Febril Nötropenide Meta-analizler: Karşı Görüşler

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Problemin tanımlanması

- Gerçekten meta-analize gerek var mı?
  - Büyük randomize kontrollü denemeler farklı sonuçlar mı vermiş?
  - Yeterli büyüklükte randomize kontrollü denemeler yok mu?
- Meta-analiz yapmak için yeterli çalışma var mı?

Gerek var mı?

- Nötropenik hastalarda kinolon profilaksisi
  - NP+A önemli morbidite ve mortalite nedeni
  - Kinolonların geniş gram (-) etkinliği var
  - Oral kullanım profilaksi için uygun
  - Direnç gelişme problemi
  - RKD'lerin hiçbirinin gücü yeterli değil (sağkalım)
  - Daha önce yapılmış MA'in yetersiz noktaları
    - Açık etiketli
    - Non-randomize çalışmaları
    - Daha sonra yapılan 2 büyük RKD MA'den farklı sonuçlar verdi

Eur J Clin Microbiol Infect Dis (2008) 27:53–63

Gerek var mı?

- Febril nötropenik hastada empirik antibiyotik tedavisi

- Mortalite %84'den %44'e düştü (1972)
- Son yıllarda %34-%20
- EORTC çalışmalarında, %21'den %7'ye düştü (1978-1994)

Gerek var mı?

ORIGINAL ARTICLE

Ciprofloxacin vs an Aminoglycoside in Combination With a β-Lactam for the Treatment of Febrile Neutropenia: A Meta-analysis of Randomized Controlled Trials

Ioannis A. Bliziotis, MD; Argyris Michalopoulos, MD; Sofia K. Kasiakou, MD; George Samonis, MD; Christos Christodoulou, MD, DSc; Stavroula Chrysanthopoulou, BSc; and Matthew E. Falagas, MD, MSc

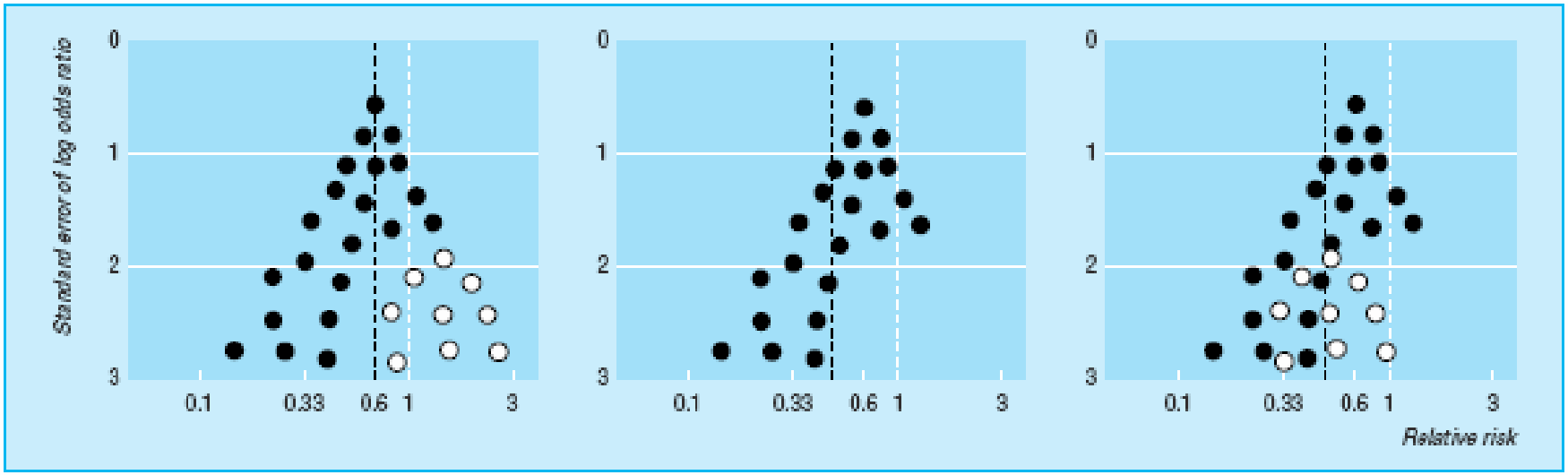
CONCLUSION: **The combination of ciprofloxacin with a β-lactam antibiotic should be considered an important therapeutic option in hospitalized febrile neutropenic patients who have not received a quinolone for prevention of infections and in settings in which quinolone resistance is not common.**

Mayo Clin Proc. 2005;80(9):1146-1156

Yayınlanmamış çalışmalar?

- Sonuçları pozitif olan çalışmalar daha fazla yayınlanmaktadır
- İngilizcesi iyi olan yazılar uluslararası dergilerde yayınlanmaktadır
- Bilinen kişi veya grupların yayınları uluslararası dergilerde daha fazla yayınlanmaktadır

Yayınlanma yanlılığı *(Publication bias)*



Problems in the Design and Reporting of Trials of Antifungal Agents Encountered During Meta-analysis

Helle Krogh Johansen, MD, DMSc
Peter C. Gøtzsche, MD, DMSc

JAMA, November 10, 1999—Vol 282, No. 18

Table. Contacts With Authors and Sponsoring Company and Outcomes*

Author and/or Employee	Means of Contact	Outcome	Sources of Support†
Anaissie et al,[13] 1996	3 Letters, personal contact at the 1997 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) meeting, fourth letter, e-mail message	3 Letters returned because of unknown address; reply to fourth letter: "I do not have access to the data (they are in the possession of the University of Texas, MD Anderson Cancer Center). I will make a request based on your letter and hope to receive a copy." Answer to e-mail message: "I am unable to provide you with data because the institution I was at has refused to give me a copy of my studies."	Pfizer grant support
Bodey et al,[14] 1994	2 Letters	Answer to second letter	Pfizer grant-in-aid
Lake et al,[16] 1996	2 Letters	No answer	None declared
Marie et al,[29] 1993	1 Letter	Answer: "It is an old trial, and all the data are with Pfizer."	Pfizer performed the randomization
Lapierre et al,[28] 1992	3 Letters	Answer to third letter (which had a more detailed address); sent a copy of a full article in French and a draft manuscript in English	Pfizer performed the randomization
Silling-Engelhardt et al,[20] 1994	1 Letter, letter to editor-in-chief of *Blood*, letter to publishers (the American Society of Hematology), letter to the German Cochrane Centre, final letter to author	The letter was returned because of unknown address. The response from *Blood* said, "We do not have an address for the authors of the abstract." No answer from publishers. The German Cochrane Centre identified the author who had changed her name to Silling. Answer to final letter: "I am waiting for an answer, whether it will be accepted . . . The published data will answer nearly all of your questions."	None declared (abstract only)
Viscoli et al,[21] 1996, Viscoli et al,[26] 1995	2 Letters, personal contact at 1997 European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)	No answer to letters; answer obtained after personal contact	Pfizer educational grant Consiglio Nazionale delle Richerche

Akiyama et al,[12] 1993	1 Letter	Answer to first letter	Pfizer thanked for statistical analysis
Menichetti et al,[17] 1994	2 Letters, personal contact at the 1997 ICAAC meeting	No answer to letters; at the personal contact, the author indicated that he would try to find the data; no answer	Pfizer grant support, Consiglio Nazionale delle Richerche
Meunier et al,[8] 1991	2 Letters	Answer to second letter: "Unfortunately, due to various reasons including my change of affiliation since 1991, I do not have access to the databases requested."	Pfizer support
Teshima et al,[24] 1994	1 Letter	Answer to first letter	None declared
Finke,[25] 1990	2 Letters, letter to the German Medical Association, letter to the German Cochrane Centre	No answer to letters; unknown to Deutsche Ärzte Verlag; new address obtained from the German Cochrane Centre; the third letter was not returned to sender; no answer	Pfizer support
Brammer,[15] 1990	2 Letters	No answer	Pfizer employee, sole author
Ninane et al,[18] 1994	3 Letters	No answer	Pfizer grant support
Philpott-Howard et al,[19] 1993	2 Letters, 3 telephone calls	Answer to first letter: "I will have to contact Pfizer as they have the original data on file, and the paper I wrote was based on data abstracted from this. I will contact the company shortly and let you know as soon as I have the answers." Indicated that he would contact Pfizer also after the telephone calls; no answer	Pfizer employee as coauthor
Troke (Pfizer Central Research, Sandwich, England)	1 Letter, 1 telephone call	Answer to letter: "I am unable to devote the time required to do this work . . . I have passed your request on to colleagues in New York who may be of assistance."	Pfizer employee

Trials

BioMed Central

Commentary

Open Access

Flaws in design, analysis and interpretation of Pfizer's antifungal trials of voriconazole and uncritical subsequent quotations

Karsten J Jørgensen[1], Helle Krogh Johansen[1,2] and Peter C Gøtzsche*[1]

Abstract

We have previously described how a series of trials sponsored by Pfizer of its antifungal drug, fluconazole, in cancer patients with neutropenia handicapped the control drug, amphotericin B, by flaws in design and analysis. We describe similar problems in two pivotal trials of Pfizer's new antifungal agent, voriconazole, published in a prestigious journal. In a non-inferiority trial, voriconazole was significantly inferior to liposomal amphothericin B, but the authors concluded that voriconazole was a suitable alternative. The second trial used amphothericin B deoxycholate as comparator, but handicapped the drug by not requiring pre-medication to reduce infusion-related toxicity or substitution with electrolytes and fluid to reduce nephrotoxicity, although the planned duration of treatment was 84 days. Voriconazole was given for 77 days on average, but the comparator for only 10 days, which precludes a meaningful comparison.

In a random sample of 50 references to these trials, we found that the unwarranted conclusions were mostly uncritically propagated. It was particularly surprising that relevant criticism raised by the FDA related to the first trial was only quoted once, and that none of the articles noted the obvious flaws in the design of the second trial.

We suggest that editors ensure that the abstract reflects fairly on the remainder of the paper, and that journals do not impose any time limit for accepting letters that point out serious weaknesses in a study that have not been noted before.

Meta-analize alma ve dışarıda bırakma kriterleri

- RKD'lerin amaçları benzer mi?
- RKD'lerdeki hastalar benzer mi?
- Kullanılan tedavi rejimler benzer mi?
  - Verilme amacı
  - Verilme şekli
- Tedavi süresi
- Sonuç değerlendirme kriterlerinin benzerliği
- Tedavi sonrası izlem süresi benzerliği

ORIGINAL ARTICLE

Ciprofloxacin vs an Aminoglycoside in Combination With a β-Lactam for the Treatment of Febrile Neutropenia: A Meta-analysis of Randomized Controlled Trials

IOANNIS A. BLIZIOTIS, MD; ARGYRIS MICHALOPOULOS, MD; SOFIA K. KASIAKOU, MD; GEORGE SAMONIS, MD; CHRISTOS CHRISTODOULOU, MD, DSC; STAVROULA CHRYSANTHOPOULOU, BSC; AND MATTHEW E. FALAGAS, MD, MSC

ADMINISTRATION OF CIPROFLOXACIN

The route of ciprofloxacin administration was intravenous in 4 studies,[19,21,34,35] intravenous followed by oral (in patients with favorable outcomes) in 2 studies,[16,23] and oral in the 2 studies of low-risk patients.[25,36] In 1 of the 2 studies in which the change from intravenous to oral ciprofloxacin was allowed, intravenous β-lactam was discontinued, which had been combined with ciprofloxacin, without subsequent use of oral β-lactam; patients in the other arm in that study continued to receive the intravenous aminoglycoside/β-lactam combination.[16]

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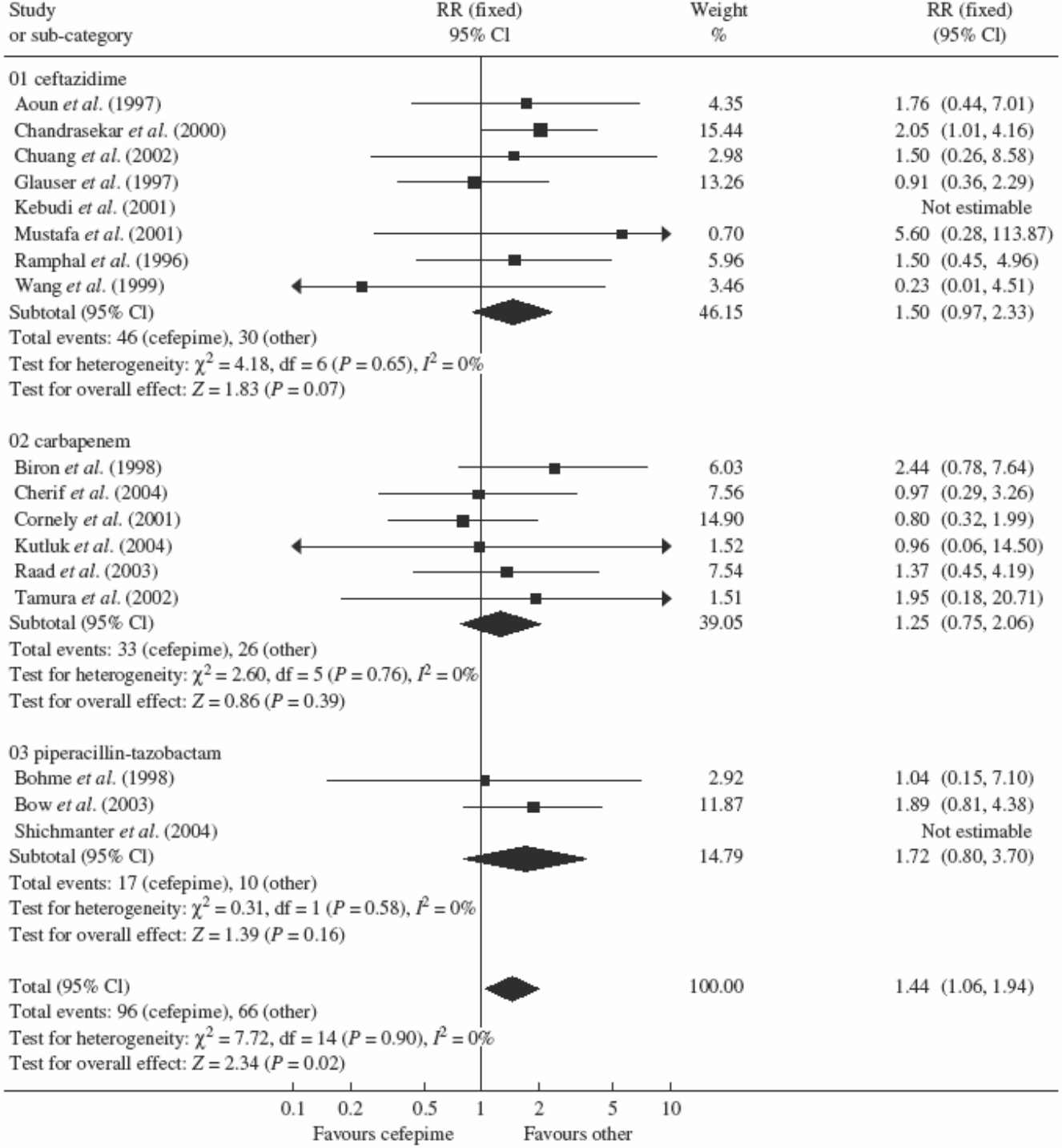
Advance Access publication 12 December 2005

JAC

Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials

Mical Paul[1,2]*, Dafna Yahav[1], Abigail Fraser[1] and Leonard Leibovici[1,2]

Conclusions: **The use of cefepime for febrile neutropenia is associated with increased mortality and should be carefully considered pending further analysis. Empirical use of carbapenems entails fewer treatment modifications, but an increased rate of pseudomembranous colitis. Ceftazidime, piperacillin/tazobactam, imipenem/cilastatin and meropenem appear to be suitable agents for monotherapy.**


Study
or sub-category
RR (fixed)
95% CI
Weight
%
RR (fixed)
(95% CI)
01 ceftazidime
Aoun et al. (1997) 4.35 1.76 (0.44, 7.01)
Chandrasekar et al. (2000) 15.44 2.05 (1.01, 4.16)
Chuang et al. (2002) 2.98 1.50 (0.26, 8.58)
Glauser et al. (1997) 13.26 0.91 (0.36, 2.29)
Kebudi et al. (2001) Not estimable
Mustafa et al. (2001) 0.70 5.60 (0.28, 113.87)
Ramphal et al. (1996) 5.96 1.50 (0.45, 4.96)
Wang et al. (1999) 3.46 0.23 (0.01, 4.51)
Subtotal (95% CI) 46.15 1.50 (0.97, 2.33)
Total events: 46 (cefepime), 30 (other)
Test for heterogeneity: $\chi^2 = 4.18$, df = 6 ($P = 0.65$), $I^2 = 0\%$
Test for overall effect: $Z = 1.83$ ($P = 0.07$)
02 carbapenem
Biron et al. (1998) 6.03 2.44 (0.78, 7.64)
Cherif et al. (2004) 7.56 0.97 (0.29, 3.26)
Cornely et al. (2001) 14.90 0.80 (0.32, 1.99)
Kutluk et al. (2004) 1.52 0.96 (0.06, 14.50)
Raad et al. (2003) 7.54 1.37 (0.45, 4.19)
Tamura et al. (2002) 1.51 1.95 (0.18, 20.71)
Subtotal (95% CI) 39.05 1.25 (0.75, 2.06)
Total events: 33 (cefepime), 26 (other)
Test for heterogeneity: $\chi^2 = 2.60$, df = 5 ($P = 0.76$), $I^2 = 0\%$
Test for overall effect: $Z = 0.86$ ($P = 0.39$)
03 piperacillin-tazobactam
Bohme et al. (1998) 2.92 1.04 (0.15, 7.10)
Bow et al. (2003) 11.87 1.89 (0.81, 4.38)
Shichmanter et al. (2004) Not estimable
Subtotal (95% CI) 14.79 1.72 (0.80, 3.70)
Total events: 17 (cefepime), 10 (other)
Test for heterogeneity: $\chi^2 = 0.31$, df = 1 ($P = 0.58$), $I^2 = 0\%$
Test for overall effect: $Z = 1.39$ ($P = 0.16$)
Total (95% CI) 100.00 1.44 (1.06, 1.94)
Total events: 96 (cefepime), 66 (other)
Test for heterogeneity: $\chi^2 = 7.72$, df = 14 ($P = 0.90$), $I^2 = 0\%$
Test for overall effect: $Z = 2.34$ ($P = 0.02$)
0.1
0.2
0.5
1
2
5
10
Favours cefepime
Favours other

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JAC

Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials

Mical Paul[1,2]*, Dafna Yahav[1], Abigail Fraser[1] and Leonard Leibovici[1,2]

!

- Sefepim vs piptaz, seftazidim, karbapenemler
  - Sefepim dışındakiler monoterapi için uygun!
- Bazı çalışmalar glikopeptid içeriyordu
  - Glikopeptid içeren rejimler, monoterapi olarak kabul edilmiş!

Comment on: Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials

Kenneth V. I. Rolston* and Gerald P. Bodey

Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Keywords: febrile neutropenia, monotherapy, ceftazidime

Sir,

The meta-analysis conducted by Paul *et al.*[1] regarding empirical antibiotic monotherapy for febrile neutropenia illustrates the dangers of relying on such analyses to make therapeutic recommendations in an area characterized by rapid changes. We are

(IDSA).[2] Having helped co-author these guidelines, we wish to point out that monotherapy is defined as the use of a 'single' broad-spectrum agent whereas the use of broad-spectrum β-lactams with vancomycin is considered combination therapy. Current epidemiological trends indicate that Gram-positive organisms account for 44–76% of documented bacterial infections in neutropenic patients.[3–6] By the authors own account,

BMJ 1997;314:1238

Meta-analysis of prophylactic or empirical antifungal treatment versus placebo or no treatment in patients with cancer complicated by neutropenia

Peter C Gøtzsche, *director*, **Helle Krogh Johansen**, *senior researcher* a
a The Nordic Cochrane Centre, Rigshospitalet, Department 7112, DK-2200 Copenhagen N, Denmark

RKD'lerde kullanılan tedavi rejimleri:

- Amfo 0.1 mg profilaktik
- Amfo 0.5 mg empirik
- Lipo amfo 2mg/kg empirik
- Flukonazol 400mg oral profilaktik
- Flukonazol 400mg iv empirik
- Ketokonazol 400mg oral profilaktik
- Miconazol 2 gm oral profilaktik
- Itrakonazol 400mg oral profilaktik

This meta-analysis failed to show an effect of prophylactic or empirical treatment with azoles on mortality, though there was a significant effect with amphotericin.

Zaman içinde standard tedavi yaklaşımı değişti mi?

- MA'ler uzun yıllara yayılmış çalışmaları içerirler

- Seftazidim monoterapi çalışmalarının %80'i, 2001 yılından önce yapılmış
- ESBL problemi 2000 yılından sonra hızla yayıldı ve arttı

β lactam monotherapy versus β lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis

Mical Paul, Karla Soares-Weiser, Leonard Leibovici

Conclusions For patients with fever and neutropenia there is no clinical advantage in treatment with β lactam-aminoglycoside combination therapy. Broad spectrum β lactams as monotherapy should be regarded as the standard of care for such patients.

BMJ VOLUME 326 24 MAY 2003 bmj.com

- 1981-2000 yılları arasındaki çalışmaları içeriyor!

RKD'lerin kalitesini değerlendirmeli mi?

- Garbage in, garbage out!
  - Randomizasyon
  - Körleme
    - Doktor
    - Hasta
    - Sonuç değerlendirmesini yapanlar
  - Randomizasyonun korunması

RKD'lerin kalitesi

- Son 20 yılda randomizasyon bilgisayar yardımıyla oluşturulan algoritmalarla yapılıyor
- Körleme hala problem
  - MA'lerin çoğunda, analize aldıkları çalışmalarda körleme yapılıp yapılmadığı belirtilmemiş
- Bazı RKD'lerde yapıldığı iddia edilse bile...
  - Amfoterisin B deoxy. çalışmaları
- Kinolon profilaksi çalışmaları

β lactam monotherapy versus β lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis

Mical Paul, Karla Soares-Weiser, Leonard Leibovici

In 21 trials (45%) randomisation procedures were adequate, and eight (17%) were blinded (table 1). Intention to treat analysis for failure was possible in 17 of the 47 trials and for fatality in 18 of 30 trials. The

Randomizasyonun korunması

- ITT analiz
- İzlemden kaybolan hastalara ne oldu?
- Randomizasyon sonrası
  - Ek tedaviler
  - Ek işlemler
  - Bazı grupların farklı değerlendirilmesi
- Subgrup analizleri

TABLE 1. **Characteristics of Randomized Controlled Trials Included in the Meta-analysis***

Reference	Drug† dosage		Study population	ITT episodes	Clinically evaluable episodes		All-cause mortality		Clinical cure		Withdrawal due to toxicity	
	CFLX group	AG group			CFLX group	AG group	CFLX arm (%)	AG arm (%)	CFLX arm (%)	AG arm (%)	CFLX arm (%)	AG arm (%)
Flaherty et al,[16] 1989	IV CFLX 300 mg/12 h + **azlocillin** 4 g/6 h (converted to oral CFLX 750 mg/12 h‡ as monotherapy)	AMK (525 mg/12 h) + **ceftazidime** 2 g/8 h	Neutropenic, adults, tumors and leukemias	86§	25	30	8.0	10.0	32.0	50.0	8.0	10.0
Griggs et al,[19] 1998	IV CFLX 400 mg/8 h + **piperacillin** 4 g/6 h	GTM (105 mg loading dose, then maintenance dosing‡) + **piperacillin** 4 g/6 h	Neutropenic for ≥7 d, mean age 45 y, tumors and leukemias, BMT (65%)	128	46	50	4.3	12.0	NR	NR	NR	NR
Hyatt et al,[21] 1991	IV CFLX 200 mg/12 h + **azlocillin** 5 g/8 h	Netilmicin (350-525 mg/d‡) + **azlocillin** 5 g/8 h	Neutropenic, >18 y, leukemias, BMT	78	37	36	NR	NR	54.1	36.1	NR	NR
Kelsey et al,[23] 1990	IV CFLX 200 mg/12 h (changed to oral CFLX 750 mg/12 h‡) + **benzylpenicillin** 1.2 g/6 h	Netilmicin (140 mg/8 h) + **piperacillin** 4 g/6 h	Neutropenic, >16 y, hematologic malignancies, BMT	103	51	46	NR	NR	NR	NR	2.0	6.5

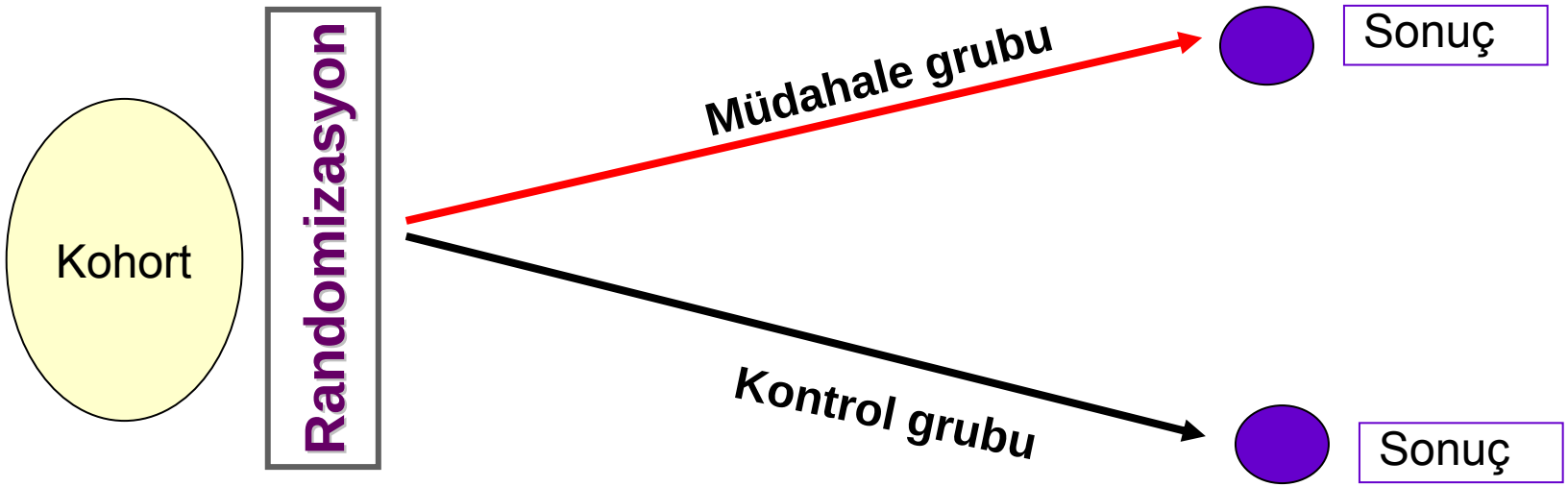
%36

%25

%7

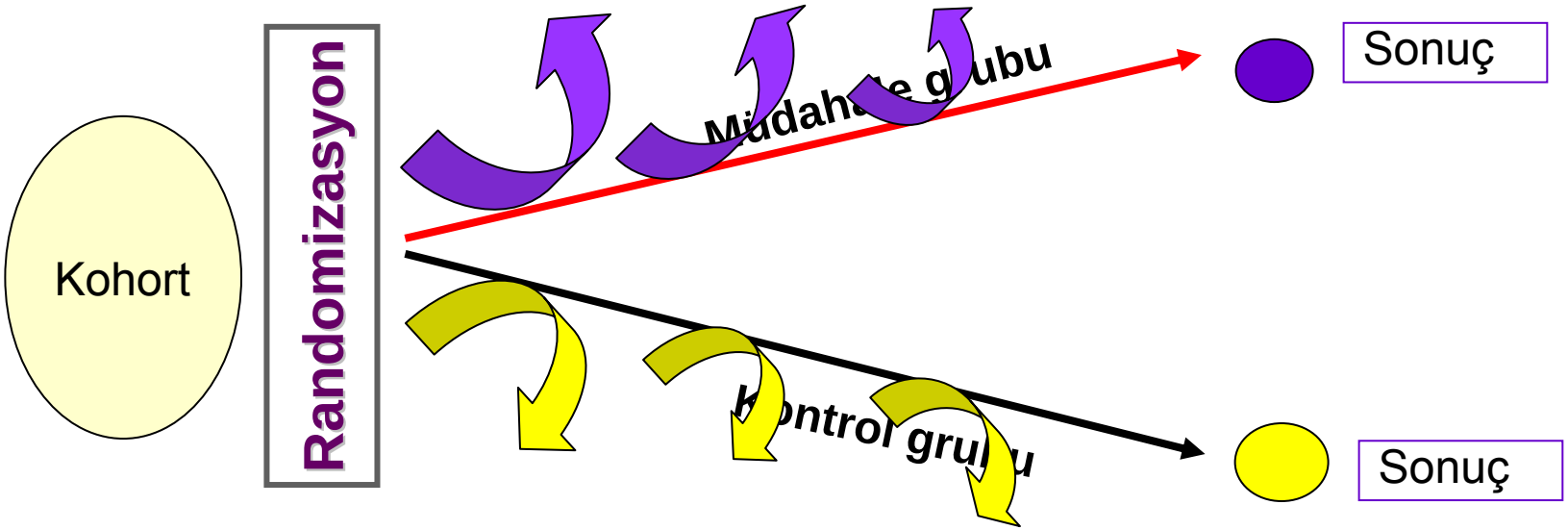
%7

Randomize kontrollü denemeler



- İlaç ve tedavi çalışmalarında ALTIN STANDARD!

Randomizasyondan sonra olanlar önemlidir!



- Antibiyotik profilaksi çalışmalarında bazı hastalar antifungal, antiviral proflaksi de alıyor
- Empirik antibiyotik çalışmalarında, bazı hastalara glikopeptid ekleniyor
- Empirik antibiyotik çalışmalarında, bazı hastalara antifungal ekleniyor
- Antifungal çalışmalarında, antibiyotik eklemeler, değişiklikler

Randomizasyonun korunması

the trial. As outcomes for re-entering patients are not independent, results may have been affected. Intention to treat analysis was possible in just over half the included trials, and adequate randomisation procedures were used in less than half of these trials.

extracted data. For the same reason, a considerable amount of interesting data could not be pooled for analysis. For example, the success of therapy with the only modification being the addition of antifungal or antiviral agents, a clinically important outcome, was not reported in some studies,

Sonuç değerlendirme kriterlerinin benzerliği

- Profilaksi ve empirik tedavi çalışmalarının en önemli problemlerinden
- Çalışmaların sonuç değerlendirme kriterleri çok farklı
  - İnfeksiyonun önlenmesi
  - Ateş çıkmaması
  - Ateşin düşmesi
  - Empirik amfo B eklenmesi
  - Yaşam süresinin uzatılması vs
- En sonunda
  - “All cause mortality” herhangi bir nedene bağlı ölüm....