Penisilin dirençli *Streptococcus pneumoniae* invaziv enfeksiyonları

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Enfeksiyon Hast ve Klinik Mikrobiyoloji Kliniği

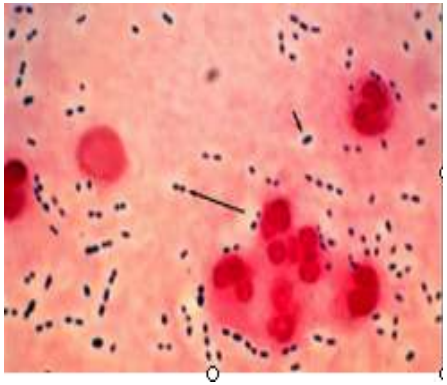
Sunum planı

- İnvaziv pnömokokal hastalık:tanım, epidemiyoloji, risk faktörleri
- Penisilin direnci
- Sık görülen invaziv enfeksiyonların tedavisi

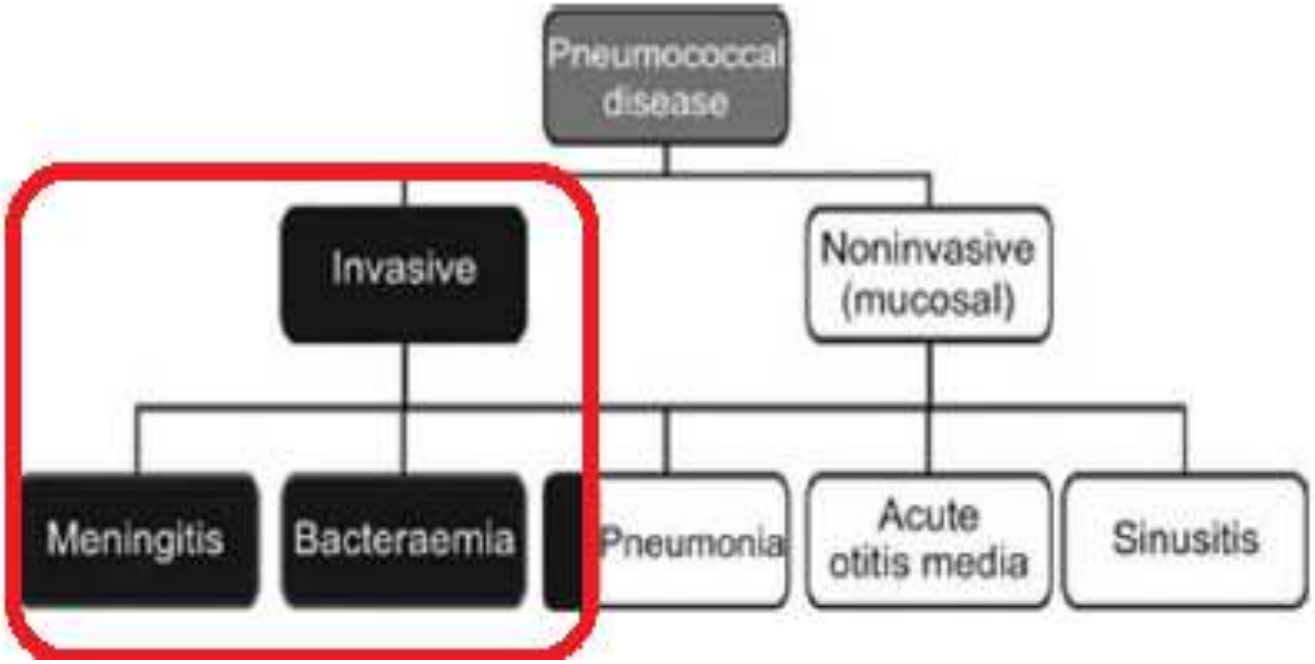
Streptococcus pneumoniae

- Gr (+) diplokok
- Polisakkarit yapıdaki kapsüle göre

  >90 dan fazla serotipi tanımlanmış
- İnvaziv hastalık etkeni >30 dan fazla serotip



Pnömökoklara bağlı enfeksiyonların sınıflaması



Drikoningen JJC et al. Clin Microbiol Infect 2014;20(Suppl 5):45-51.

National Notifiable Diseases Surveillance System (NNDSS)

- **İnvaziv Pnömokok hastalığı (İPH)**
- **Doğrulanmış olgu:** Klinik bulgularla birlikte *S.pneumoniae*' nın steril bölgelerden izole edilmesi
- **Olası olgu:** İnvaziv enfeksiyon kliniği olan olguda kültür dışı yöntemlerle (PCR gibi) *S.pneumoniae*' nın gösterilmesi

CDC.gov 2017

Rekürren İPH

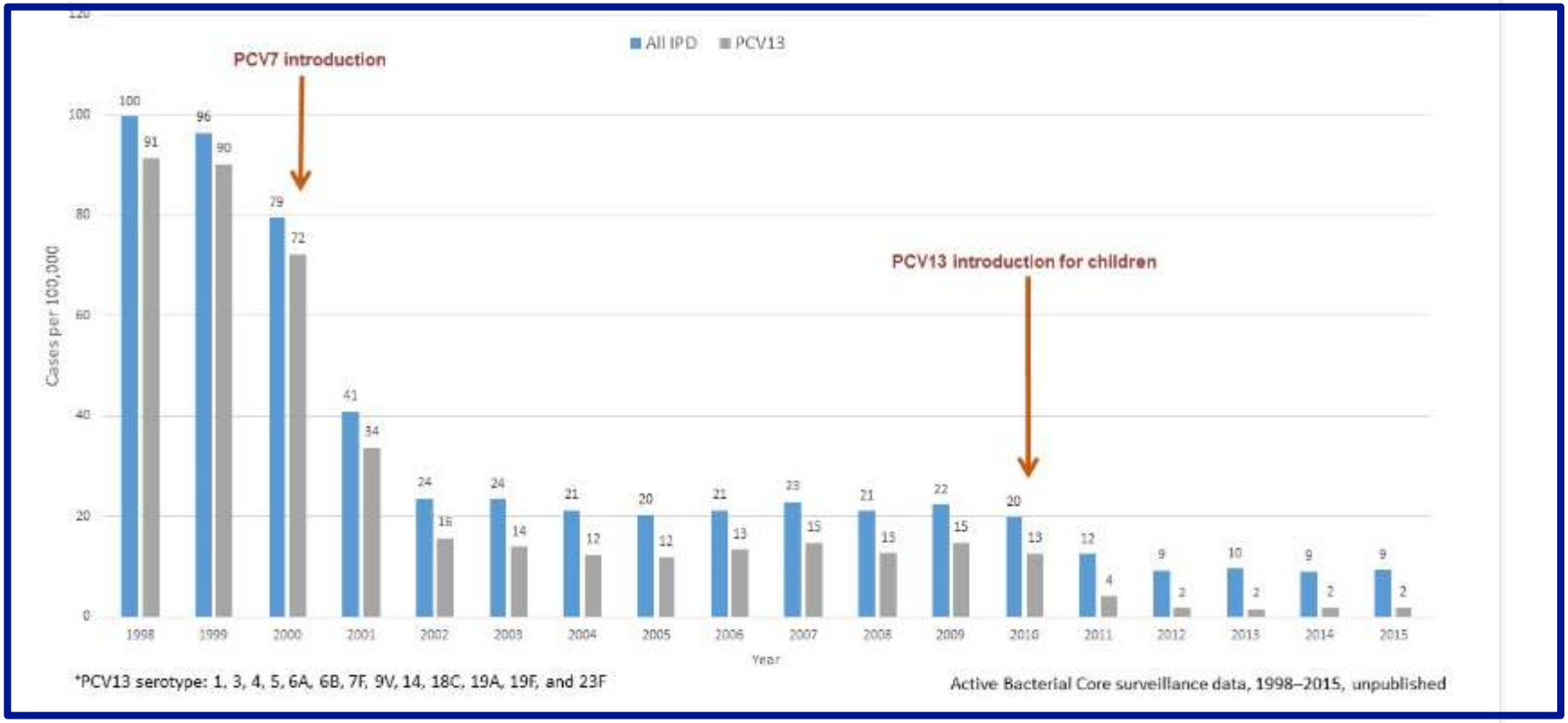
- Aynı serotiple > 4 hafta uzun bir ara ile ≥ 2 atak veya farklı serotip ile < 4 hafta kısa aralıkla oluşan atak
- Nadir (%2.3-5.3)
- En sık bakteriyemik pnömoni veya primer bakteriyemi şeklinde
- Rekürren epizodda mortalite daha yüksek

Einorsdottir HM et al. Clin Microbiol Infect 2005;11:744-49

İPH risk faktörleri

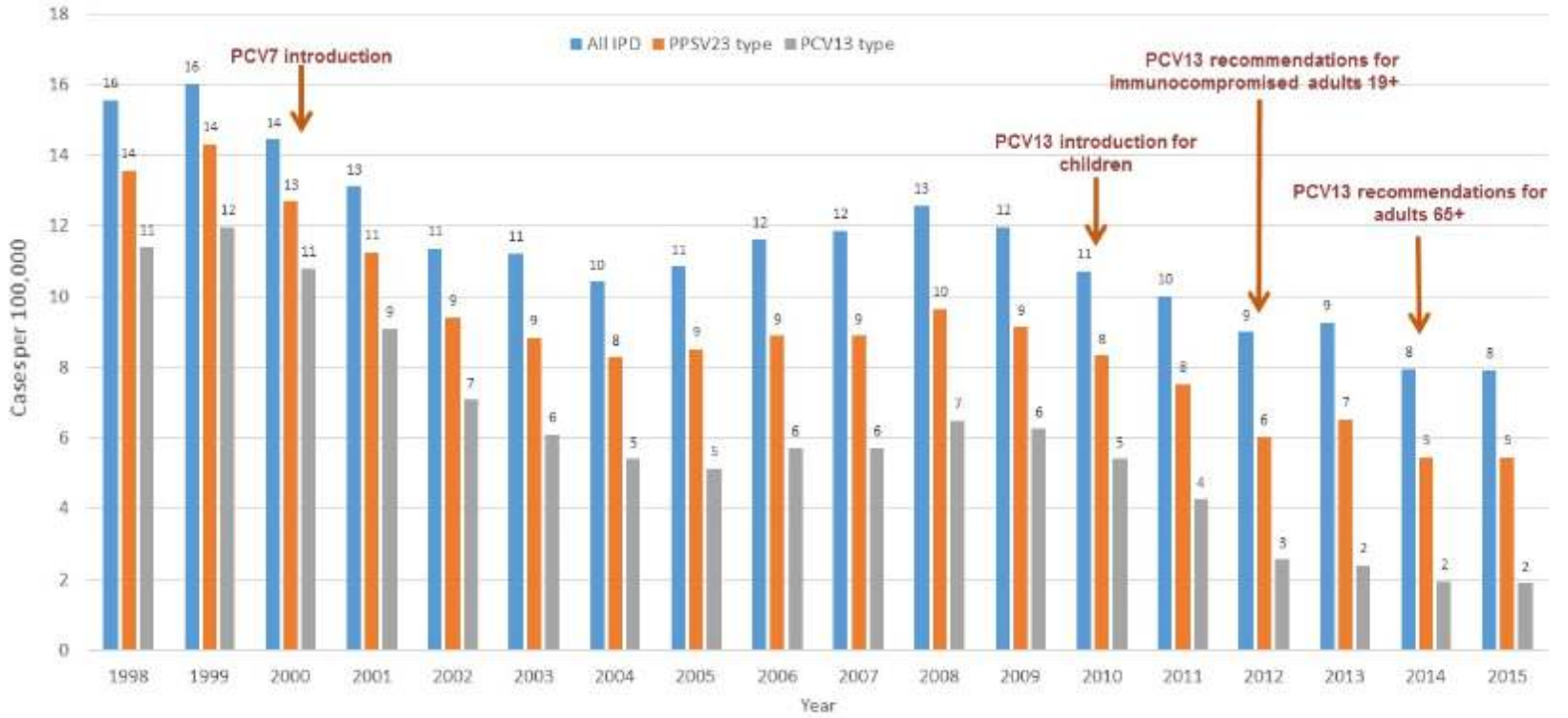
- Yaş : <2yaş, ≥ 65 yaş
- Eşlik eden hastalıklar
  - DM, KBY, KOAH
  - Kr karaciğer hastalığı
  - Humoral immün yetmezlik (agamaglobulinemi gibi)
  - Kompleman eksikliği
  - Nötropeni
  - Splenektomi/aspleni
  - HIV…
  - Malignensi
- Serotip
  - yüksek 1,4, 14, 18C, 19A, 7F
  - düşük 3,5, 6B, 15 B,15 C
- Çevresel faktörler
  - Kalabalık ortam
  - Bakım merkezinde kalma
  - Soğuk
- Sigara ve alkol tüketimi
- Aşı durumu
- Coğrafya

Pneumococcal Disease



Active Bacterial Core surveillance (ABCs): Surveillance Reports(https://www.cdc.gov/abcs/reports findings/surv-reports.html)

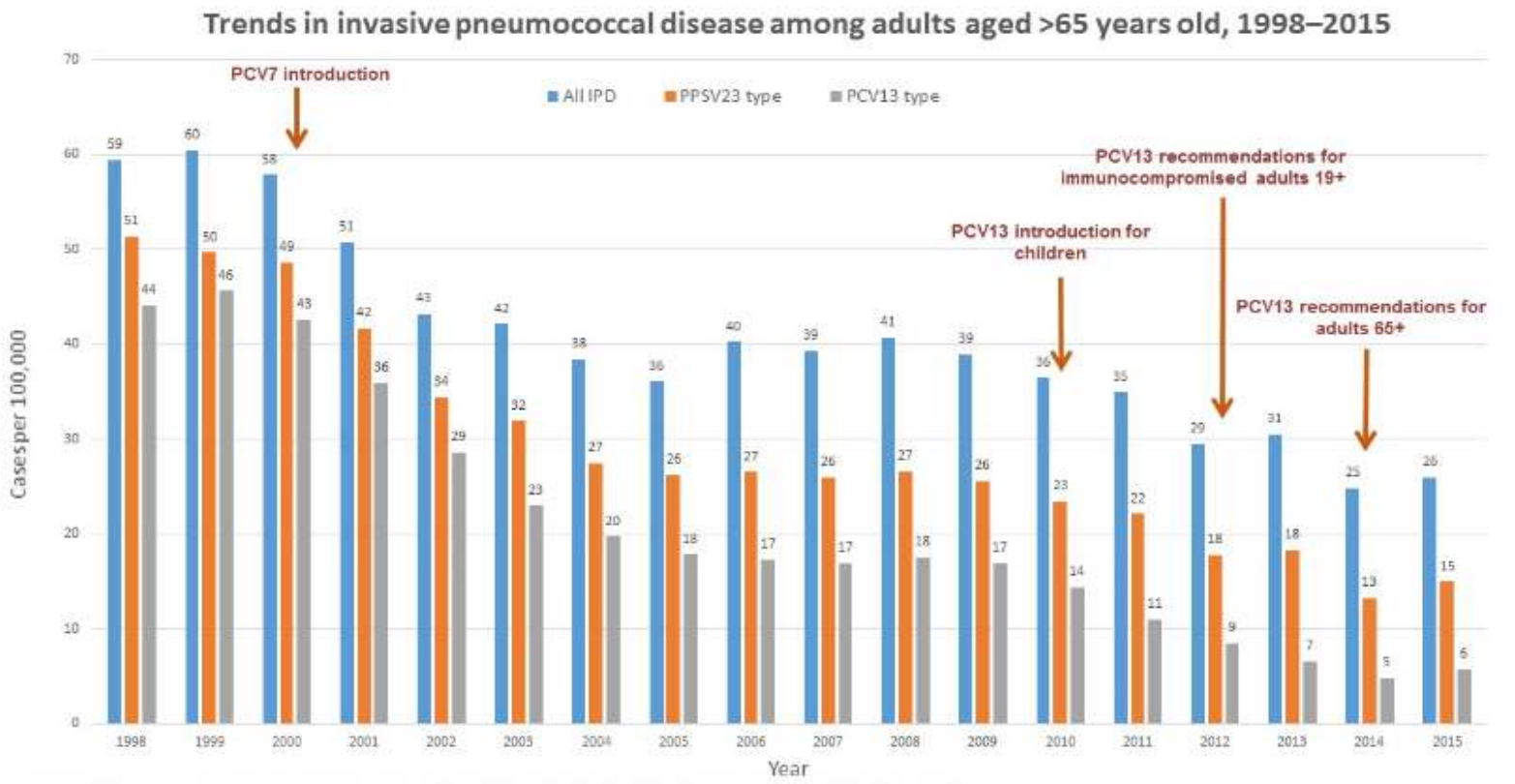
Pneumococcal Disease



*PPSV23 serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F
†PCV13 serotype: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

Active Bacterial Core surveillance data, 1998–2015, unpublished

Pneumococcal Disease



İnvaziv hastalık insidensi

	1998/ 100000	2015/100000
<5 yaş	100	9
PCV 13	91	2
19-64 yaş	16	7
PCV 13	11	2
PPS 23	14	5
>65 yaş	59	23
PCV 13	44	5
PPS 23	51	13

PPS 23 1983
PCV 7 2000
PCV13 2010

IPH serotip dağılımı

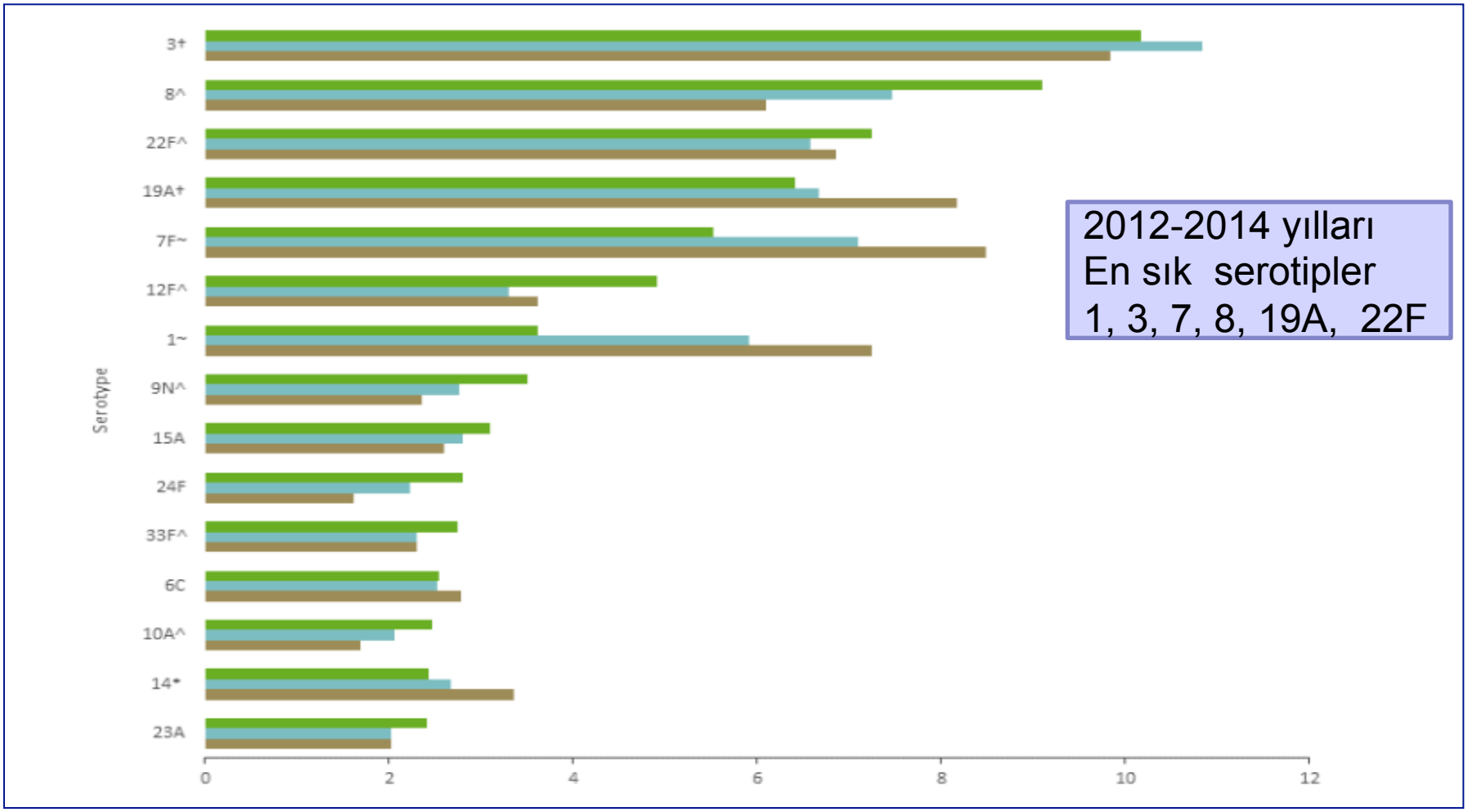
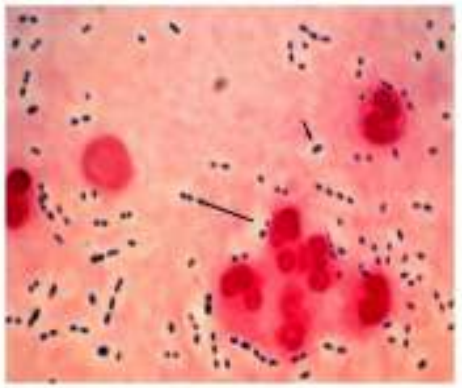


Figure 6. Distribution of confirmed cases of invasive pneumococcal disease: most common serotypes in 2014 (n=12 980), 2013 (n=14 811) and 2012 (n=14 845)

Antibiyotik direnci

- 1967 ilk penisilin dirençli infeksiyon etkeni
- 1967 eritromisin direnci
- 1977 G. Afrika' da çoğul direnç
- 1974 çocukta penisilin dirençli menenji
- 1983 erişkin menenjit olgusu



Caputo MG et al. Arch Intern Med 1993; 153(14): 1301-8.
Schreiber JR et al. PPediatrics Clin of Morth America 1995;42(3):519-37.

Penisilin direnç mekanizması

- Penisilin bağlayan proteinlerde değişiklik (PBP) sonucu oluşur.
- Duyarlı pnömokok suşlarında 6 PBP bölgesi vardır. PBP 1a, 1b, 2a, **2b**, 2x ve 3
- Sefalosorin direnci PBP 1a ve 2x

Schreiber JR et al. Pediatrics Clin of Morth America 1995;42:519-37.

- **MDR *S. pneumoniae*:** ≥ 3 den fazla antibiyotik sınıfına direnç
- Tüm dünyada MDR *S. pneumoniae* %20-30
- **XDR *S. pneumoniae*** : Vankomisin ve linezolid hariç diğer antibiyotiklere direnç

Moran GJ et al. Am J Emerg Med 2013;31:602-12.
Choi SY et al. Emerg Infect Dis 2014;20:5

EUCAST ve CLSI MİK aralıkları (µg/ml)

	EUCAST hassas	EUCAST dirençli	CLSI hassas	CLSI orta direnç	CLSI yüksek direnç
2008 öncesi			≤ 0.06	0.12-1	≥ 2
2008 sonrası Penisilin parenteral					
menenjit	< 0.06	**> 0.06**	≤ 0.06		**≥ 0.12**
menenjit dışı IV oral	≤ 0.06 -	**> 2** -	**2** ≤ 0.06	4 0.12-1	**≥ 8** ≥ 2
Seftriakson					
menenjit	≤ 0.5	> 2	≤ 0.5	1	≥ 2
menenjit dışı	≤ 0.5	**> 2**	≤ 0.5	2	**≥ 4**

The CAESAR network is a joint initiative of the Regional Office, the ESCMID and the National Institute for Public Health and the Environment, the Netherlands .

Table 28. Patient characteristics of 10 377 isolates from Turkey in 2013, by pathogen

Pathogen	Total isolates (N)	Isolate source (%)		Sex (%)		Age category (years) (%)					Hospital department (%)		
		Blood	CSF	Male	Female	0–4	5–19	20–64	≥ 65	Unknown	ICU	Non-ICU	Unknown
E. coli	3 286	99	1	51	49	7	7	38	34	14	19	77	4
K. pneumoniae	1 635	98	2	58	42	13	4	35	32	16	42	54	4
P. aeruginosa	1 123	97	3	59	41	8	7	33	36	16	45	53	2
Acinetobacter spp.	0	-	-	-	-	-	-	-	-	-	-	-	-
S. aureus	2 133	100	0	66	34	7	5	37	35	16	29	67	4
S. pneumoniae	147	94	6	65	35	6	7	36	25	26	18	76	6
E. faecalis	1 136	100	0	56	44	6	3	27	43	21	49	47	4
E. faecium	917	100	0	52	48	7	4	26	40	23	47	49	4

Table 32. Resistance levels for *S. pneumoniae* among blood and CSF isolates in Turkey

Antibiotic class	*S. pneumoniae*	
	N	Resistance (%)
Penicillins (R)[a]	82	54
Penicillins (I+R)[a]	82	55
Macrolides (R)[b]	106	42
Macrolides (I+R)[b]	106	42
3rd-generation cephalosporins (R)[c]	58	5
3rd-generation cephalosporins (I+R)[c]	58	19
Fluoroquinolones (R)[d]	79	0
Moxifloxacin (R)	0	-

Ulusal antimikrobiyal direnç surveyans sistemi (UAMDSS)

Tablo 9. UAMDSS 2013 *S.pneumoniae* izolatlarında (n=191) antibiyotik duyarlılık sonuçları

Antibiyotik Adı	Enfeksiyon Bölgesi	Sayı	Dirençli (%)	Duyarlı (%)	Direnç-GA %95
Penisilin G	Menenjit Dışı	79	17.20	82.80	10.90-27.60
Penisilin G	Menenjit	79	54.40	45.60	43.50-65.00
Seftriakson	Menenjit Dışı	34	9.10	90.90	3.00-23.00
Seftriakson	Menenjit	34	26.40	73.60	14.60-43.10
Sefotaksim	Menenjit Dışı	27	3.70	96.30	0.70-18.00
Sefotaksim	Menenjit	27	25.60	74.40	13.20-44.70
Levofloksasin		72	0.00	100.00	0.00-5.10
Eritromisin		100	45.00	55.00	35.60-54.80

Steril bölgelerden izole edilen S.pneumoniae suşlarında antibiyotik direnci

Ocak 2000-2005

165 steril bölge izolatı

Kan	52 (%31.5)
BOS	46 (%27.9)
Plevra	25 (%15.2)
Diğer	42

- Penisilin orta direnç

  tümünde 31 **(%18.8)**

  BOS **10 (%21.7)** orta direnç, 2008 sonrası kriterler ile direnç
- Seftriakson direnci % 0
- Eritromisin direnci % 5.4
- Levofloksasin 1 izolat (% 0.6)

Ak Ö et al. Mikrobiyoloji Bül 2006; 40;179-84.

İPH Klinik

- Bakteriyemi

  Primer odak olmaksızın

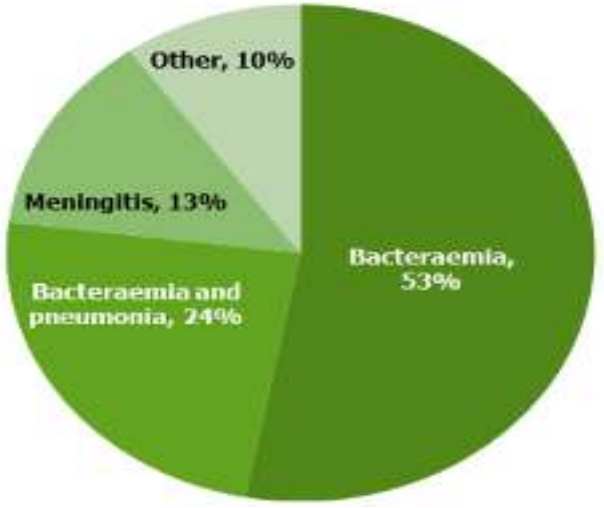
  Pnömoniye sekonder (bakteriyemik pnömoni)

- Menenjit
- Diğerleri

  peritonit,

  septik artrit

  perikardit….



10.383 doğrulanmış IPH olgu /2012

Source: European Centre for Disease Prevention and Control. Surveillance of invasive bacterial diseases in Europe, 2012. Stockholm: ECDC; 2015.

Menenjit

- Bakteriyel menenjit olgularının yaklaşık %50 sinin,
- Erişkin bakteriyel menenjitin en sık, çocukta 2. sıklıkta etkenidir.
- Mortalite çocuklarda %8, erişkinde %16-37
- Nörolojik sekel %30-52
- Bakteriyel menenjitte antibiyotik tedavisi acildir. yaklaşımı gerekir. Etken izolasyonuna kadar empirik başlanır.

Antibiyotik kararında

- Hastanın yaşı, eşlik eden hastalıkları
- Antibiyotiğin özellikleri
- Epidemiyolojik olarak direnç durumunun bilinmesi
- Etken izole edilirse kültür ve antibiyotik duyarlılığına göre tedavi düzenlenmelidir.

International Journal of Infectious Diseases 19 (2014) 13–19

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Mortality indicators in pneumococcal meningitis: therapeutic implications

- 1998-2012, çok merkezli
- 306 hasta (301 BOS,

  7 si kan ve BOS, 5 kan)
- Penisilin duyarlı %79.2 , **direnç % 20.8**

H. Erdem et al. Int J of Infect Dis 2014; 13–19.

J Antimicrob Chemother. 2005 Nov;56(5):979-82. Epub 2005 Sep 20.

Evaluation of ceftriaxone, vancomycin and rifampicin alone and combined in an experimental model of meningitis caused by highly cephalosporin-resistant Streptococcus pneumoniae ATCC 51916.

Ribes S[1], Taberner F, Domenech A, Cabellos C, Tubau F, Liñares J, Fernández Viladrich P, Gudiol F.

Abstract

OBJECTIVES: The aim of the study was to assess the in vitro and in vivo efficacy of ceftriaxone, vancomycin and rifampicin alone and combined against Streptococcus pneumoniae ATCC 51916 (MIC of ceftriaxone: 32 mg/L).

METHODS: In vitro killing curves were performed with clinically achievable CSF antibiotic concentrations. In the rabbit model of pneumococcal meningitis, we studied the efficacy of and effects on inflammation of treatment with ceftriaxone 100 mg/kg/day, vancomycin 30 mg/kg/day and rifampicin 15 mg/kg/day, alone and combined, over a 26 h period.

RESULTS: Time-kill curves showed that vancomycin was bactericidal, and ceftriaxone and rifampicin produced a bacteriostatic effect. An additive effect was observed when combinations of ceftriaxone plus vancomycin were studied at subinhibitory concentrations. Emergence of resistance to rifampicin was detected both when rifampicin was studied alone and when combined with ceftriaxone or vancomycin. In the rabbit meningitis model, ceftriaxone was bacteriostatic, whereas rifampicin and vancomycin were bactericidal at 24 h. Although not synergistic, the combinations of ceftriaxone plus vancomycin or rifampicin, and vancomycin plus rifampicin, improved the efficacy of any antibiotic tested alone--all combinations were bactericidal from 6 h--and significantly decreased inflammatory parameters in CSF compared with control and ceftriaxone groups.

CONCLUSION: Ceftriaxone plus vancomycin, and vancomycin plus rifampicin appeared to be effective in the therapy of experimental pneumococcal meningitis caused by highly cephalosporin-resistant strains such as ATCC 51916. Our results provide an experimental basis for using these combinations as empirical therapy for pneumococcal meningitis, regardless of the degree of cephalosporin resistance of the causative strain.

Combined treatment with ceftriaxone and linezolid of pneumococcal meningitis: a case series including penicillin-resistant strains

F. Faella[1], P. Pagliano[1], U. Fusco[1], V. Attanasio[1] and M. Conte[2]

Table 2. Susceptibility of *Streptococcus pneumoniae* isolates, therapy and outcome for 16 adult patients with pneumococcal meningitis

Patient[b]	Penicillin MIC (mg/L)	Ceftriaxone MIC (mg/L)	Days of combined therapy[a]	Days of monotherapy	Outcome (GOS)
1	0.125	0.016	20	–	5
2	0.5	0.016	20	–	5
3	0.5	0.016	20	–	5
4	1	0.125	20	–	5
5	2	0.250	20	–	5
6	2	2	20	–	3
7	2	0.250	6	–	1
8	0.016	0.008	2	18	5
9	0.016	0.016	3	17	5
10	0.008	0.016	3	18	5
11	0.016	0.016	2	18	5
12	0.016	0.016	2	18	5
13	0.016	0.008	3	17	5
14	0.032	0.016	3	17	5
15	0.032	0.016	3	17	4
16	0.016	0.008	2	7	1

- Tümü başlangıçta seftriakson 2x2 + linezolid 2x600mg + dekzametazon
- Penisilin duyarlı linezolid stoplanmış.
- Tümünde 48 saat sonra hücre sayısı azalmış ve BOS steril.
- 2 ex, 3 sekel.
- Linezolid BOS geçişi iyi, dekzametazon dan etkilenmiyor.

Clin Microbiol Infect 2006; 12: 391–394

Daptomisin

J Antimicrob Chemother. 2014 Nov;69(11):3020-6. doi: 10.1093/jac/dku231. Epub 2014 Jun 23.

Experimental study of the efficacy of daptomycin for the treatment of cephalosporin-resistant pneumococcal meningitis.

Vivas M[1], Force E[2], Garrigós C[2], Tubau F[3], Platteel AC[2], Ariza J[2], Cabellos C[2].

Int J Antimicrob Agents. 2015 Jul;46(1):

Effect of dexamethaso
pneumococcal mening

Vivas M[1], Force E[2], Tubau F[3], El Ha

Daptomisin: yüksek doz (25mg/kg/gün)

✓dirençli *S.pneumoniae* menenjitte etkili olduğu

✓ dekzametazon ile kullanımda bakterisidal etkinlik değişmediği gösterilmiş

Intensive Care Med (2007) 33:924–925

Efficacy of Ceftaroline Fosamil against Penicillin-Sensitive and -Resistant *Streptococcus pneumoniae* in an Experimental Rabbit Meningitis Model

P. Cottagnoud,[a] M. Cottagnoud,[b] F. Acosta,[b] A. Stucki[c]

Clinic of Internal Medicine, Clinic Sonnenhof, Bern, Switzerland[a]; Zieglerspital, Bern, Switzerland[b]; Berner Reha Zentrum, Heiligenschwendi, Switzerland[c]

Ceftaroline is a new cephalosporin with bactericidal activity against resistant Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae*, as well as common Gram-negative organisms. This study tested the prodrug, ceftaroline fosamil, against a penicillin-sensitive and a penicillin-resistant strain of *S. pneumoniae* in an experimental rabbit meningitis model. The penetration of ceftaroline into inflamed meninges was approximately 14%. Ceftaroline fosamil was slightly superior to ceftriaxone against the penicillin-sensitive strain and significantly superior to the combination of ceftriaxone and vancomycin against the penicillin-resistant strain.

TABLE 2 Efficacies of drugs against the penicillin-resistant strain

Antibiotic (no. of rabbits)	Inoculum at 0 h (CFU/ml)	ΔKilling/h (CFU/ml)	ΔKilling/8 h (CFU/ml)
Controls (5)	$6.04 \pm 0.65 \log_{10}$	$+0.12 \pm 0.05 \log_{10}$	$+0.95 \pm 0.47 \log_{10}$
Ceftaroline (10)	$5.54 \pm 0.61 \log_{10}$	$-0.71 \pm 0.06 \log_{10}$[a]	$-5.54 \pm 0.61 \log_{10}$[b]
Ceftriaxone + vancomycin (10)	$5.76 \pm 0.54 \log_{10}$	$-0.59 \pm 0.11 \log_{10}$[a]	$-4.65 \pm 1.00 \log_{10}$[b]

[a] Ceftaroline versus ceftriaxone: $P < 0.009$, highly significant.

[b] Ceftaroline versus ceftriaxone plus vancomycin: $P < 0.03$, significant.

AAC 2013,57:4653-55.

Diğer antibiyotikler

- Karbapenemler
- Florokinolonlar

  özellikle moksifloksasin BOS penetrasyonu %50-85

  deneysel çalışmalarda levofloksasin, gemifloksasin, etkili olduğu gösterilmiş.
- Glikopeptidler:

  Teikoplanin

  Oritavansin, televansin. deneysel çalışmalar da BOS penetrasyonları düşük,

Hameed N et al. Curr Infect Dis Report 2010; 12:274-281

ORIGINAL ARTICLE

ESCMID guideline: diagnosis and treatment of acute bacterial meningitis

D. van de Beek[1], C. Cabellos[2], O. Dzupova[3], S. Esposito[4], M. Klein[5], A. T. Kloek[1], S. Leib[6], B. Mourvillier[7], C. Ostergaard[8], P. Pagliano[9], H. W. Pfister[5], R. C. Read[10], O. Resat Sipahi[11] and M. C. Brouwer[1], for the ESCMID Study Group for Infections of the Brain (ESGIB)

Clin Microbiol Infect 2016; -: 1.e1–1.e26

	Standart tedavi	Alternatif
Penisilin duyarlı MIC<0.1 µg/ml	penisilin / ampisilin/ amoksisilin	seftriakson sefotaksim kloramfenikol
Penn dirençli **MIC > 0.1**µg/ml 3. kuşak sefalosp duyarlı **MIC<2**µg/ml	seftriakson / sefotaksim	sefepim meropenem moksifloksasin
Pen dirençli **MIC > 0.1** 3. kuşak sefalosporin dirençli **MIC > 2**µg/ml	vanko + rifampisin vanko + seftriak/sefotaksim Rifampisin + seftriak/sefotaks	Vankomisin + moksifloksasin linezolid

Süre 10-14 gün

Bakteriyemi

- <2 yaş İPH en sık formu primer bakteriyemi(yaklaşık %70 bakteriyemi)
- Erişkinde daha çok (>%80) pnömoniye sekonder (bakteriyemik pnömoni şeklinde) gelişir
- Vaka-fatalite oranı: %20 (yaşlılarda ve splenektomili kişilerde daha yüksek)

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Journals.ASM.org

Impact of Penicillin Nonsusceptibility on Clinical Outcomes of Patients with Nonmeningeal *Streptococcus pneumoniae* Bacteremia in the Era of the 2008 Clinical and Laboratory Standards Institute Penicillin Breakpoints

Seong-Ho Choi,[a] Jin-Won Chung,[a] Heungsup Sung,[b] Mi-Na Kim,[b] Sung-Han Kim,[c] Sang-Oh Lee,[c] Yang Soo Kim,[c] Jun Hee Woo,[c] and Sang-Ho Choi[c]

- Değişen penisilin MIC değerleri ile menenjitte 2008 öncesine göre direnç oranları artmış durumda
- Diğer klinik tablolarda ise MIC değerleri yükseldiği için direnç oranı düştü.
- Penisilin direnci tedavide özellikle menenjit açısından önem taşımakta
- Diğer klinik formlarda mortalite tedavi başarısı üzerine etkisi??

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Journals.ASM.org

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Seong-Ho Choi,[a] Jin-Won Chung,[a] Heungsup Sung,[b] Mi-Na Kim,[b] Sung-Han Kim,[c] Sang-Oh Lee,[c] Yang Soo Kim,[c] Jun Hee Woo,[c] and Sang-Ho Choi[c]

- Ocak 1997- Şubat 2011, 117 *S. pneumoniae*

TABLE 1 Penicillin and ceftriaxone susceptibilities of 117 *S. pneumoniae* isolates causing nonmeningeal bacteremia

Antibiotic	Susceptibility breakpoint (μg/ml) Susceptible	No. (%) of isolates (*n* = 117)
Penicillin	≤2	
Ceftriaxone[a]	≤1	

30 günlük mortalite penisilin dirençli ve duyarlı %30.8-23.1 (p=0.37)
Seftriakson direnci ise mortalite açısından önemli

ORIGINAL ARTICLE 10.1111/j.1469-0691.2011.03672.x

Guidelines for the management of adult lower respiratory tract infections - Full version

M. Woodhead[1], F. Blasi[2], S. Ewig[3], J. Garau[4], G. Huchon[5], M. Ieven[6], A. Ortqvist[7], T. Schaberg[8], A. Torres[9], G. van der Heijden[10], R. Read[11] and T. J. M. Verheij[12] Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases

- Menenjit dışında penisilin dirençli *S.pneumoniae* enfeksiyonları tedavisinde :
- MIC ≤ 4 µg/ml ise

  Pen G 6x2 MU veya

  Seftriakson 2gr/gün veya sefotaksim 4x2gr

  Amox/CLA (2gr/125mg) 2x1 şeklinde yeni formulasyonu ile amoksisilin MIC 4-8 µg/ml olan suşlarda bile etkili

ORIGINAL ARTICLE 10.1111/j.1469-0691.2011.03672.x

Guidelines for the management of adult lower respiratory tract infections - Full version

M. Woodhead[1], F. Blasi[2], S. Ewig[3], J. Garau[4], G. Huchon[5], M. Ieven[6], A. Ortqvist[7], T. Schaberg[8], A. Torres[9], G. van der Heijden[10], R. Read[11] and T. J. M. Verheij[12] Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases

- Penisilin dirençli *S. pneumoniae* MIC ≥ 8 µg/ml

  Levofloksasin

  Moksifloksasin

  Vankomisin

  Teikoplanin

  Linezolid

Clin Microbiol Infect 2011; 17(Suppl. 6): E1–E59

Bakteriyemik pnömoni tedavisi

Kombinasyon/ monoterapi ?

Combination Antibiotic Therapy Lowers Mortality among Severely Ill Patients with Pneumococcal Bacteremia

Larry M. Baddour, Victor L. Yu, Keith P. Klugman, Charles Feldman, Ake Ortqvist, Jordi Rello, Arthur J. Morris, Carlos M. Luna, David R. Snydman, Wen Chien Ko, M. Bernadete F. Chedid, David S. Hui, Antoine Andremont, Christine C. C. Chiou, and the International Pneumococcal Study Group

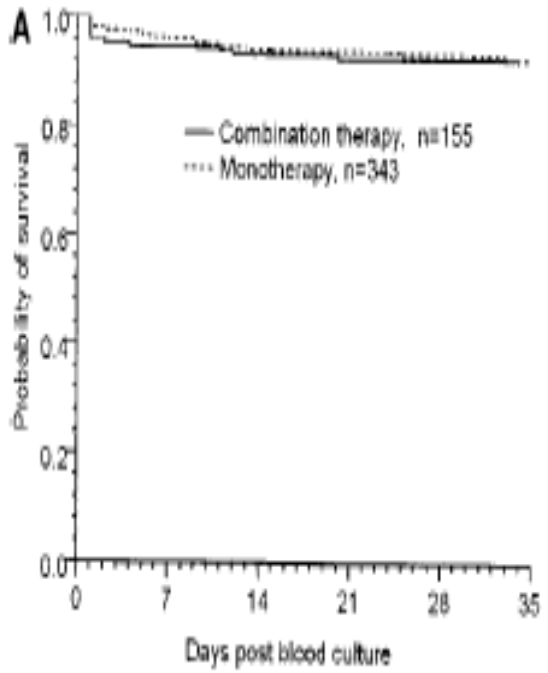
- 10 ülke, 21 hastane, prospektif, multisenter, gözlemsel
- Monoterapi /beta laktam, azitromisin,
- Kombinasyon: beta laktam + makrolid veya vankomisin ve diğer
- Makrolidli kombinasyonların daha üstün olduğu gösterilmiş.

Kombinasyon tedavisi 14 günlük mortalite daha düşük

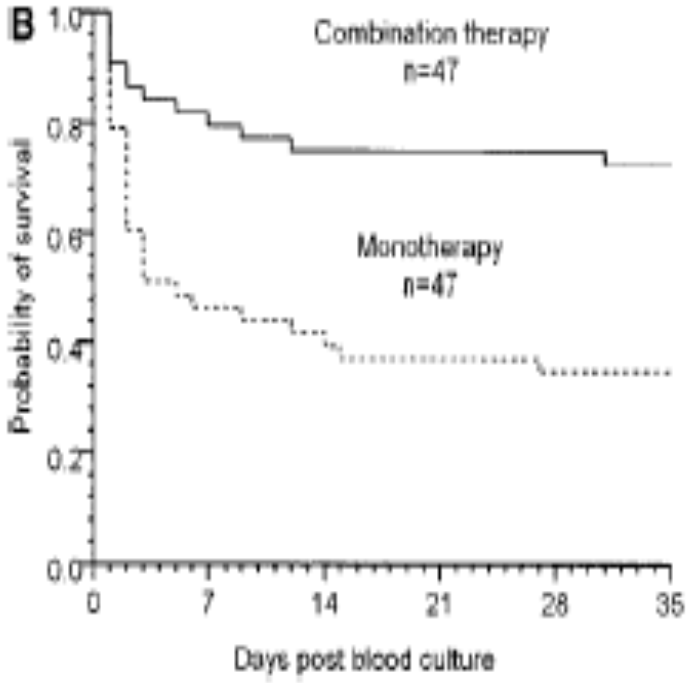
(%23.4- %55.3, $p < 0.001$)

Am J Respir Crit Care Med Vol 2004;170: 440–444.

kombinasyon ted > monoterepi



Kritik hastalığı olmayan



Kritik hastalığı olan

REVIEW Open Access

Combination antibiotic therapy for community-acquired pneumonia

Jesus Caballero* and Jordi Rello

Table 1 Published studies that favor combination therapy for in-hospital patients with CAP

Author	Year	Cohort	Site	Outcome	Study design
Gleason et al. [16]	1999	Patients aged ≥ 65 years with CAP	Ward	Lower 30-day mortality with β-lactam plus macrolide	Multicenter, retrospective
Dudas et al. [17]	2000	CAP	Ward	Lower mortality with β-lactam plus macrolide and reduced LOS	Multicenter, prospective
Waterer et al. [19]	2001	Pneumococcal bacteremia	Ward	Lower hospital mortality with combination	Multicenter, retrospective
Brown et al. [21]	2003	CAP	Ward	Lower 30-day mortality with β-lactam plus macrolide	Multicenter, retrospective
Martínez et al. [20]	2003	Pneumococcal bacteremia	Ward	Lower in-hospital mortality with β-lactam plus macrolide	Monocenter, retrospective
Baddour et al. [22]	2004	Pneumococcal bacteremia	Ward ICU	Lower 14-day mortality with combination	Multicenter, prospective
Weiss et al. [5]	2004	Pneumococcal bacteremia	Ward	Lower mortality with combination	Monocenter, retrospective
García-Vázquez et al. [23]	2005	CAP	Ward	Lower mortality with β-lactam plus macrolide	Multicenter, prospective
Mortensen et al. [24]	2006	CAP	Ward ICU	Lower 30-day mortality with β-lactam plus other than FQ	Multicenter, retrospective
Rodríguez et al. [25]	2007	CAP	ICU	Lower 28-day mortality with combination	Multicenter, retrospective
Metersky et al. [26]	2007	Pneumococcal bacteremia	Ward	Lower 30-day mortality with β-lactam plus macrolide	Multicenter, retrospective
Restrepo et al. [27]	2009	Severe sepsis pneumonia	Ward	Lower 30- and 90-day mortalities with combination plus macrolide	Multicenter, retrospective
Tessmer et al. [28]	2009	CAP	Ward	Lower 14- and 30-day mortalities with β-lactam plus macrolide	Multicenter, retrospective
Martín-Loeches et al. [29]	2010	Intubated CAP	ICU	Lower ICU mortality IDSA/ATS combination plus macrolide	Multicenter, prospective

Cabellero J et al. Annals of Intensive Care 2011;1:48

Table 2 Trials without significant difference between antibiotic monotherapy and combination therapy for CAP

Author	Year	Cohort	Outcome	Study design
Burgess and Lewiss [30]	2000	Hospitalized CAP without identified microorganism	Nonstatistical differences third-generation cephalosporin ± macrolide	Bicenter, retrospective
Dwyer et al. [31]	2006	Bacteremic pneumococcal CAP	No significant difference in case fatality if initial β-lactam + macrolide	Multicenter, retrospective
Harbarth et al. [32]	2005	Pneumococcal sepsis	Lack of effect of combo therapy	Multicenter, retrospective
Leroy et al. [33]	2005	CAP without vasopressors	Levofloxacin vs. cefotaxime + ofloxacin	Multicenter, retrospective

Cabellero J et al. Annals of Intensive Care 2011;1:48

Table 3 Resume of recommendations for monotherapy or combination therapy in CAP

Ambulatory setting	**Previously healthy patients**	**Monotherapy**
	Previous antibiotic therapy	Combination or respiratory fluoroquinolone
	Comorbidities without previous antibiotic therapy	Monotherapy with macrolides or respiratory fluoroquinolone
	Comorbidities and previous antibiotic therapy	Combination therapy
Nursing home without hospitalization	CAP	Combination therapy
Hospitalized CAP	Moderate disease	Monotherapy with respiratory fluoroquinolones or combination therapy
	Severe CAP	Combination therapy
	Bacteremic pneumococcal CAP	Combination therapy
	CAP and shock	Combination therapy
	Ventilation support	Combination therapy

Cabellero J et al. Annals of Intensive Care 2011;1:48

Special Articles

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

Septik şoktaki bakteriyemik *S.pneumoniae* infeksiyonlarında (Grade 2B) kombinasyon tedavisi (beta laktam + makrolid)

Crit Care Med 2013; 41:580–637

Kombinasyon hangi antibiyotikler

- Geniş spektrumlu sefalosporin veya beta laktam /BLI

  + makrolid veya pnömokoklara etkili florokinolon

- Makrolidl ve florokinolonlar kombinasyonda sinerjistik etki yanısıra immünmodülatuar etkileri mevcut.
- Makrolid ler akciğerde IL-6, TNF alfa, IFN gama, IL-8 seviyesini azaltıp, IL-10 düzeyini artırıyor.
- Bakterinin solunum epiteline adezyonunu azaltmakta

Yeni antibiyotikler

- Seftaroline
- Linezolid

Bakteriyemik ve penisilin dirençli *S.pneumoniae* *etkili.*

Diğer invaziv enfeksiyonlar

- Daha az sıklıkta görülmekte
- Daha çok bakteriyemik olgularda septik komplikasyon sonucu gelişmekte
- Tedavi duyarlılık sonucuna ve enfeksiyon yerine göre planlanmalı

- Pnömokok aşıları ile İPH insidensi azalmakla beraber mortalitesi yüksek
- Penisilin ve diğer antibiyotiklere direnç artmakta
- Tedavi seçenekleri kısıtlı
- Esas hedefimiz '' hastalıkların oluşmadan önlenmesi' '
- Rutin çocukluk çağı ve risk gruplarının aşılamaya gereken önemi vermeliyiz.

Teşekkür ederim