INFECCIÓN NEUMOCÓCICA EN EL SIGLO XXI

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XXIX Congreso SEMI, A Coruña, 21 Nov 2008

- Biología de la infección neumocócica
- Mecanismos de defensa contra la infección
- Factores de riesgo de la infección neumocócica
- Neumonía neumocócica

  Tratamiento y prevención. 2008

Caso clínico

- Varón de 36 años que ingresa con fiebre > 39ºC, grandes escalofríos, dolor pleurítico izquierdo y tos de 12 h de evolución.
- Diagnosticado de VIH en 1992. Multiples ingresos por neumonia en los últimos 5 años. Cumplimiento tratamiento retroviral inconstante. Con penicilina-benzatina, 2.4 millones U/21-28 días desde hace 2 años.
- A su ingreso: PA 110/70, P 110/min, RR 26. Hipofonesis base izquierda. Radiografía de torax: infiltrado denso LII..Leucos11.000, 15% bandas, Hb 11, creatinina 1,1. CD4+ 559, HIV-RNA <40 copias/ml
- Tratado empíricamente con ceftriaxona, 2 g/IV/24h. Al día siguiente, afebril, menos dolor y recobrando el apetito.
- Los dos hemocultivos iniciales: *Streptococcus pneumoniae*, S a la penicilina

Tratamiento antiretroviral

- D4T + 3TC + Nelfinavir
- 2001 D4T + 3TC + Efavirenz
- 2002 LPV/r+ABC + 3TC
- 2003 LPV/r+ABC + 3TC
- 2004 Tripanavir + Rit + DDI + 3RC + AZT
- 2005 Tricivir
- 2006 Kivexa + Fuzeon
- 2007 Darunavir + Ritonavir + Fuzeon
- 2008 Raltegravir + Maraviroc + Truvada

Antecedentes personales

- 1992 Infección VIH
- 1996 . Mayo. Vacuna antineumocócica polisacárida (23 ST)
- 2003, Abril. Neumonia neumocócica bacteriémica. Serotipo 4
- 2003. Octubre. Neumonia neumocócica
  CD4+ 300/mm^3; HIV-RNA > 75.000 copias/ml
- 2005, Junio. Neumonia neumocócica bacteriémica. Serotipo 1
  CD4+ 267/mm^3; HIV-RNA > 24.300 copias/ml
- 2005, Agosto. Vacuna antineumocócica polisacárida (23 ST)
- 2005, Noviembre. Neumonia neumocócica bacteriémica. Serotipo 12
  CD4+ 179/mm^3; HIV-RNA > 35.100 copias/ml
- 2006, Mayo. Neumonia neumocócica.
  CD4+ 322/mm^3; HIV-RNA > 2.000 copias /ml
- 2006, Diciembre. Neumonia neumocócica bacteriémica. Serotipo 9N
  CD4+ 124/mm^3; HIV-RNA > 238.000 copias /ml
- 2007, Septiembre. Neumonia neumocócica bacteriémica. Serotipo 7F
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Biología de la Infección neumocócica

1. Adherencia y replicación in situ
2. Transporte y replicación intracelular
3. Evasión de la fagocitosis
4. Lesión tisular

Biología de la Infección neumocócica

- Adherencia y replicación in situ
  - Adhesina de superficie (ApsaA)
  - Choline-binding protein (CBP)
- Transporte y replicación intracelular
- Evasión de la fagocitosis
- Lesión tisular

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  Adhesina de superficie (ApsaA)

  Choline-binding protein (CBP)

- Transporte y replicación intracelular

  - Trompa de Eustaquio, senos, bronquios
  - Penetración barrera mucosa (CBP A y su receptor)
  - Endocitosis y paso a través de la membrana interna
  - Torrente circulatorio y siembra de los órganos

- Evasión de la fagocitosis
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- Evasión a la fagocitosis

  - En ausencia de anticuerpo anti capsular:
    Importancia de la cápsula y otros factores de virulencia

- Lesión tisular

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- Evasión a la fagocitosis
  - En ausencia de anticuerpo anti capsular:
    Importancia de la cápsula y otros factores de virulencia
- Lesión tisular
  - Pneumolisina
  - Activación del complemento y ↑ regulación PMNs vía TLRs

ANTICUERPOS ANTICAPSULARES

- Aparecen a los 5-8 días de la infección (la fiebre desaparece en ausencia de tratamiento)

  Extraordinario aumento de la fagocitosis (opsonización)
- Pocos datos sobre otros Acs. Pero hay pacientes que se curan sin producción de Ac capsulares específicos.
- Ocasionalmente, individuos que no producen Acs capsulares y que viven hasta la vejez sin infección neumocócica
- Hasta el 33% de adultos sanos tienen Acs capsulares frente a los serotipos más comunes. 2/3 de los infectados los producen. La colonización conduce a la producción de Acs capsulares

EL BAZO

- El órgano principal en la depuración de *Streptococcus pneumoniae* no opsonizados. Los microorganismos opsonizados son, en gran parte, depurados en el hígado

FACTORES PREDISPONENTES INFECCIÓN NEUMOCÓCICA

PRODUCCION DE ANTICUERPOS

Primaria

- Agammaglobulinemia
- Hipogammaglobulinemia común variable
- Deficiencia selectiva subclases IgG

Secundaria

- Mieloma múltiple
- Leucemia linfática crónica
- Linfoma
- VIH

DEFECTOS EN EL SISTEMA COMPLEMENTO

- Disminución a ausencia C1, C2, C3 y C4
  “ “ C3b

FACTORES PREDISPONENTES. II

GRANULOCITOPENIA

- Neutropenia cíclica
- Neutropenia secundaria a fármacos
- Hemopatía maligna

ASPLENIA

- Congénita
- Esplenectomia
- Drepanocitemia

FACTORES PREDISPONENTES. III

ENFERMEDADES ASOCIADAS

- Alcoholismo
- Cirrosis hepática
- Diabetes mellitus
- Tratamiento corticoideo
- Insuficiencia renal crónica

FACTORES PREDISPONENTES. IV

MULTIFACTORIALES O INCIERTOS

- Malnutrición
- Exposición al frío

AUMENTO RIESGO DE EXPOSICIÓN

- Guarderías
- Campamentos militares
- Prisiones
- Asilos

INFECCIÓN RESPIRATORIA PREVIA

- Influenza
- Otros virus

ENFERMEDAD PULMONAR CRÓNICA

- COPD
- Astma

GENETICS OF PNEUMONIA

- Genetic risk for pneumonia is unrecognized and understimated
- Classic genetic diseases are rare and do not explain even a small fraction of all cases of pneumonia.
- More common genetic variations that may impact in the development, complications or mortality of pneumonia are now investigated
- The mutation has to be common enough to affect a significant portion of the population; most association studies have examined polymorfisms-mutations occurring in > 5% of the population

Wunderink RG et al. Curr Opin Crit Care. 2003;9:384-389

POLIMORFISMS IN GENES ENCODING FOR MOLECULES IMPORTANT IN THE PATHOGENESIS OF PNEUMONIA

- **Tumour necrosis factor**

  - LTA+250 AA genotype, a risk factor for septic shock in patients with CAP (Waterer et al. 2001)

  - Heat shock protein 70-2+1267 AA homozygotes have an increased risk of septic shock in adults with CAP (Waterer et al. 2003)

- **Interleukin-10**

  - IL-10-1082 genotype is associate with increased IL-10 release, a risk factor for septic shock in pneumococcal infection (Schaaf et al. 2003)

- **FcγRIIa-R131**

  - Homozygosity is associated with bacteremic pneumococcal pneumonia (Yee et al. 2000)

- **Mannose-binding leptin**

  - Homozygosity for MBL codon variants twice as common in patients with IPD (Roy S et al, Lancet 2002;359:1569-73)

Infección neumocócica: síndromes clínicos

- Neumonia
- Otitis media aguda
- Rinosinusitis aguda
- Exacerbación COPD
- Meningitis postraumática
- Bacteriemia primaria
- Sepsis secundaria
  - Meningitis
  - Endocarditis
  - Artritis
  - Peritonitis
  - Otras

	Relative frequency (%)
Streptococcus pneumoniae	35–80
Haemophilus influenzae	5–6
Legionella spp*	2–15
Mycoplasma pneumoniae	2–14
Chlamydia spp†	4–15
Staphylococcus aureus‡	3–14
Enteric gram-negative bacilli§	6–12
Pseudomonas aeruginosa¶	4–9
Mycobacterium tuberculosis	<1–5
Coxiella burnetii	2–4
Moraxella catarrhalis	<1
Influenza A virus	10–15
Other viruses||	5–10
Unknown	15–40

*Vary in importance between countries; more than 95% are *L pneumophila* serogroup 1; outbreaks are common. †More than 99% due to *Chlamydophila pneumoniae* in adults. ‡Increasing in areas with high prevalence of community-acquired meticillin-resistant S *aureus*. §Main species associated with CAP are *Escherichia coli* and *Klebsiella pneumoniae*. ¶Risk factors include chronic steroid therapy, structural lung disease, previous hospitalisation. ||Including respiratory syncytial virus, adenovirus, parainfluenza virus, metapneumovirus, varicella-zoster virus, measles, and hantavirus.

Table: **Pathogens associated with community-acquired pneumonia**

Garau J et al, Lancet 2008;371:455-58

Caso clínico. Estudios inmunidad realizados

- Proteinas totales, 76,5 g/L
- Electroforesis proteica: gammaglobulinas, 2.900 mg/dl.
- IgG: 2.770; IgM: 600; IgA: 180
- Subtipos IgG: IgG1, IgG2 e IgG4, normales.
  IgG3, disminución discreta
- CD4+, desde 124 a 559 cell/mm3; HIV-RNA, de < 40 a 238.000 copias/ml
- CH50, C1, C3, C4, normales.
- Pendientes: C3b, anticuerpos capsulares específicos a serotipos 1, 4, 12, 7F, 9N.

MORTALITY IN PNEUMOCOCCAL PNEUMONIA

- Age
- Comorbidity
- Severity of diseae
- Genetic background
- Immunosuppression
- Suboptimal antibiotic treatment ?

Clinical characteristics and outcome in 331 patients with pneumococcal bacteremia by age-group

Characteristics	Aged ≥ 80 y N=77 Nº (%)	Aged 19-79 y N=254 Nº (%)	*P*	OR (95%CI)
Age, y, mean (range)	85 (80-94)	57 (19-79)		
Gender, male	30 (39)	173 (68)	<0.001	3.3 (2-6)
COPD	37 (48)	49 (19.3)	<0.001	0.19 (0.1-0.4)
Diabetes mellitus	17 (22)	44 (17.3)	0.43	0.23 (0.37-1.4)
Cancer	12 (15.5)	51 (20)	0.47	1.36 (0.7-2.9)
Hepatic cirrhosis	1 (1.3)	12 (4.7)	0.31	3.7 (0.5-26)
Shock	5 (6.5)	23 (9)	0.63	1.4 (0.5-4.5)
Pen Resistant*	9 (11.8)	9 (3.7)	0.01	0.3 (0.09-0.8)
Macrolide Resistant	12 (21.8)	23 (12.3)	0.15	0.5 (0.2-1.2)
30 Day-mortality	23 (30%)	17 (6.7)	<0.001	0.16(0.07-0.35)

* Pen MIC ≥ 2 µg/ml

Garau J et al, unpublished

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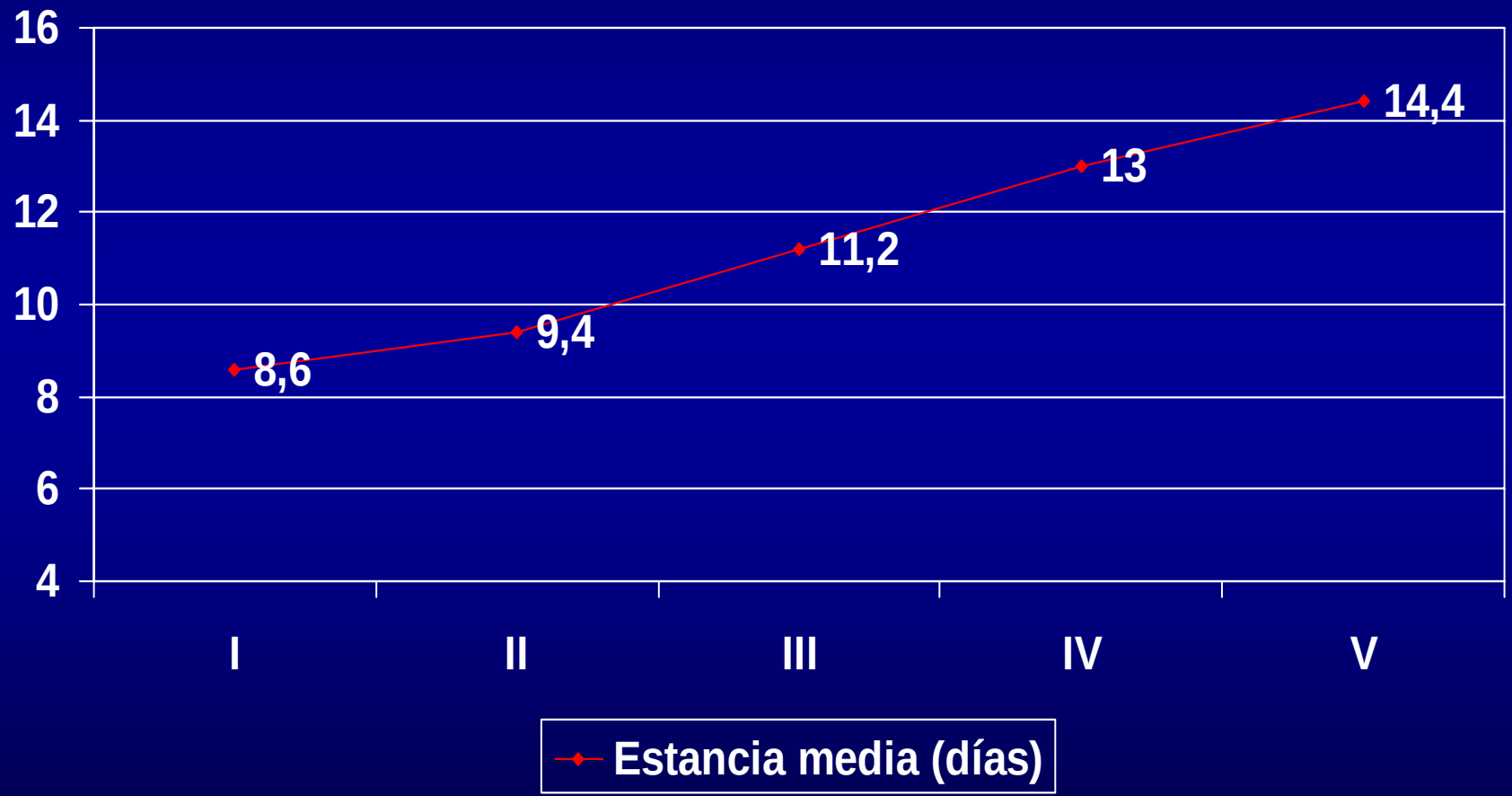
Factors impacting on lenth of stay and mortality in CAP

Outcome measure	Patients in PSI risk class (%)[a]					
	I	II	III	IV	V	Total
Patients	403 (12.5)	492 (15.2)	711 (22.0)	1145 (35.4)	482 (14.9)	3233 (100)
Admission to the ICU	10 (2.5)	18 (3.7)	28 (3.9)	57 (5.0)	49 (10.2)	162 (5.0)
Mechanical ventilation	6 (1.5)	6 (1.2)	20 (3.8)	40 (3.5)	28 (5.8)	100 (3.1)
Aetiological diagnosis	118 (29.3)	123 (25.0)	174 (24.5)	252 (22.0)	95 (19.7)	762 (23.6)
LOS, mean days	8.6	9.4	11.2	13.0	14.4	11.5
Early death[b]	0	1 (0.2)	2 (0.3)	15 (1.3)	36 (7.5)	54 (1.7)
Late death[c]	2 (0.5)	10 (2.0)	18 (2.5)	98 (8.6)	98 (20.3)	226 (7.0)
Total deaths	2 (0.5)	11 (2.2)	20 (3.8)	113 (9.9)	134 (27.8)	280 (8.7)

LOS, length of stay (calculated excluding patients who died or were discharged home); ICU, intensive care unit.
[a]Data are numbers of patients (%), unless otherwise indicated.
[b]Died ≤48 h after admission to the hospital.
[c]Died >48 h after admission to the hospital.

Garau J, et al. Clin Microbiol and Infect 2008; 14(4):322-329.

TIEMPO DE ESTANCIA POR PSI



(excluyendo pacientes que murieron o que fueron **dados de alta**)

Factors impacting on lenth of stay and mortality in CAP

Characteristics	Sites[a] 1 (n = 410)	2 (n = 712)	3 (n = 231)	4 (n = 235)	5 (n = 255)	6 (n = 376)	7 (n = 187)	8 (n = 336)	9 (n = 288)	10 (n = 203)	Total (n = 3233)	p value
PSI risk class												
Low-risk[b]	164 (40)	392 (55)	90 (39)	125 (53)	122 (48)	190 (51)	108 (58)	214 (64)	112 (39)	89 (44)	1606	
High-risk[c]	246 (60)	320 (45)	141 (61)	110 (47)	133 (52)	186 (49)	79 (42)	122 (36)	176 (61)	114 (56)	1627	<0.001
Aetiological diagnosis	30 (7)	297 (42)	73(32)	48 (20)	43 (17)	61 (16)	44 (24)	93 (28)	43 (15)	30 (15)	762	<0.001
LOS (days)	10.8 ± 6.5	11.0 ± 7.5	9.2 ± 5.3	11.1 ± 7.5	14.7 ± 8.1	13.3 ± 8.3	10.0 ± 5.8	7.8 ± 7.4	12.8 ± 7.6	17.3 ± 16.3	11.5 ± 8.4	<0.001
Deaths	45 (11.0)	59 (8.3)	10 (4.3)	19 (8.1)	34 (13.3)	35 (9.3)	2 (1.1)	7 (2.1)	29 (10.1)	40 (19.7)	280 (8.7)	<0.001

PSI, pneumonia severity index risk class; LOS, length of stay (calculated excluding patients who died or were discharged home).
[a]Data are presented as n (%) or mean ± SD unless otherwise indicated.
[b]PSI classes I–III.
[c]PSI classes IV and V.

- Exceso de tiempo de estancia hospitalaria:
  - Media = 11,5 + 8,4 días
  - Mediana = 9 días

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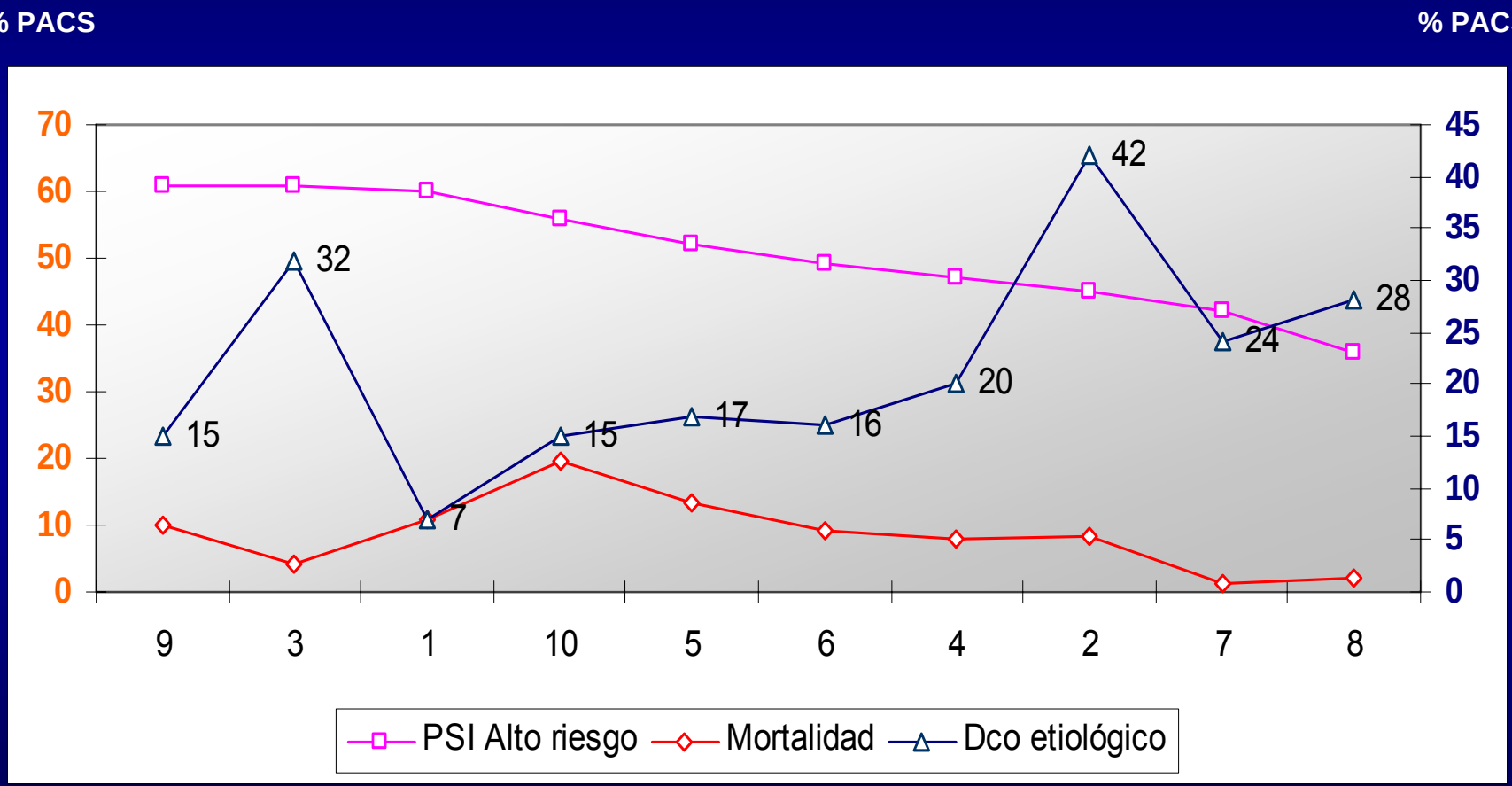
Factors impacting on lenth of stay and mortality in CAP



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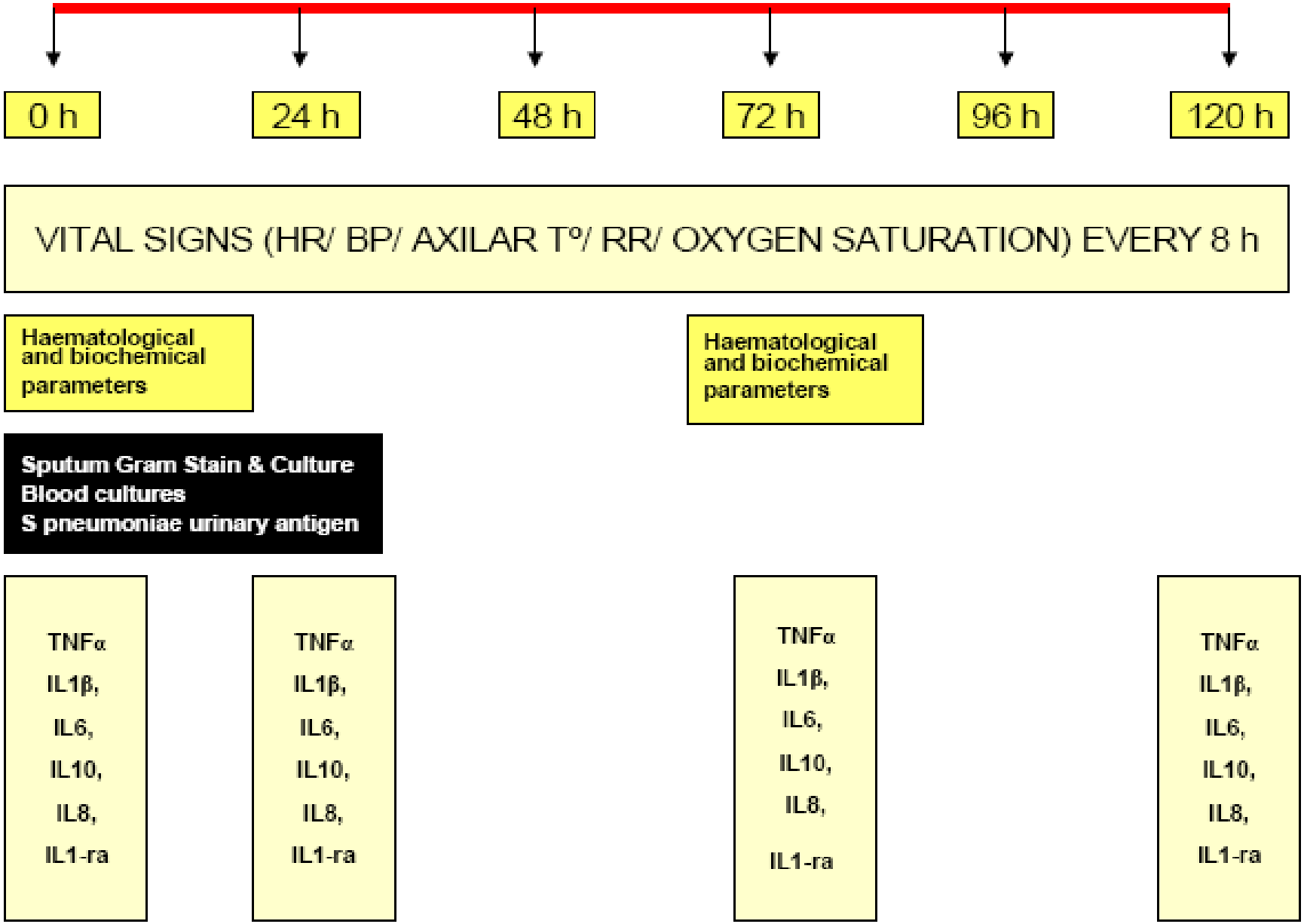


HR: Heart rate; BP: blood pressure; AXILAR Tº: axilar temperature; RR: respiratory

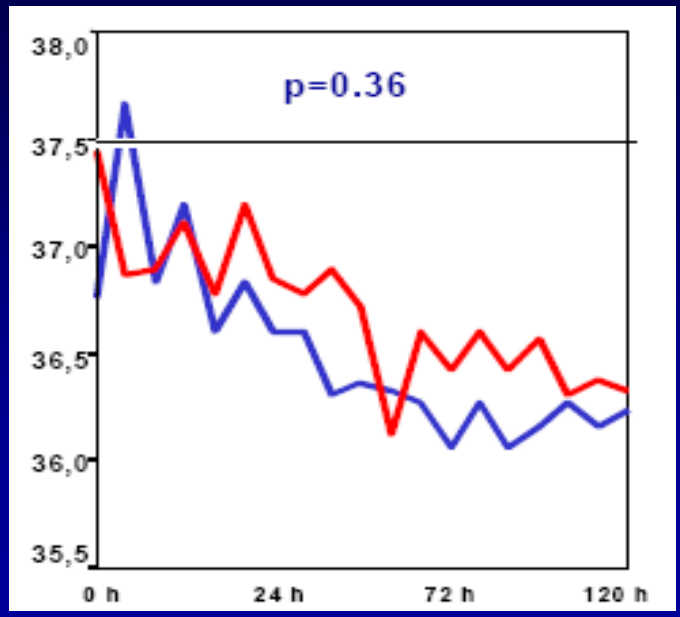
Calbo E et al. AAC 2008

Results

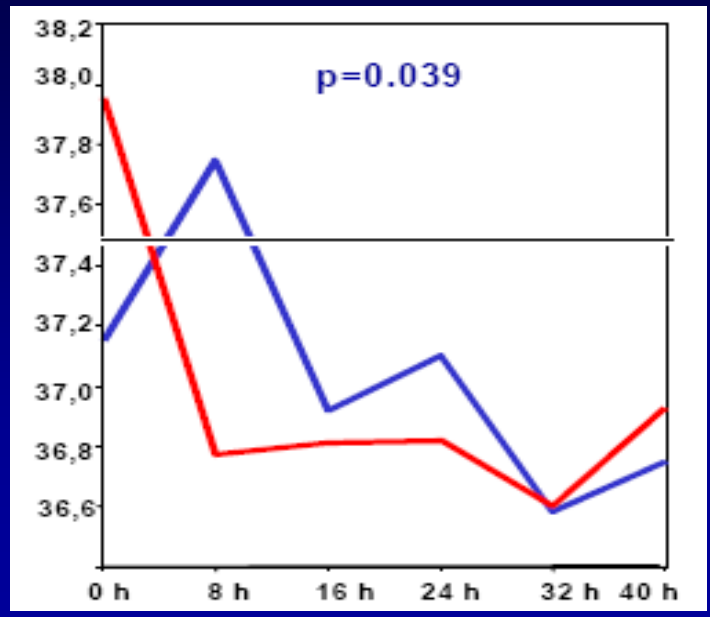
- All cytokines were detected in venous blood with the single exception of IL-1β
- All cytokines studied showed a similar pattern of progressive decrease over time
- No significant differences in the concentrations of any of the cytokines studied were found with the exception of TNF-α, for which lower concentrations were obtained at 120 h in the levofloxacin group ($p < 0.01$)

Calbo E et al, AAC 2008

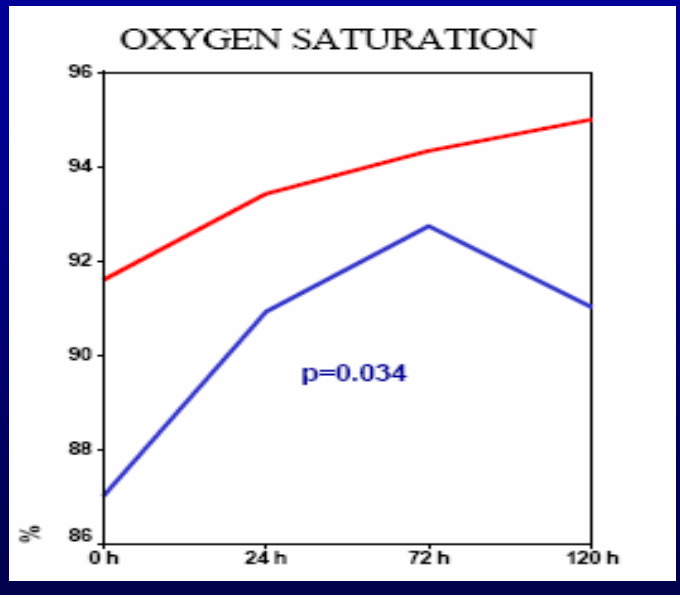
A temperature: over 120 h

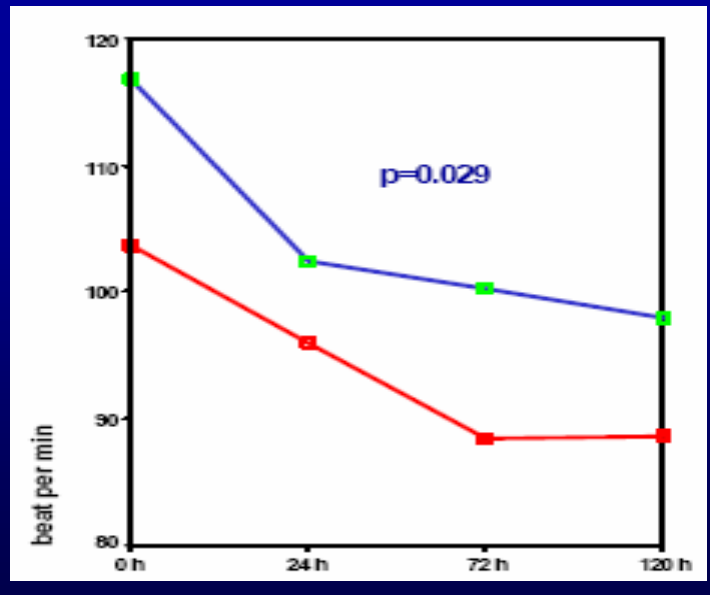


Amplification first 40 h



Heart Rate





levofloxacin

ceftriaxone

CONCLUSIONS

- Levofloxacin treated patients reached clinical stability earlier (expressed as an earlier recovery of O2 saturation, a slower cardiac rate and earlier defervescence) in parallel with lower TNFα levels at 120 h.
- Fluoroquinolone ability to inhibit cytokine production coupled with the beta-lactam cell wall activity (that might result in a second wave of TNFα production), could explain these findings.

Calbo E et al, AAC 2008

VIH Y NEUMOCOCO. 2008

INCIDENCIA DE ENFERMEDAD PNEUMOCÒCICA INVASIVA EN PACIENTES CON ENFERMEDADES CRÓNICAS (1999-2000)

Categoria	Tasa de incidència (95% CI), casos/100.000 personas/año	RR (95% CI)
Ninguna	8.8 (8.5 -9.0)	Referencia
Diabetes mellitus	51.4 (49.2 -53.9)	3.4 (1.8 -6.4)
Cardiopatia	93.7 (87.4 -100.9)	6.4 (3.7 -10.9)
COPD	62.9 (59.8 -66.3)	5.6 (3.2 -9.9)
Tumor sòlido	300.4 (272.6 -334.6)	22.9 (11.9 -44.3)
Infecció por VIH	422.9 (378.3 -479.4)	48.4 (24.8 -94.6)
Neoplàsia hematològica	503.1 (422.2 -622.3)	38.3 (15.9 -92.2)
Enolismo	100.4 (94.1 -107.7)	11.4 (5. 9-21.9)

Kyaw et al. J Infect Dis 2005;192:377-86

Effectiveness of polysaccharide pneumococcal vaccine in HIV-infected patients: a case-control

	Bivariate analysis		Multivariate analysis	
Risk factor	OR (95% CI)	*P*	OR (95% CI)	*P*
Male sex	1 (0.68–1.45)	1		
Smoking	0.84 (0.56–1.28)	.43		
Alcohol use	3.03 (1.86–4.91)	<.001	2.15 (1.11–4.19)	.02
Active injection drug use	3.33 (2–5.55)	.03		.46
CD4 lymphocyte count >200 cells/μL	1.04 (0.75–1–46)	.79		
HIV load <5000 copies/mL	0.38 (0.26–0.54)	<.001		.24
CDC HIV infection stage	0.85 (0.60–1.20)	.37		
TMP-SMZ use	0.66 (0.45–0.97)	.04		.80
Receipt of ART	0.23 (0.16–0.32)	<.001	0.23 (0.14–0.36)	<.001
HBV infection	0.71 (0.38–1.35)	.30		
HCV infection	1 (0.69–1.44)	1		
COPD	2.58 (1.3–5.1)	<.001	2.90 (1.21–6.94)	.02
Cirrhosis	6.05 (3.2–11.4)	<.001	5.64 (2.53–12.53)	<.001
Receipt of 23-valent PPV	0.39 (0.24–0.65)	<.001	0.44 (0.22–0.88)	.02

NOTE. ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; COPD, chronic obstructive pulmonary disease; HBV, hepatitis B virus; HCV, hepatitis C virus; PPV, polysaccharide pneumococcal vaccine; TMP-SMZ, trimethoprim-sulfamethoxazole.

Peñaranda M et al, CID 2007;45: e82-7

Effectiveness of polysaccharide pneumococcal vaccine in HIV-infected patients: a case-control

	Bivariate analysis		Multivariate analysis	
Risk factor	OR (95% CI)	*P*	OR (95% CI)	*P*
Male sex	1 (0.68–1.45)	1		
Smoking	0.84 (0.56–1.28)	.43		
Alcohol use	3.03 (1.86–4.91)	<.001	2.15 (1.11–4.19)	.02
Active injection drug use	3.33 (2–5.55)	.03		.46
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Peñaranda M et al, CID 2007;45: e82-7

- Biología de la infección neumocócica
- Mecanismos de defensa contra la infección
- Factores de riesgo de la infección neumocócica
- Neumonía neumocócica

  Tratamiento y prevención. 2008

MORTALITY OF LOBAR PNEUMONIA (1905, 1927) AND BACTEREMIC PNEUMOCOCCAL PNEUMONIA (1964, 1997) IN THE LAST CENTURY IN USA

AUTHOR	YEAR	NUMBER	%
• Ashton and Landis,	1905	991	**53,0**
• Cecil et al,	1927	342	**30,8**
• Austrian and Gold	1952-62	1,130	**13%**
• Fine(metaanalisis)	1966-95	4,432	**12%**

Hefron, Pneumonia. 1939; Ann Int Med 1964; JAMA 1996

Community-acquired Respiratory Tract Infections caused by *Streptococcus pneumoniae* -Therapeutic options

- Cloramphenicol
- Tetracyclines
- Cotrimoxazol
- Macrolides/azalides
- B-lactams
- Fluoroquinolones

MACROLIDES

Susceptibility results for *S. pneumoniae* isolates in European Countries

Erythromycin , 2006 (*) and 2007

COUNTRY	S	I	R
Austria	90.8	2.6	6.6
Belgium*	68.8	0.1	31.1
Bulgaria	83.3	4.2	12.5
Croatia	89.7	0.0	10.3
Cyprus	81.8	9.1	9.1
Czech Republic	91.9	0.0	8.1
Denmark*	94.5	1.1	4.4
Finland *	75.6	0.4	24
France *	63.8	0.3	35.9
Germany*	88.3	0.0	11.7
Hungary*	80.6	0.7	18.8
Iceland*	90.2	0.0	9.8
Ireland	84.5	0.0	15.5
Israel	87.1	0.0	12.9
Italy*	68.2	2.1	29.6
The Netherlands*	91.7	0.9	7.4
Norway*	89.8	0.3	9.9
Portugal*	78.6	0.0	21,4
Romania	75.0	0.0	25.0
Slovenia*	87.3	0.0	12.7
Spain	81.5	1.8	16.7
Sweden	94.8	0.0	5.2
Turkey	86.7	0.0	13.3
United Kingdom *	88.5	0.1	11.4

www. EARSS.com

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Denmark*	94.5	1.1	4.4
Finland *	75.6	0.4	24
France *	63.8	0.3	35.9
Germany*	88.3	0.0	11.7
Hungary*	80.6	0.7	18.8
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United Kingdom *	88.5	0.1	11.4

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Emergence of Macrolide-Resistant *S. pneumoniae* in vivo (during therapy)

1.- **Dixon JMS. The Lancet 1967**

63 y. o. man. Lung cancer. Pneumonia treated with erythromycin first; lincomycin afterwards. Same serotype recovered from empyema, now R to ERY (MIC, 100 μg/ml) and Lincomycin.

2.- **Musher D et al. NEJM 2002**

28 y. o. man. Previously healthy. Pneumonia treated with IV azithromycin. Initial improvement. On day 4, sudden worsening, increasing infiltrates, pleural effusion.

Second isolate (BAL and pleural fluid) identical genotype; R to ERY/AZI/CLA, MICs, 2-4 μg/ml;

Mutation: ribosomal protein L22

3.- **Buttler J et al. CID 2003**

46 y. o. man. Alcohol abuser. Bacteremic pneumonia treated with CEFURO, then erythromycin. Recurrence of fever; endocarditis and epidural abscess.

Second isolate (blood culture) identical genotype; R to ERY (MIC, 100 μg/ml)

Mutation: 23S rRNA A2058T (2/4 alleles)

4.- **Perez-Trallero E et al. EID 2003**

71 y. o. man. COPD. Pneumonia treated with IV LEVO, then clarithromycin, on and off for 25 days. AECB, pleural effusion. Vancomycin.

5th isolate (pleural fluid) with identical genotype. R to ERY/CLARI > 128 μg/ml

Mutation: 23S rRNA A2058G (4/4 alleles)

5.- Smith-Vaughan HC et al, J clin Microbiol 2007

2.5-month-old indigenous infant. Highly ERY R strain (< 256mg/l) after the infant received a single dose of azithromycin (125 mg) as routine prophylaxis following a trachoma contact

Mutation: 23S rRNA A2059G

MACROLIDE-RESISTANT PNEUMOCOCCI SUMMARY

- Increasing worldwide; associated with penicillin-resistance
- Failures in the animal model and increasing number of documented failures of macrolides in the treatment of ERSP infection (pneumonia, AOM). Recent studies indicate that in vitro R, any level, is a predictor of failure.
- Emergence of resistance while on therapy

The prevalence of R will dictate the need to reassess current recommendations for the treatment of CAP.

B-LACTAMS

B-LACTAMS

- B-lactam resistance in pneumococci is due to genetic alteration of the PBPs; main mechanism: import of foreign DNA from other streptococci by transformation

- The best PK/PD parameter that predicts eradication (and clinical response)

$$T > MIC$$

PENICILLIN G

FDA new susceptibility breakpoints for pneumonia caused by *Streptococcus pneumoniae*

	Minimum Inhibitory Concentration (MIC) (mcg/mL)		
	Susceptible (S)	Intermediate (I)	Resistant (R)
Updated	≤2	4	≥8
Previous	≤0.06	0.12-1.0	≥2

The susceptible breakpoint for meningitis caused by *S. pneumoniae* remains unchanged (0.06 mcg/mL).

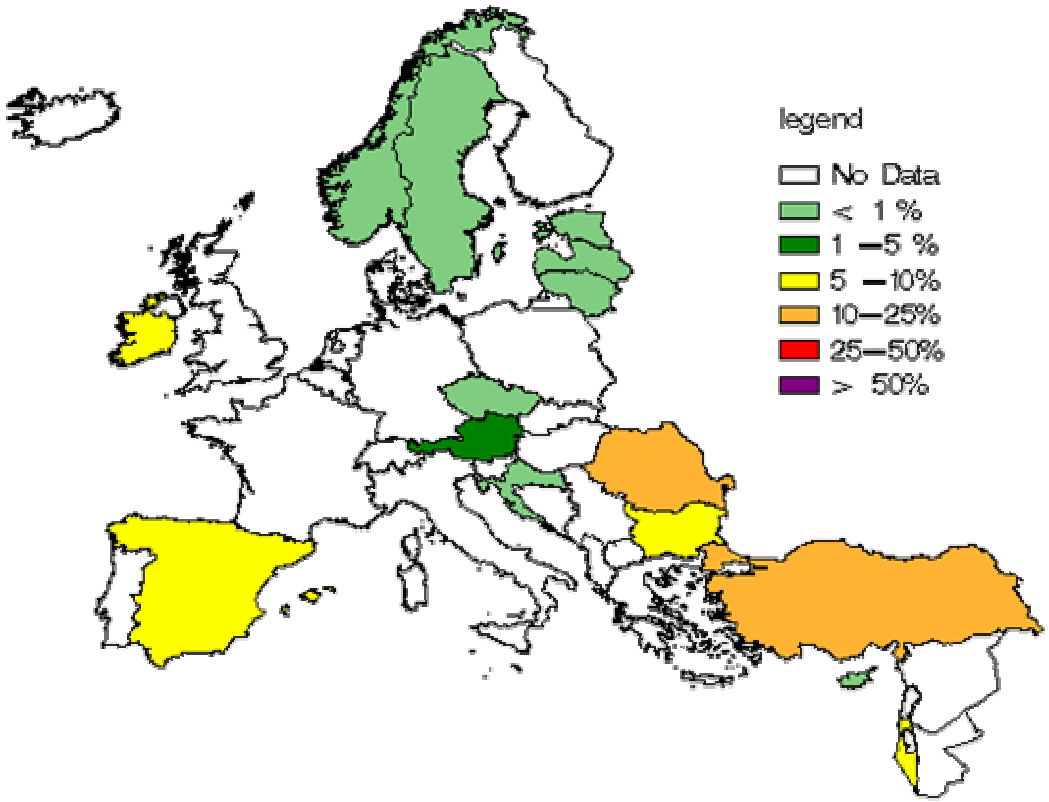
Emergent *Streptococcus pneumoniae* serotype 19A in the United States, 2005

- The incidence of IPD due to serotype 19A increased from 0.8 to 2.5 cases per 100,000 population between 1998 and 2005 ($P < .05$), whereas the overall incidence of IPD decreased from 24.4 to 13.8 cases per 100,000 population ($P < .05$).
- Simultaneously, the incidence of IPD due to penicillin-resistant 19A isolates increased from 6.7% to 35% ($P < .0001$).
- Of 151 penicillin-resistant 19A isolates, 111 (73.5%) belonged to the rapidly emerging clonal complex 320, which is related to multidrug-resistant Taiwan(19F)-14. The remaining penicillin-resistant strains were highly related to other clones of PCV7 serotypes or to isolates within major 19A clonal complex 199 (CC199). In 1999, only CC199 and 3 minor clones were apparent among serotype 19A isolates. During 2005, 11 multiple-isolate clonal sets were detected, including capsular switch variants of a serotype 4 clone

Moore M R et al, JID 2008

Proportion of Penicillin high resistant S. pneumoniae isolates in participating countries in 2007

(c) EARSS



T>MIC of 10 B-lactam antibiotics against *Streptococcus pneumoniae* Pen R (MIC > 1 mg/L)

Antibiotico	Dose	MIC_{50-90} mg/L	T>MIC (%)	Break point PK/PD (mg/L)
Penicilin G	2 MU/q6h	2-4	50-41	4
Ampicillin	1 g/q6h	2-4	71-54	2
Cefuroxime	750 mg/q8h	8-16	36-0	4
Cefotaxime	1 g/q8h	1-2	63-52	2
Ceftriaxone	1 g/q24h	1-2	76-48	2
Ceftazidime	1 g/q8h	32	< 35	8
Cefepime	1 g/q12h	2-4		
Imipenem	0.5 g/q8h	1	75-70	1
Meropenem	0.5 g/q8h	2	70-64	1
Ertapenem	1 g/q24h	2	20-24	2

Adapted from MR Jacobs, 2002

T>MIC for adult amoxicillin/clavulanate formulations

AMX/CA formulation	Dosing regimen	Mean time above MIC for amoxicillin (% of dosing interval) for MICs (mg/L) of: 1	2	4	8
500/125 mg	bid	36%	–	–	
500/125 mg	tid	55%	43%	_	
875/125 mg	bid	44%	40%	_	
875/125 mg	tid	69%	57%	34%	
1000/125 mg	tid	>65%	55%	41%	
2000/125 mg	bid	>70%	60%	49%	35%

FLUOROQUINOLONES

Re-establisment of susceptibility to fluoroquinolones in *Streptococcs pneumoniae* in at-risk populations in Toronto, Canada

	2000-2002 (N=857)		2003-2005 (N=943)		2006-2007 (N=752)	
	Lev R	**Mox R**	**Lev R**	**Mox R**	**Lev R**	**Mox R**
Invasive disease						
All adults	1.8%	0.50%	1.3%	0.33%	0.35%	0
Adults >65y	3.2%	1.0%	1.2%	0.41%	0	0
Hospital-acquired	7.4%	0	3.9%	0	0	0
Nursing home acquired	8.6%	2.5%	2.5%	0	2.1%	0
Failing FQ therapy	21.4%	7.1%	27.3%	9.1%	0	0
FQ prior 3 months	4.8%	1.6%	1.9%	0.93%	1.5%	0
Respiratory isolates	**2002 (N=352)**		**2003-2005 (N=1317)**		**2006-2007 (N=912)**	
All adults	5.7%	1.2%	3.4%	1.6%	2.6%	1.4%
Adults >65y	8.6%	1.7%	4.0%	1.8%	4.0%	2.6%
Hospital-acquired	8.7%	4.4%	0.8%	0.4%	2.7%	2.1%
Nursing home acquired	9.1%	0	10.7%	7.1%	4.0%	0
Current FQ therapy	60.0%	20%	25.0%	9.4%	42.9%	28.6%
FQ prior 3 months	15.4%	0	7.4%	3.7%	3.8%	1.9%

McGeer AQ et al, 48th ICAAC, Washington DC, 2008

Emergence of FQ-Resistant S. pneumoniae in vivo (during or after therapy)

REFERENCE	N	EPISODE	INITIAL ISOLATE LEVO MIC(μg/ml)	ANTIBIOTIC TREATMENT (mg/day)	FINAL ISOLATE LEVO MIC(μg/ml)	MUTATION(S)
Davidson et al. NEJM 2002	1	Pneumonia	1	LEVO (500)	8	parC(S79F) gyrA(S81F)
	2	Pneumonia	4	LEVO (500)	16	parC(S79F) gyrA(S81F)
De la Campa A et al. AAC 2003	3	Bronchiectasis	1	CIPRO (1000) For months, intermittently	16	parC(S79F) gyrA(S81F)
Anderson KB et al. CID 2003	4	Pneumonia	1	LEVO (500)	16	parC(S79Y) gyrA(S81F)
	5	Pneumonia	1	LEVO (500)	8	parC(D83Y) gyrA(S81Y)
	6	Pneumonia	1	LEVO (500)	16	parC(S79F) gyrA(S81F)
	7	Pneumonia	1	LEVO (500)	16	parC(S79F) gyrA(S81F)
Perez-trallero E et al. EID 2003	8	Pneumonia	2	LEVO (500) CIPRO (400 IV)	16	parC(S79F) gyrA(S81F)

EMERGENCE OF FQ-RESISTANT PNEUMOCOCCI IN ADULTS DURING OR AFTER THERAPY FOR CAP

- Ability of pneumococcus to give rise to in vivo mutants resistant to fluoroquinolones

- It has occurred during or after therapy in:
  - Immunocompromised; probably, at a greater risk (lack of immune response to reduce colonization, length of carriage, and density of organisms)
  - Patients with structural lung disease
  - Previously healthy adults

It may be prudent not to use FQ monotherapy when the patient has a history of FQ therapy in the past 4 months

In patients with documented pneumococcal infection caused by strains with LEVO MICs $\geq$ 1 µg/ml, FQs should be avoided in cases of severe disease, or used in combination

Anderson KB et al. CID 2003;307:376 Austrian R. JAC 1986;18 (Suppl A):35
De la Campa A et al. AAC 2003:47;1419 Davidson R et al. NEJM 2002:346;750

VACUNAS

- Polisacarida 23 serotipos
- Conjugada heptavelente
- Conjugada 13 serotipos