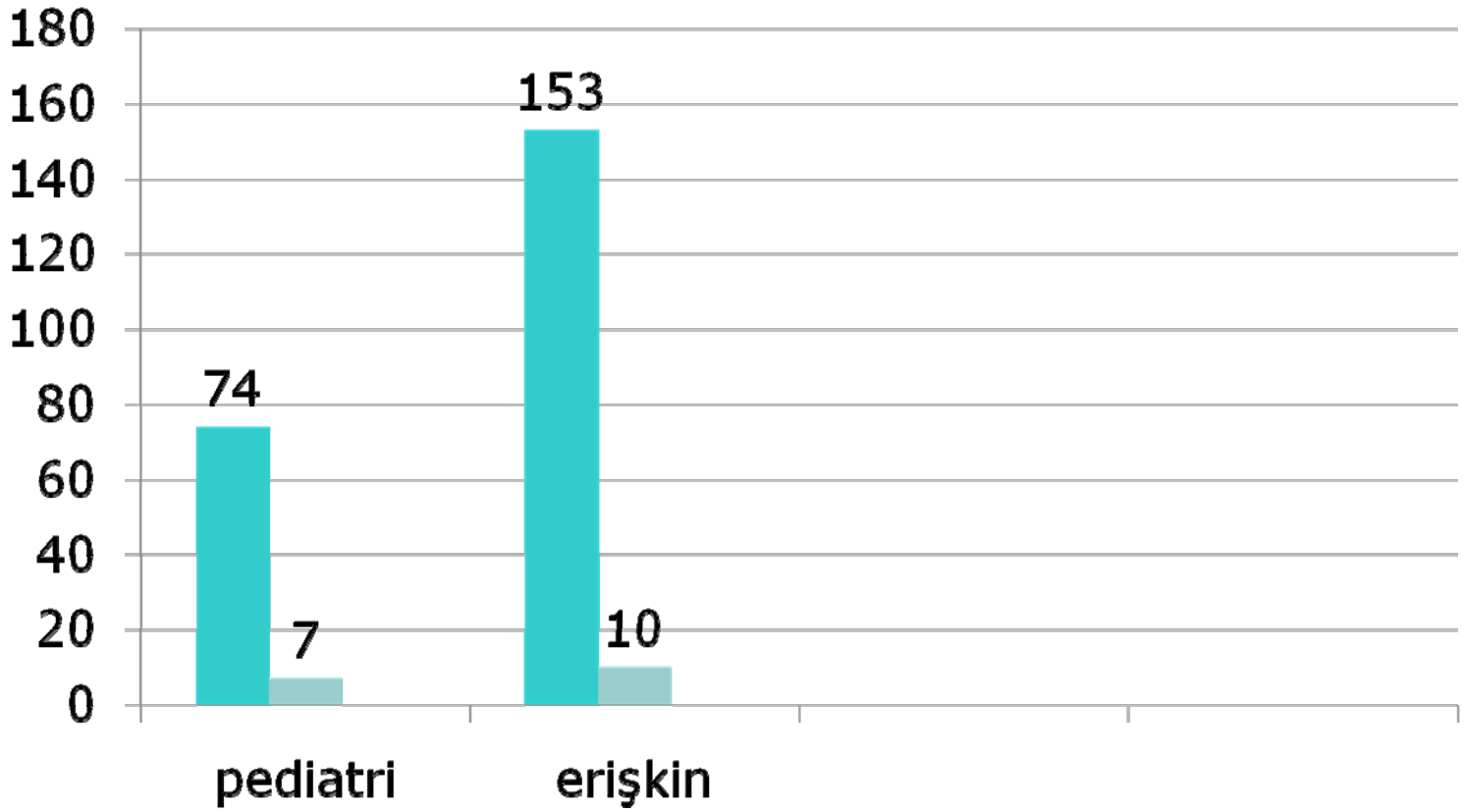
Son bir (iki) yılda febril nötropenide neler oldu?

Antibakteriyel tedavi ve profilaksi

Lütfiye Mülazımoğlu

Marmara Üniversitesi Tıp Fakültesi

2006-2008



2005-2006

- sefepim monoterapisi diğer betalaktam tedavilere kıyasla tüm nedenlere bağlı mortalitede anlamlı artışa neden olur
  - Paul M, Yahav D, Fraser A, Leibovici L. Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials.J Antimicrob Chemother. 2006;57(2):176-89. Review

A Randomized, Open-Label, Multicenter Comparative Study of the Efficacy and Safety of Piperacillin-Tazobactam and Cefepime for the Empirical Treatment of Febrile Neutropenic Episodes in Patients with Hematologic Malignancies

E. J. Bow,[1,2] C. Rotstein,[3] G. A. Noskin,[10] M. Laverdière,[5] A. P. Schwarer,[6] B. H. Segal,[9] J. F. Seymour,[8] J. Szer,[7] and S. Sanche[4]

agents, such as glycopeptides [54–58]. The all-cause mortality among cefepime recipients was nonsignificantly higher in our study (3% in the piperacillin-tazobactam group vs. 5.7% in the cefepime group), a finding that is in keeping with a recent systematic review [46].

Clinical Infectious Diseases 2006; 43:447–59

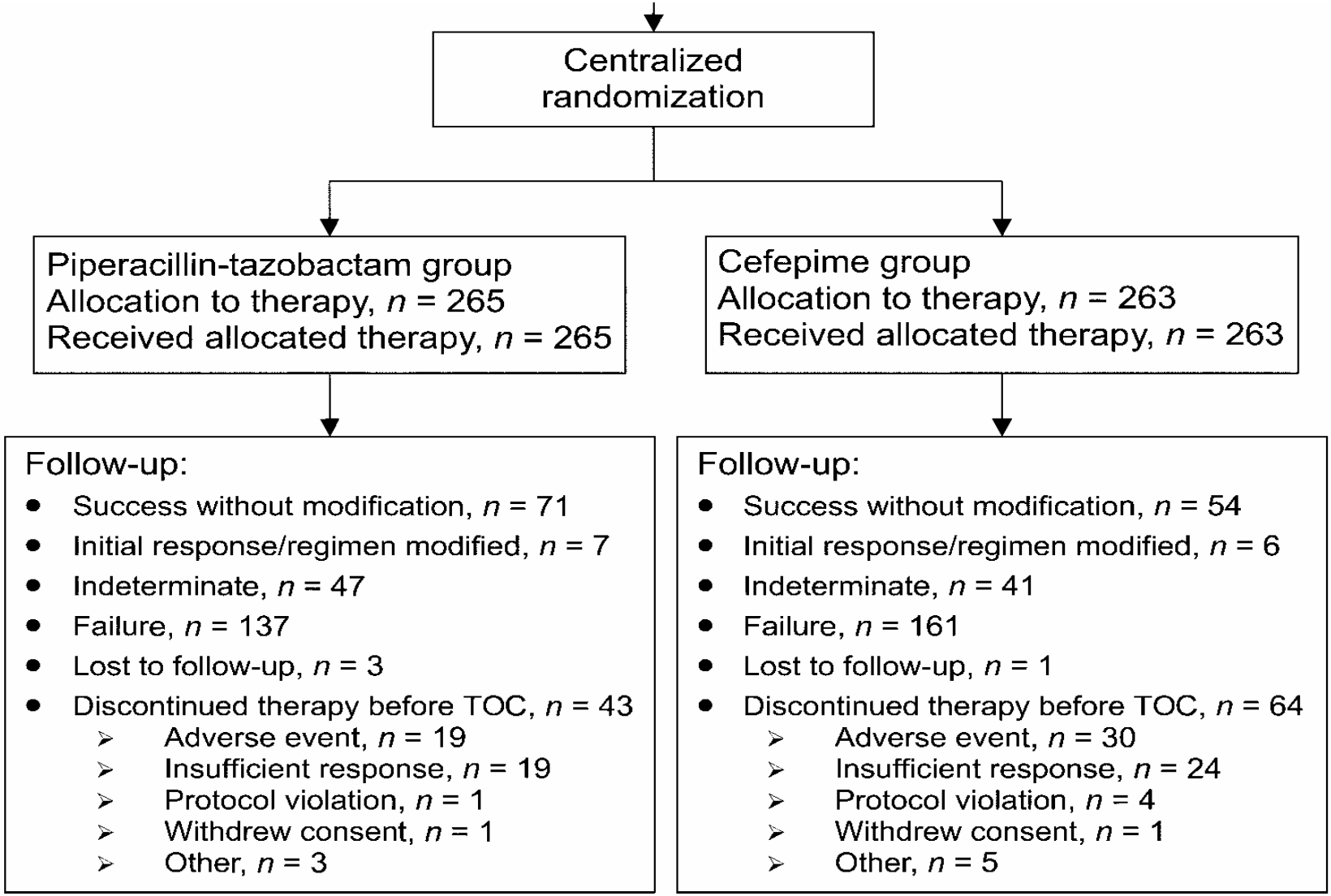
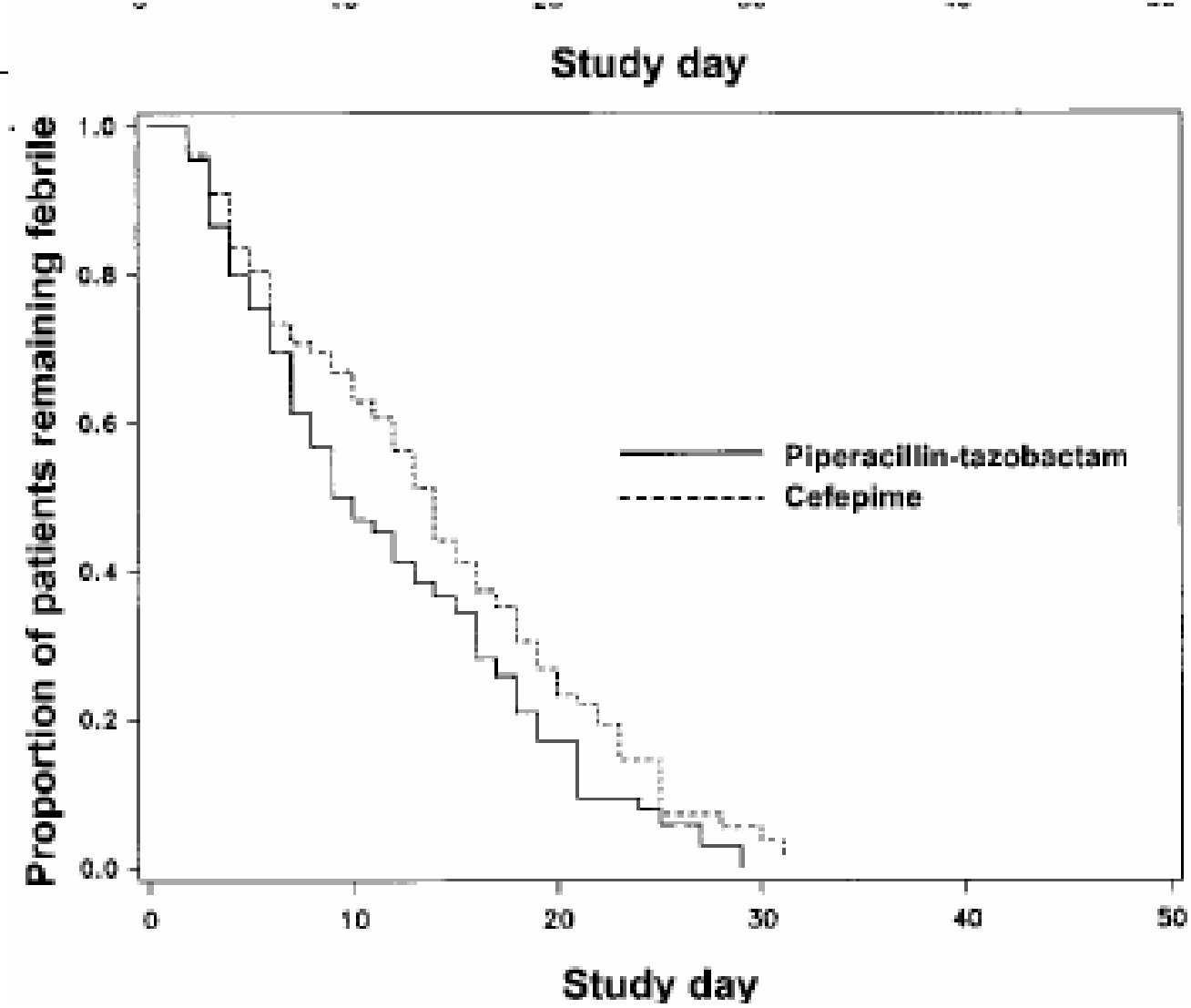

Centralized randomization
Piperacillin-tazobactam group
Allocation to therapy, n = 265
Received allocated therapy, n = 265
Cefepime group
Allocation to therapy, n = 263
Received allocated therapy, n = 263
Follow-up:
Success without modification, n = 71
Initial response/regimen modified, n = 7
Indeterminate, n = 47
Failure, n = 137
Lost to follow-up, n = 3
Discontinued therapy before TOC, n = 43
Adverse event, n = 19
Insufficient response, n = 19
Protocol violation, n = 1
Withdrew consent, n = 1
Other, n = 3
Follow-up:
Success without modification, n = 54
Initial response/regimen modified, n = 6
Indeterminate, n = 41
Failure, n = 161
Lost to follow-up, n = 1
Discontinued therapy before TOC, n = 64
Adverse event, n = 30
Insufficient response, n = 24
Protocol violation, n = 4
Withdrew consent, n = 1
Other, n = 5

Table 2. Response to treatment, by randomization and by classification of febrile neutropenic episodes at the test-of-cure time point for the modified intent-to-treat population.

Classification	Piperacillin-tazobactam recipients (n = 265)	Cefepime recipients (n = 263)
Success	71 (26.8)	54 (20.5)
IR:RM	7 (2.6)	6 (2.3)
Indeterminate	47 (17.7)	41 (15.6)
Failure	137 (51.7)	161 (61.2)
Regimen modification	118	134
Glycopeptide	106	117
Breakthrough infection	10	13
No improvement	5	3
Not reported	1	4
Lost to follow-up	3	1


Study day
Proportion of patients remaining febrile
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Piperacillin-tazobactam
Cefepime
Study day

Monoterapi mi? Hangi ab ile?

- pediatrik febril nötropeni vakalarında sefepim, meropenem ve piperasilin/tazobaktam monoterapileri eşdeğer etkinliklerdedir…..
  - Corapcioglu F, Sarper N, Zengin E. Monotherapy with piperacillin/tazobactam versus cefepime as empirical therapy for febrile neutropenia in pediatric cancer patients: a randomized comparison. Pediatr Hematol Oncol. 2006;23(3):177-86.
  - Oguz A, Karadeniz C, Citak EC, Cil V, Eldes N. Experience with cefepime versus meropenem as empiric monotherapy for neutropenia and fever in pediatric patients with solid tumors. Pediatr Hematol Oncol. 2006;23(3):245-53.

Corapcioglu F, Sarper N, Zengin E. Monotherapy with piperacillin/tazobactam versus cefepime as empirical therapy for febrile neutropenia in pediatric cancer patients: a randomized comparison. Pediatr Hematol Oncol. 2006;23(3):177-86.

TABLE 3 Treatment Response of the Study Groups

	All episodes $n = 50$	PIP/TAZO $n = 25$	Cefepime $n = 25$	p
Success without modification	26 (52)	14 (56)	12 (48)	0.778
Persistant fever at 72nd hour	22 (44)	12 (48)	10 (40)	0.776
Modification day (mean ± SD)	5.1 ± 0.9	4.8 ± 0.8	5.3 ± 1.3	0.650
(Range)	(4–10)	(4–7)	(4–10)	
Total number of modifications[a]	35	15	20	0.470
Glycopeptide	18 (36)	9 (36)	9 (36)	1.0
Antifungal	7 (14)	5 (20)	2 (8)	0.417
Change in the empirical regimen	10 (20)	1 (4)[b]	9 (36)[c]	0.011
Median duration of fever (days)	3	3	2	0.777
(Range)	(1–28)	(1–20)	(2–28)	
Mean duration of treatment (days)	11.3 ± 6.4	10.8 ± 4.9	11.8 ± 7.7	0.882
(Range)	(4–40)	(5–25)	(4–40)	
Mean duration of neutropenia (days)	10.4 ± 5.6	7.5 ± 4.0	8.1 ± 4.5	0.218
(Range)	(3–25)	(5–25)	(3–24)	

Oguz A, Karadeniz C, Citak EC, Cil V, Eldes N. Experience with cefepime versus meropenem as empiric monotherapy for neutropenia and fever in pediatric patients with solid tumors. Pediatr Hematol Oncol. 2006;23(3):245-53.

	Cefepime ($n = 32$)	Meropenem ($n = 33$)	95% confidence interval of the difference (p)
Total Success			
Success	21 (65.6%)	20 (60.6%)	–.19–.20 (.68)
Failure	11(34.4%)	13 (39.4%)	
Addition of other antimicrobials			
Aminoglycosides	3	4	
Glycopeptides	7	13	
Antifungals	4	6	
Metranidazole	4	0	

- EORTC
- yüksek risk grubunda yer alan febril nötropenik 763 hasta
- piperasilin/tazobaktam monoterapisini

etkin ve güvenilir bulmuştur.

- Viscoli C, Cometta A, Kern WV, Bock R, Paesmans M, Crokaert F, Glauser MP, Calandra T; International Antimicrobial Therapy Group of the European Organization for Research and Treatment of Cancer. Piperacillin-tazobactam monotherapy in high-risk febrile and neutropenic cancer patients.Clin Microbiol Infect. 2006;12(3):212-6.

Problem	Recommendation	Grading
BL monotherapy is as efficacious as BL+AG as empirical therapy of febrile neutropenia	YES	A I
BL+ AG combination is more nephrotoxic and ototoxic than BL monotherapy	YES	A I
OD dosing of AG are as efficacious as and less nephrotoxic than MDD	YES	A I
Empirical addition of AG to the initial regimen in patients with persistent fever	NO	C III
Empirical use of BL+AG combination in patients in whom a resistant Gram-negative infection[2] is suspected	YES	C III
Addition of AG to the initial regimen in case of documented *P. aeruginosa* infection	NO	C III
Use of BL+AG combination in patients with severe sepsis or septic shock	YES	C III
Use of BL+AG in neutropenic patients with pneumonia	NO	C III
Use of BL+AG combination to prevent emergence of resistance during therapy	NO	B I

2005-2006

- nötropenik hastalarda antibiyotik proflaksisi mortaliteyi azalttır
  - Gafter-Gvili A, Fraser A, Paul M, Leibovici L.Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med. 2005;142(12 Pt 1):979-95. Erratum in: Ann Intern Med. 2006;144(9):704.

İlişkili soru ve kaygılar

- Bu kadar yaygın kullanımda direnç problemi?
- Her kemoterapi epizodunda mı?

Journal of Antimicrobial Chemotherapy (2007) **59**, 5–22
doi:10.1093/jac/dkl425
Advance Access publication 30 October 2006

JAC

Effect of quinolone prophylaxis in afebrile neutropenic patients on microbial resistance: systematic review and meta-analysis

Anat Gafter-Gvili[1,2]*, Mical Paul[1,2], Abigail Fraser[3] and Leonard Leibovici[1,2]

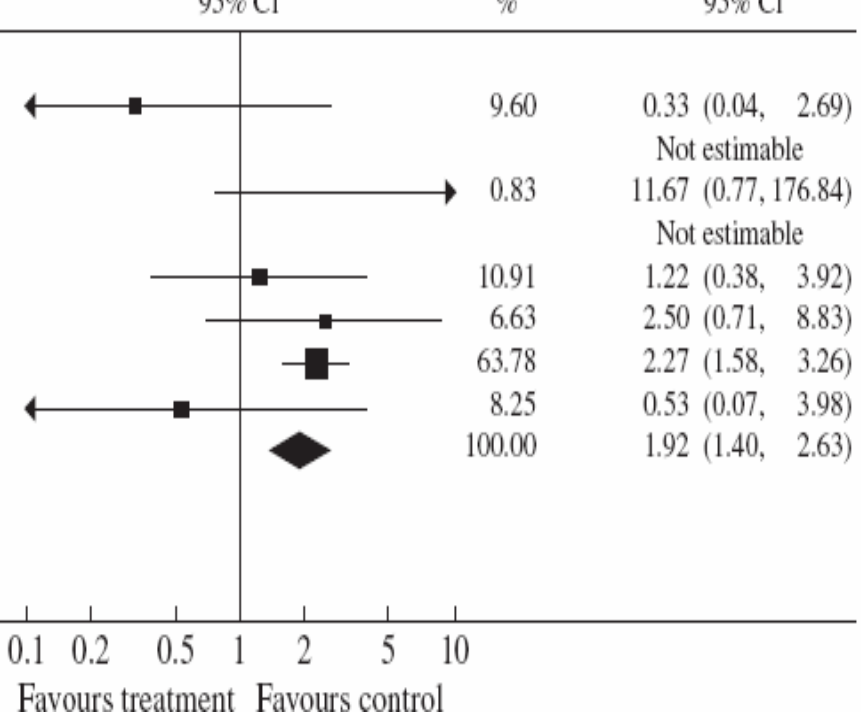
- 56 çalışma
- 7878 hasta

- Kinolon vs plasebo
- Kinolon vs diğer ab

Kinolon px kinolon dirençli bakterilerle oluşan infeksiyonların ~~oranını artırmamaktadır….~~

Figure 2. Infection with bacteria resistant to quinolones: quinolones versus placebo or no intervention.

Study or sub-category	Quinolone n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
01 quinolone versus placebo/no intervention					
Karp *et al.* (1987)	1/20	4/26		9.60	0.33 (0.04, 2.69)
Casali *et al.* (1988)	0/4	0/19			Not estimable
Schroeder *et al.* (1992)	2/2	0/6		0.83	11.67 (0.77, 176.84)
Tsutani *et al.* (1992)	0/7	0/20			Not estimable
Talbot *et al.* (1993)	4/17	5/26		10.91	1.22 (0.38, 3.92)
Lee *et al.* (2002)	5/14	3/21		6.63	2.50 (0.71, 8.83)
Bucaneve *et al.* (2005)	41/74	32/131		63.78	2.27 (1.58, 3.26)
Cullen *et al.* (2005)	1/16	7/59		8.25	0.53 (0.07, 3.98)
Subtotal (95% CI)	154	308		100.00	1.92 (1.40, 2.63)
Total events: 54 (quinolone), 51 (Control)					
Test for heterogeneity: $\chi^2 = 7.54$, df = 5 ($P = 0.18$), $I^2 = 33.7\%$					
Test for overall effect: $Z = 4.02$ ($P < 0.0001$)					



- **yoğun antibiyotik kullanımı→ direnç problemi→hematolojik malignensili hastalarda kinolon kullanımı→ kinolon dirençli E.coli suşlarında artış**

  - **Cattaneo C, Quaresmini G, Casari S, Capucci MA, Micheletti M, Borlenghi E, Signorini L, Re A, Carosi G, Rossi G. Recent changes in bacterial epidemiology and the emergence of fluoroquinolone-resistant Escherichia coli among patients with haematological malignancies: results of a prospective study on 823 patients at a single institution. J Antimicrob Chemother. 2008 Jan 24**

- 823 hasta
- beklenen febril nötropeni süresi >7 gün→levofloksasin→%39.4 hasta
- 164 patojen→%49.4 Gram negatif--%40.9 Gram pozitif
- Escherichia coli (%23.2)→%86.8 kinolon dirençli
- Fluorokinolon direnci ile metisilin direnci en fazla

FQ-R-Met-R: Multivariet analiz

- **FQ-R**
- **Proflaksi (P < 0.001)**
- **neutropeni >7 gün (P = 0.02)**
- **Bağımsız değişken**

- **Met-R**
- **proflaksi (P = 0.041)**
- **santral venöz kateter (P = 0.036)**
- **Bağımsız değişken**

Sonuç:

- Levofloksasin proflaksisi:
- Kinolon direncinde artış
- Kinolon dirençli suşlar ile infekte hastalarda febril nötropenin seyri daha kötü olmamıştır

QUALITY OF EVIDENCE

High risk patients
(expected duration of neutropenia > 7 days)

Acute Leukemia and Auto-HSCT

Antibacterial prophylaxis with fluoroquinolones showed to be effective in reducing (quality of evidence I) :

- Mortality
- Febrile episodes
- Bacterial infections and bacteremias
- Gram-negative infections and bacteremias
- Gram-positive infections but not bacteremias
- The use of empirical antibiotics

Allo-HSCT

Because the expected duration of neutropenia is more than seven days also in allo HSCT patients, this group is considered at high risk.

Data on efficacy of quinolone prophylaxis are available only for bone marrow transplated but not for allo HSCT patients.

2007-2008

- florokinolon proflaksisi lenfoma ve solid tümörlü ayaktan hastalarda febril epizod riskini ve mortaliteyi azaltır
  - Imran H, Tleyjeh IM, Arndt CA, Baddour LM, Erwin PJ, Tsigrelis C, Kabbara N, Montori VM. Fluoroquinolone prophylaxis in patients with neutropenia: a meta-analysis of randomized placebo-controlled trials. Eur J Clin Microbiol Infect Dis. 2008;27(1):53-63.

Cullen MH, Billingham LJ, Gaunt CH, Steven NM. Rational selection of patients for antibacterial prophylaxis after chemotherapy.J Clin Oncol. 2007 Oct 20;25(30):4821-8.

- SIGNIFICANT (Simple Investigation in Neutropenic Individuals of the Frequency of Infection after Chemotherapy +/- Antibiotic in a Number of Tumours)
- 1565 hasta
- Solid kanser, lenfoma
- Proflaktik levofloksasin sadece ilk myelosupresif tedavi esnasında
- Ve ilk ateş epizodunu takib eden diğer epizodda kullanılmalıdlr
- Kinolon (levofloksasin) proflaksisi yaş, performans durumu veya tümör türünden bağımsız etkilidir.

von Baum H, Sigge A, Bommer M, Kern WV, Marre R, Döhner H, Kern P, Reuter S.
Moxifloxacin prophylaxis in neutropenic patients.
J Antimicrob Chemother. 2006 Oct;58(4):891-4.

Characteristic	Study period (prophylaxis with)			*P* value
	1 (levofloxacin)	2 (moxifloxacin)	3 (levofloxacin)	
Length of study period, weeks	67	50	19	
Patients, no.	241	180	48	
Neutropenic episodes, no.	399	282	53	
Median duration of neutropenia per episode, days	11	11	10	0.26
Gram-negative bacteraemia	22 (6%)	30 (11%)	3 (6%)	0.04
E. coli	14	26	2	
other Enterobacteriaceae	2	3	1	
P. aeruginosa	4	1	–	
other non-fermentative bacilli	2	–	–	
Fluoroquinolone resistance among Gram-negative isolates	15 (68%)	28 (93%)	3 (100%)	
Gram-positive bacteraemia	52 (13%)	50 (18%)	7 (13%)	0.28
staphylococci	41	34	5	
enterococci	8	14	–	
other	3	2	2	
Levofloxacin/moxifloxacin resistance among Gram-positive isolates	90%/67%	94%/86%	71%/57%	
Diarrhoea incidence per episode, no. (%)	159 (40%)	132 (47%)	24 (45%)	0.18
CDAD episodes, no. (%)	10 (6%)	43 (33%)	3 (13%)	<0.001
Patients with at least one episode of CDAD, no. (%)	10 (4%)	37 (21%)	2 (4%)	<0.001
Overall mortality, no. of patients (%)	18 (8%)	12 (7%)	5 (10%)	0.25
Death from infection, no. of patients (%)	10 (4%)	10 (6%)	3 (6%)	0.41

CDAD, *Clostridium difficile* toxin A-associated diarrhoea.
Statistical significance was tested by ANOVA or χ^2 analysis.

2005-2006

- glikopeptidlerin febril nötropenik hastada başlangıç emprik tedavisinde kullanılmasını destekleyecek yeterli kanıt yoktur
  - Vardakas KZ, Samonis G, Chrysanthopoulou SA, Bliziotis IA, Falagas ME. Role of glycopeptides as part of initial empirical treatment of febrile neutropenic patients: a meta-analysis of randomised controlled trials.Lancet Infect Dis. 2005;5(7):431-9

CONCLUSION 1

	Glycopeptide	CDC grading system
At onset of fever	Not recommended	I D
Persistent fever	Not recommended	I D

CONCLUSION 2

	Glycopeptide	CDC grading system
Known colonisation with MRSA	recommended	III C
Hypotension or shock	recommended	III C
Skin and soft tissue infections including cath-related infections	recommended	III C

Teicoplanin vs Vankomisin

- Multivariet analiz:
- amfoterisin B kullanımı($p < 0.001$)
- vankomisin kullanımı ($p = 0.002$)

- Nefrotoksisite ile ilişkili bağımsız değişkenler

  - Hahn-Ast C, Glasmacher A, Arns A, Mühling A, Orlopp K, Marklein G, Von Lilienfeld-Toal M. An Audit of Efficacy and Toxicity of Teicoplanin Versus Vancomycin in Febrile Neutropenia: Is the Different Toxicity Profile Clinically Relevant? Infection. 2008 Feb;36(1):54-58. Epub 2008 Jan 12

Glikopeptid vs Linezolid

- linezolid ve vankomisinin febril nötropenik hastada uygun indikasyonda eşdeğer etkinlik sağladığını gösterilmiştir

  - Jaksic B, Martinelli G, Perez-Oteyza J, Hartman CS, Leonard LB, Tack KJ. Efficacy and safety of linezolid compared with vancomycin in a randomized, double-blind study of febrile neutropenic patients with cancer. Clin Infect Dis. 2006;42(5):597-607.

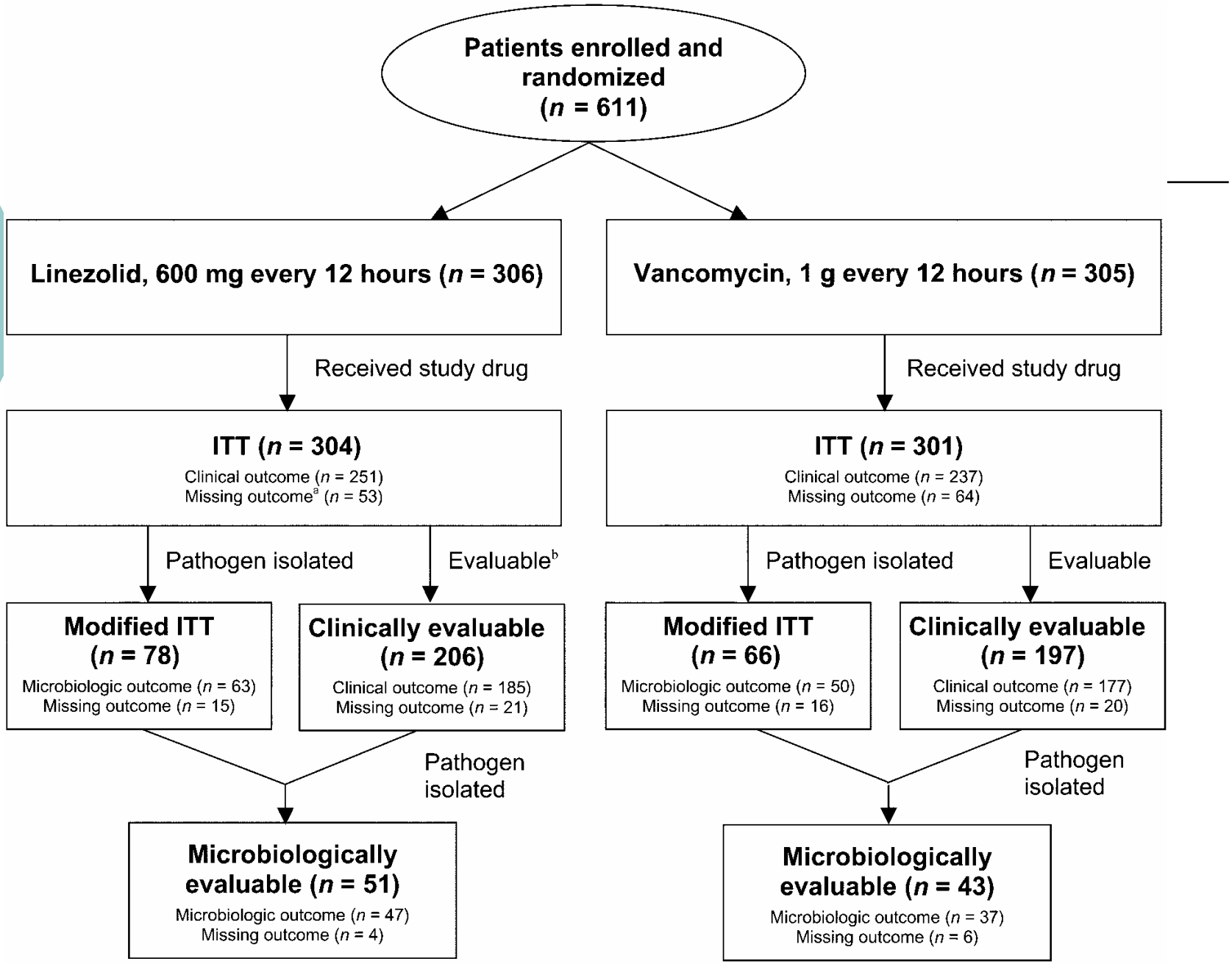

Patients enrolled and randomized (n = 611)
Linezolid, 600 mg every 12 hours (n = 306)
Vancomycin, 1 g every 12 hours (n = 305)
Received study drug
Received study drug
ITT (n = 304)
Clinical outcome (n = 251)
Missing outcome[a] (n = 53)
ITT (n = 301)
Clinical outcome (n = 237)
Missing outcome (n = 64)
Pathogen isolated
Evaluable[b]
Pathogen isolated
Evaluable
Modified ITT (n = 78)
Microbiologic outcome (n = 63)
Missing outcome (n = 15)
Clinically evaluable (n = 206)
Clinical outcome (n = 185)
Missing outcome (n = 21)
Modified ITT (n = 66)
Microbiologic outcome (n = 50)
Missing outcome (n = 16)
Clinically evaluable (n = 197)
Clinical outcome (n = 177)
Missing outcome (n = 20)
Pathogen isolated
Pathogen isolated
Microbiologically evaluable (n = 51)
Microbiologic outcome (n = 47)
Missing outcome (n = 4)
Microbiologically evaluable (n = 43)
Microbiologic outcome (n = 37)
Missing outcome (n = 6)

Table 6. Hematologic variables before and after treatment.

Hematologic variable, treatment group	Baseline		End of treatment		7 Days after completion of therapy	
	Mean ± SD	P^a	Mean ± SD	P^a	Mean ± SD	P^a
Hemoglobin, g/dL						
Linezolid	8.8 ± 1.6		9.4 ± 1.5		10.0 ± 1.6	
Vancomycin	8.8 ± 1.6	.58	9.3 ± 1.5	.43	10.0 ± 1.7	.80
Platelet count, × 10^3 cells/mm^3						
Linezolid	28.2 ± 30.5		74.7 ± 115.8		141.0 ± 148.4	
Vancomycin	31.5 ± 53.6	.36	75.2 ± 98.6	.96	149.9 ± 165.3	.52
WBC count, × 10^3 cells/mm^3						
Linezolid	0.77 ± 2.43		3.85 ± 5.16		4.79 ± 5.16	
Vancomycin	1.18 ± 9.04	.44	4.39 ± 5.54	.22	5.12 ± 6.45	.51
ANC, cells/mm^3						
Linezolid	118 ± 341		2480 ± 4136		2991 ± 4412	
Vancomycin	107 ± 290	.71	2788 ± 4365	.41	2935 ± 3592	.88

NOTE. ANC, absolute neutrophil count.

[a] Determined by analysis of variance.

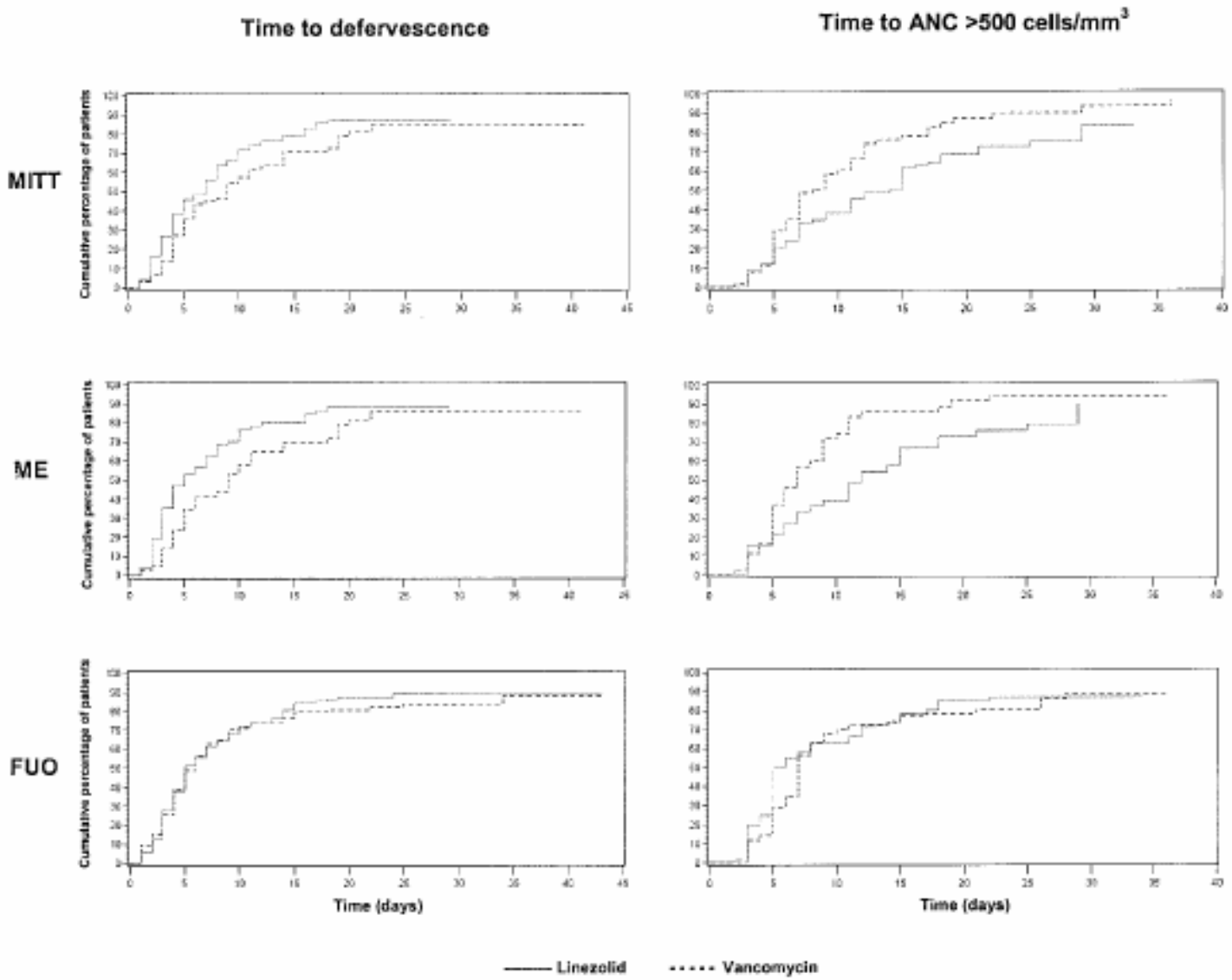


Figure 2. Kaplan-Meier analyses of time to defervescence and to neutrophil recovery in the modified intent-to-treat (MITT), microbiologically evaluable (ME), and fever of uncertain origin (FUO) populations. ANC, absolute neutrophil count.

Empirik vs Konvensiyonel Tx

- hematopoietik kök hücre transplantasyonu yapılan hastalarda empirik-nötropenin başlangıç günü-tedavi kolunda kan dolaşım infeksionları azalır
- ancak yatış süresi, engrafmente dek geçen süre, ilave antibiyotik kullanımı ve 30 günde mortalite açısından fark yoktur
  - Slavin MA, Grigg AP, Schwarer AP, Szer J, Spencer A, Sainani A, Thursky KA, Roberts AW. A randomized comparison of empiric or pre-emptive antibiotic therapy after hematopoietic stem cell transplantation. Bone Marrow Transplant. 2007;40(2):157-63.

G-CSF kullanımı?

- 65 yaş üstü hastalar
- %20 nin üstünde FN oranı olan rejimler

- FN oranı %10-20 arası olan durumlarda hasta ilişkili risk faktörleri değerlendirilmelidir

Eur J Cancer. 2006 Oct;42(15):2433-53.

EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours.

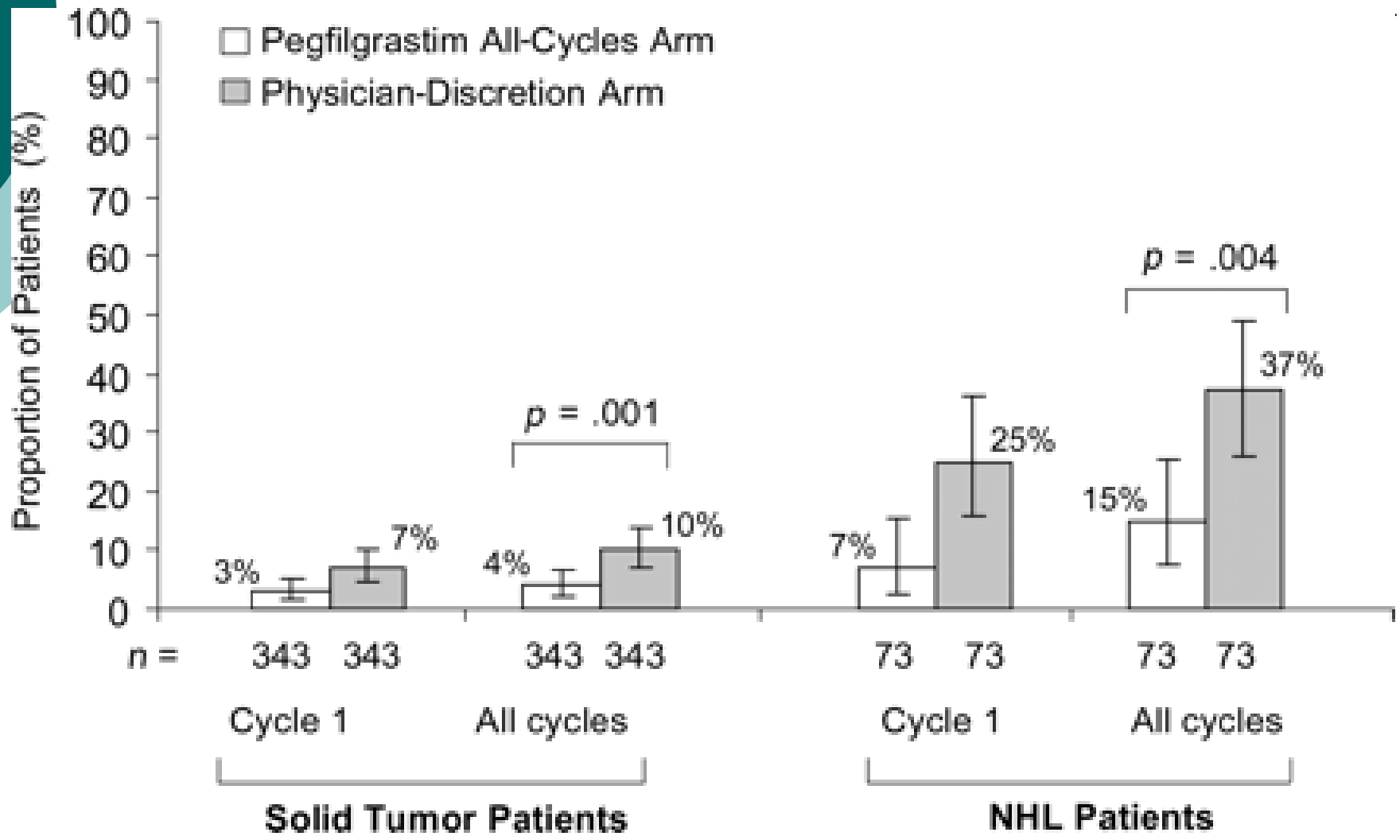
EORTC-2

- doz veya içerik yoğun kemoterapi uygulamalarında kemoterapiyi sürdürebilmek adına önerilebilir
- filgrastim, lenograstim ve pegfilgrastim klinik olarak etkindir

Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J. Meta-analysis: effect of prophylactic hematopoietic colony-stimulating factors on mortality and outcomes of infection. Annals of internal medicine 2007;147(6):400-11.

- 148 çalışma
- İnfeksiyon oranını azaltmakta
- Mortalite üzerine sınırlı etkide veya etkisiz

Balducci L, Al-Halawani H, Charu V, Tam J, Shahin S, Dreiling L, Ershler WB. Elderly cancer patients receiving chemotherapy benefit from first-cycle pegfilgrastim.Oncologist. 2007 Dec;12(12):1416-24



Pinto L, Liu Z, Doan Q, Bernal M, Dubois R, Lyman G.

Comparison of pegfilgrastim with filgrastim on febrile neutropenia, grade IV neutropenia and bone pain: a meta-analysis of randomized controlled trials. Curr Med Res Opin. 2007 Sep;23(9):2283-95.

- 5 RANDOMİZE ÇALIŞMA
- 617 Hasta
- Tek doz pegfilgrastim (100ug/kg) vs filgrastim (5ug/kg) hergün 10-14 gün süre ile
- **Nötropeni ve febril nötropeni oranları, nötropeniden çıkış, kemik ağrıları açısından pegfilgrastim daha avantajlı**

Klastersky J, Paesmans M, Georgala A, Muanza F, Plehiers B, Dubreucq L, Lalami Y, Aoun M, Barette M.
Outpatient oral antibiotics for febrile neutropenic cancer patients using a score predictive for complications.
J Clin Oncol. 2006 Sep 1;24(25):4129-34.

178 hasta oral tedavi----%95 başarı

Table 1. The MASCC Risk-Index Score

Characteristic	Weight
Burden of febrile neutropenia with no or mild symptoms*	5
No hypotension (systolic blood pressure > 90 mmHg)	5
No chronic obstructive pulmonary disease†	4
Solid tumor or hematologic malignancy with no previous fungal infection‡	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms*	3
Outpatient status	3
Age < 60 years	2

Max.score:26 MASCC 21 ve üstü düşük risk

Ayaktan tedavi-MASCC risk indeksi

- Innes H, Lim SL, Hall A, Chan SY, Bhalla N, Marshall E.Management of febrile neutropenia in solid tumours and lymphomas using the Multinational Association for Supportive Care in Cancer (MASCC) risk index: feasibility and safety in routine clinical practice. Support Care Cancer. 2007 Sep 25
- MASCC indeksi açısından pozitif prediktif değer %96.7% (95% CI 95.0-98.6%)

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HIV dışı immunkompromize hastada PCP proflaksisi

- 595 erişkin
- akut lösemi-organ tx

- 520 çocuk
- akut lösemi

- Toplam 11 çalışma

Green H, Paul M, Vidal L, Leibovici L.
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PCP-profilaksi

- 1 PCP vakasını engellemek için 15 hastaya proflaksi vermek gerekli

- SXT-yan etki düşük
  - -maliyet etkin
  - -diğer faydalar

  - önerilir

Pürin analogları-PCP proflaksisi?

Rolston KV, Bodey GP.

Comment on: empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials.
J Antimicrob Chemother. 2006 Aug;58(2):478; author reply 479-80. Epub 2006 May 12.

Making general therapeutic recommendations based solely on statistical analysis of old data, without duly considering current epidemiology and resistance patterns, can be misleading. Based on current local information and the proper definition of monotherapy, ceftazidime is not a suitable agent for this indication at our institution. We strongly urge colleagues at other institutions to make therapeutic decisions based on current epidemiological/resistance patterns as well.