11:00-11:30 Reducción de duración del tratamiento antibiótico ¿opción o elección?

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Does this reflect a deep-rooted belief in the sacred numbers 1, 3, 5 and 7, as held by Pythagoras, or do we subconsciously follow an unwritten ‘rule’ that we publicly consider to be superstition namely: ‘The duration of antibiotic treatment is 5 or 7 days or multiples thereof’.

Duration of antibiotic treatment: are even numbers odd?
Emine Alp,
J. Antimicrob. Chemother. (August 2005) 56 (2): 441-442.

- ¿Por qué?
- ¿Cuál es la duración óptima?
- ¿Todos igual?
- ¿Cómo se reduce la duración del antibiótico?

¿Por qué?

- A five day, high dose course of amoxicillin for respiratory tract infections in children resulted in a significantly lower rate of carriage of penicillin resistant *Streptococcus pneumoniae* than the standard duration of treatment.
  - Schrag SJ, Pena C, Fernandez J, Sanchez J, Gomez V, Perez E, et al. *Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcal carriage: a randomized trial. JAMA 2001;286: 49–56.*
  - Guillemot D, Carbon C, Balkau B, Geslin P, Lecoeur H, Vauzelle-Kervroedan F, t al. *Low dosage and long treatment duration of beta-lactam: risk factors for carriage of penicillin-resistant Streptococcus pneumoniae. JAMA 1998;279: 365–70.*

¿Por qué?

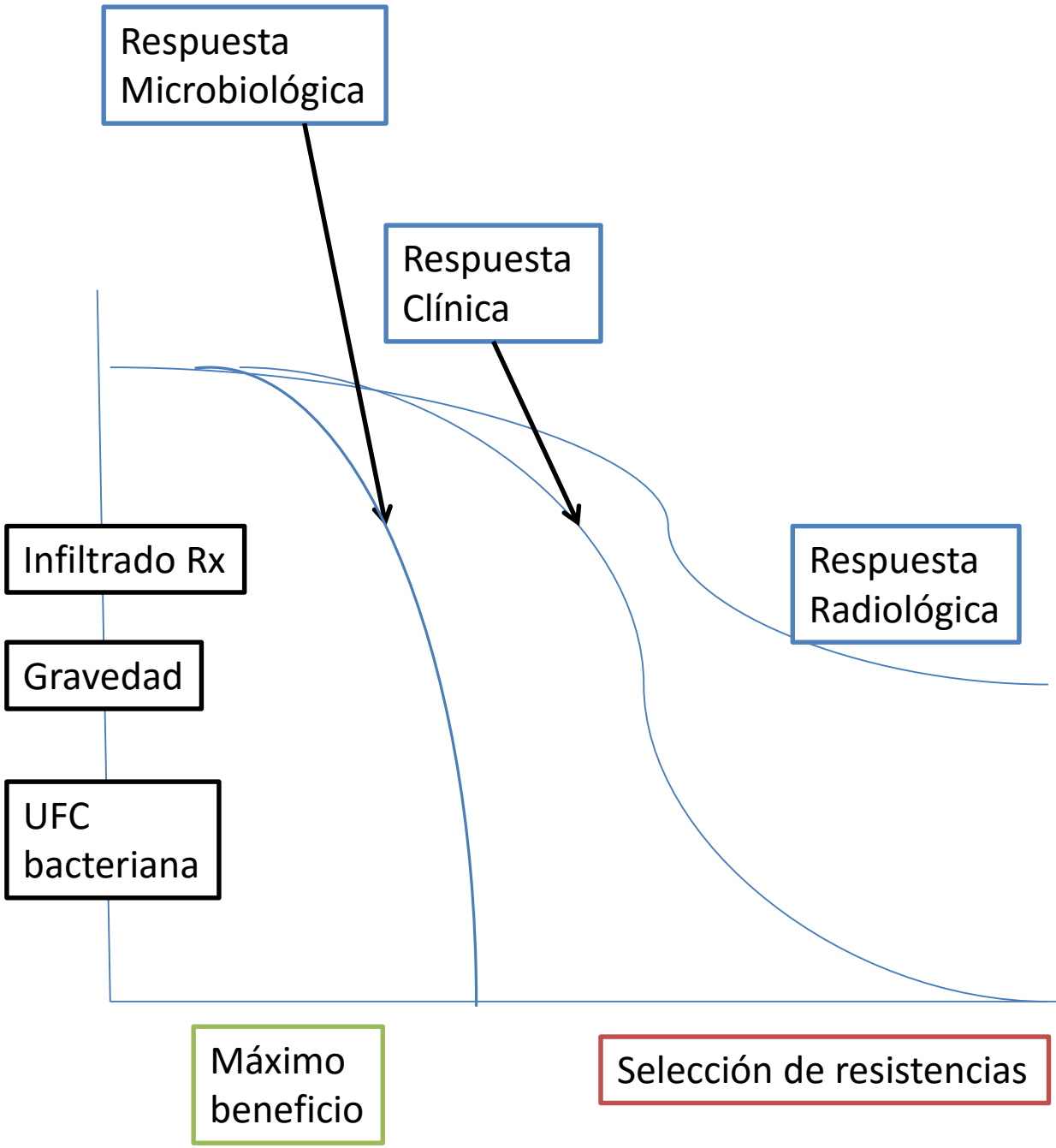
- Among patients who developed recurrent infections, multiresistant pathogens emerged less frequently in those who had received 8 days of antibiotics (42.1% vs 62.0% of pulmonary recurrences, *P* = .04).
  - Chastre J, Wolff M, Fagon J-Y, et al. Comparison of 8 vs 15 Days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 2003; 290:2588–98.

¿Cuál es la duración óptima?

- La mayoría de las veces la necesaria para erradicar la infección curar el proceso agudo y evitar su recidiva?

o

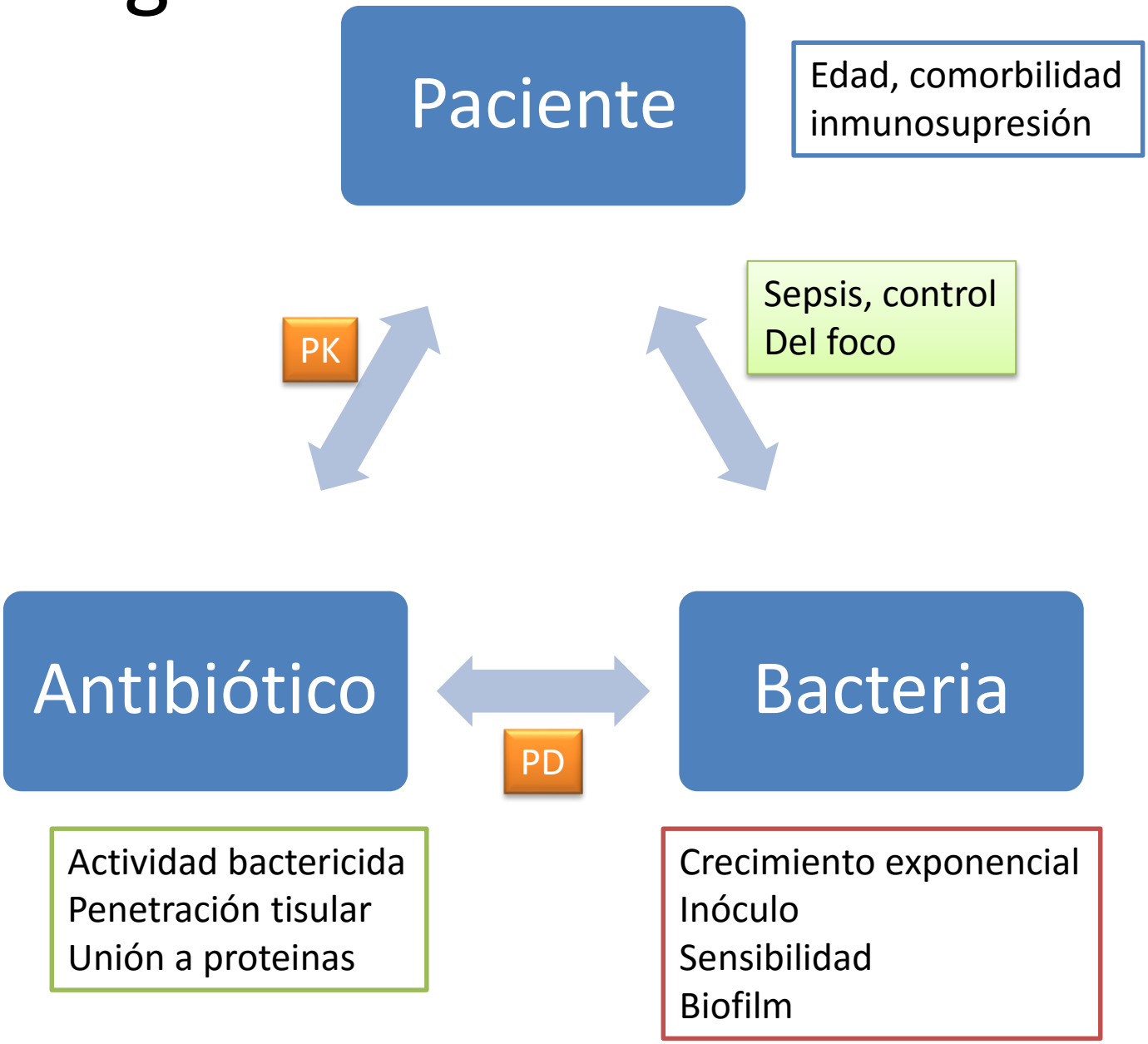
- A veces la necesaria para disminuir la carga bacteriana y mejorar los síntomas.
- Exponiendo al paciente a los menores efectos secundarios.
- Evitando la presión selectiva de microorganismos mutliresistentes y *C. difficile*.



Usual duration of findings in treated community-acquired pneumonia	
Abnormality	Duration (days)
Tachycardia and hypotension	2
Fever, tachypnea, and hypoxia	3
Cough	14
Fatigue	14
Infiltrates on chest radiograph	30

Adaptada de Julio Ramirez

¿Todos igual?


Paciente
Edad, comorbilidad
inmunosupresión
PK
Sepsis, control
Del foco
Antibiótico
PD
Bacteria
Actividad bactericida
Penetración tisular
Unión a proteinas
Crecimiento exponencial
Inóculo
Sensibilidad
Biofilm

CARACTERÍSTICAS DEL ANTIBIÓTICO IDEAL PARA TRATAMIENTOS CORTOS

Antibióticos bactericidas

Inicio rápido de acción

Adecuada penetración tisular

Actividad no afectada por bajo pH y presencia de pus

Dosis óptima

Escasa inducción de resistencia

CONDICIONES PARA REALIZAR TRATAMIENTOS CORTOS DE ANTIBIOTICOTERAPIA

Sitio de infección accesible a los antibióticos

- **El sitio de infección no puede ser drenado o removido pero la penetración del antibiótico es adecuada**: neumonía, meningitis, celulitis...
- **El sitio de infección puede ser drenado adecuadamente:** peritonitis secundaria, infección urinaria secundaria obstrucción, abscesos superficiales...

Patógeno totalmente susceptible al antibiótico

Paciente no inmunocomprometido

Ausencia de cuerpos extraños (prótesis, válvulas...)

Ausencia de abscesos o colecciones no drenables

NO son infecciones candidatas a tratamientos cortos

El sitio de infección no puede ser drenado y el antibiótico presenta escasa penetración potencial

- Endocarditis.
- Osteomielitis.
- Prostatitis.
- Infecciones asociadas a dispositivos.

Determinados microorganismos: *S. aureus, M tuberculosis…*

NO son pacientes candidatos a tratamientos cortos

- Inmunosuprimidos
- Pacientes con mala evolución clínica en las primeras 48-72 horas.

estrategias

- Aplicar el conocimiento a la práctica clínica.
  - Guías, ayudas a la prescripción
  - PROA
- Antibiotic time-out
- Parada automática de profilaxis.
- Biomarcadores

XIII. Should ASPs Implement Interventions to Reduce Antibiotic Therapy to the Shortest Effective Duration?

Recommendation

We recommend that ASPs implement guidelines and strategies to reduce antibiotic therapy to the shortest effective duration (strong recommendation, moderate-quality evidence).

Recommending a duration of therapy based on patient-specific factors is an important activity for ASPs. Suitable approaches include:

- developing written guidelines with specific suggestions for duration,
- including duration of therapy recommendations as part of the preauthorization or prospective audit and feedback process,
- or specifying duration at the time of antibiotic ordering (eg, through an electronic order entry system).

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7 días

The available studies suggest that adults with mild to moderate community-acquired pneumonia can be safely and effectively treated with an antibiotic regimen of 7 days or less. Reduction in patient exposure to antibiotics may limit the increasing rates of antimicrobial drug resistance, decrease cost, and improve patient adherence and tolerability.

Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis. Li JZ, Winston LG, Moore DH, Bent S. Am J Med. 2007;120(9):783.

5 días

These data demonstrate that 750 mg of levofloxacin per day for 5 days is at least as effective as 500 mg per day for 10 days for treatment of mild-to-severe CAP.

High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. Dunbar LM, Wunderink RG, Habib MP, Smith LG, Tennenberg AM, Khashab MM, Wiesinger BA, Xiang JX, Zadeikis N, Kahn JB. Clin Infect Dis. 2003;37(6):752.

5 días

Leophonte P, Choutet P, Gaillat J, et al. Efficacy of a ten day course of **ceftriaxone** compared to a shortened **five** day course in the treatment of community-acquired pneumonia in hospitalized adults with risk factors.Medecine et Maladies Infectieuses 2002; 32:369–81.

Leophonte P, File T, Feldman C. **Gemifloxacin once daily for 7** days compared to amoxicillin/clavulanic acid thrice daily for 10 days for the treatment of community-acquired pneumonia of suspected pneumococcal origin. Respir Med 2004; 98:708–20.

Tellier G, Niederman MS, Nusrat R, Patel M, Lavin B. Clinical and bacteriological efficacy and safety of **5 and 7 day regimens of telithromycin** once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate community-acquired pneumonia. J Antimicrob Chemother 2004; 54:515–23.

File TM Jr., Mandell LA, Tillotson G, Kostov K, Georgiev O. **Gemifloxacin once daily for 5** days versus 7 days forthe treatment of community-acquired pneumonia: a randomized, multicentre, doubleblind study. J Antimicrob Chemother 2007; 60:112–20.

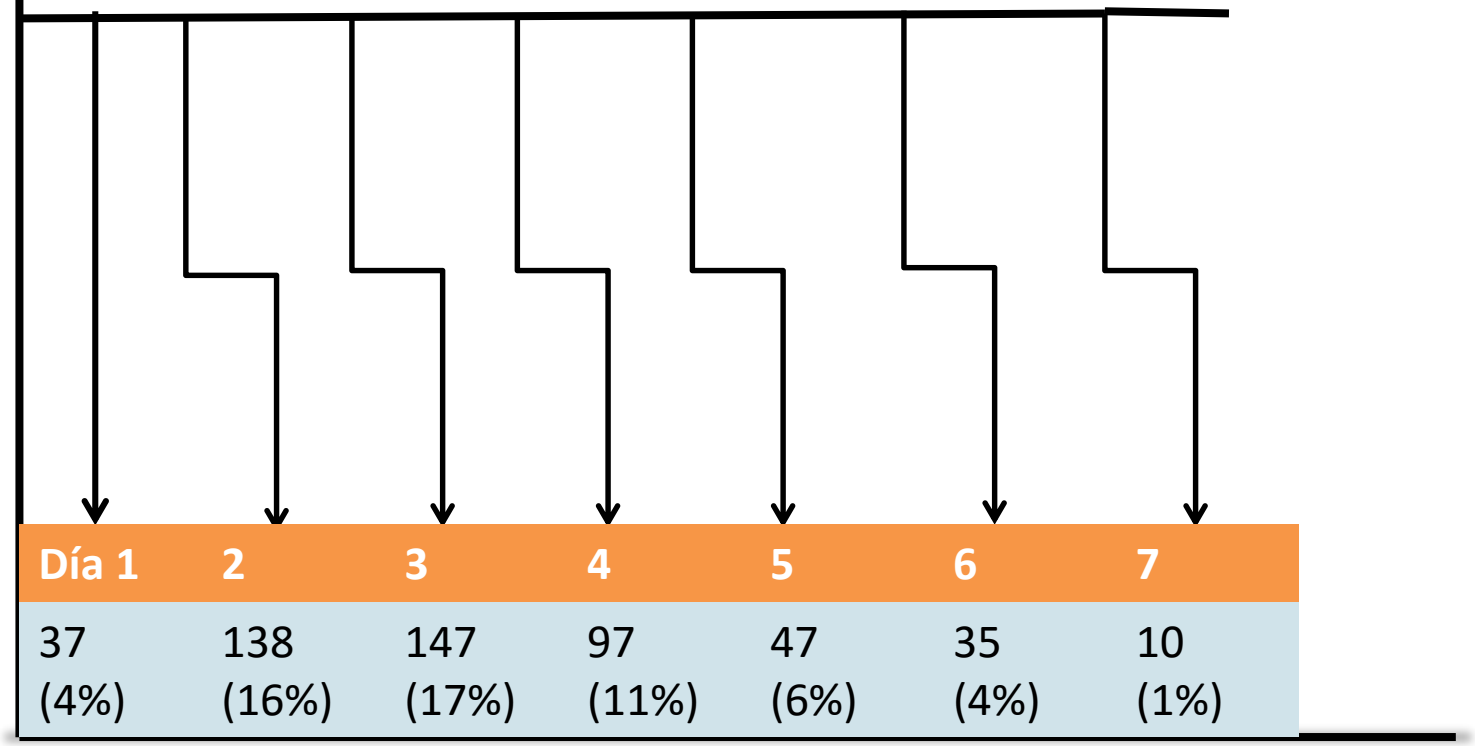
3 días

outcomes	Three day treatment group	Eight day treatment group	Difference (95% CI)
Day 10:			
Clinical cure (per protocol analysis)	50/54 (93)	56/60 (93)	0.1 (−9 to 10)
Clinical cure	50/56 (89)	56/63 (89)	0.4 (−11 to 12)
Bacteriological success	22/25 (88)	19/20 (95)	-7 (−23 to 9)
Radiological success	48/56 (86)	52/63 (83)	3 (−10 to 16)
Day 28:			
Clinical cure (per protocol analysis)	47/52 (90)	49/56 (88)	2 (−9 to 15)
Clinical cure	47/56 (84)	49/63 (78)	6 (−8 to 20)
Bacteriological success	20/25 (80)	15/20 (75)	5 (−20 to 30)
Radiological success	48/56 (86)	50/63 (79)	6 (−7 to 20)

el Moussaoui R, de Borgie CA, van den Broek P, et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. BMJ 2006; 332:1355–360.

868
Pacientes ingresado con neumonía

Candidatos a switch:
1. Mejoría de tos y disnea
2. Afebril
3. Leucos en descenso
4. Tolerancia oral



Día 1	2	3	4	5	6	7
37 (4%)	138 (16%)	147 (17%)	97 (11%)	47 (6%)	35 (4%)	10 (1%)

Días de tratamiento

VAP. 8 DAYS

- Among patients who had received appropriate initial empirical therapy, with the possible exception of those developing nonfermenting gram-negative bacillus infections, comparable clinical effectiveness against VAP was obtained with the 8- and 15-day treatment regimens. The 8-day group had less antibiotic use.
- Among patients who developed recurrent infections, multiresistant pathogens emerged less frequently in those who had received 8 days of antibiotics (42.1% vs 62.0% of pulmonary recurrences, *P* = .04).

Chastre J, Wolff M, Fagon J-Y, et al. Comparison of 8 vs 15 Days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 2003; 290:2588–98.

From: **Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults: A Randomized Trial**

JAMA. 2003;290(19):2588-2598. doi:10.1001/jama.290.19.2588

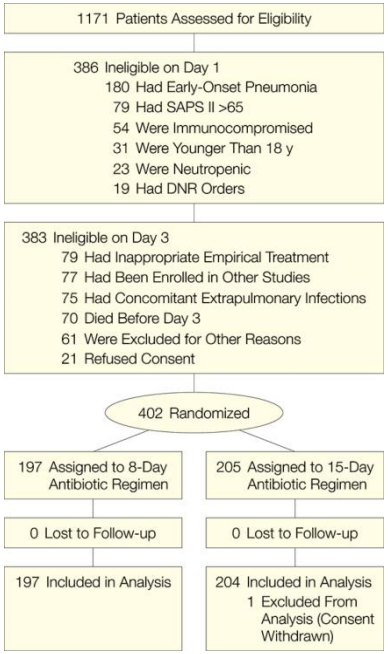


Figure Legend:

DNR indicates do not resuscitate; SAPS II, Simplified Acute PhysiologicScore II.

From: **Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults: A Randomized Trial**

JAMA. 2003;290(19):2588-2598. doi:10.1001/jama.290.19.2588

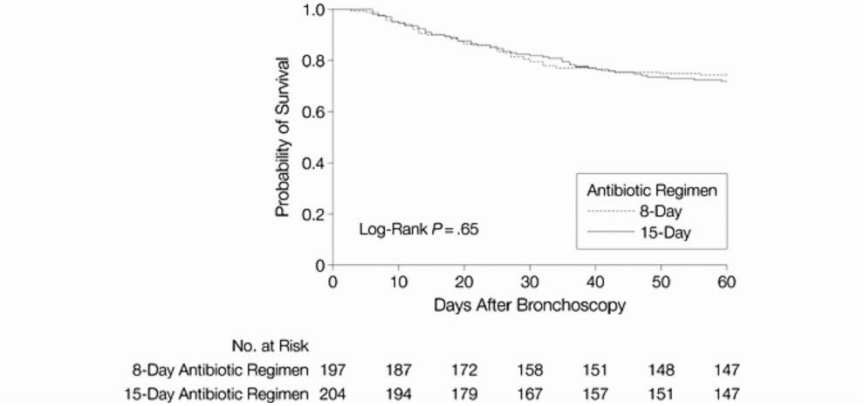
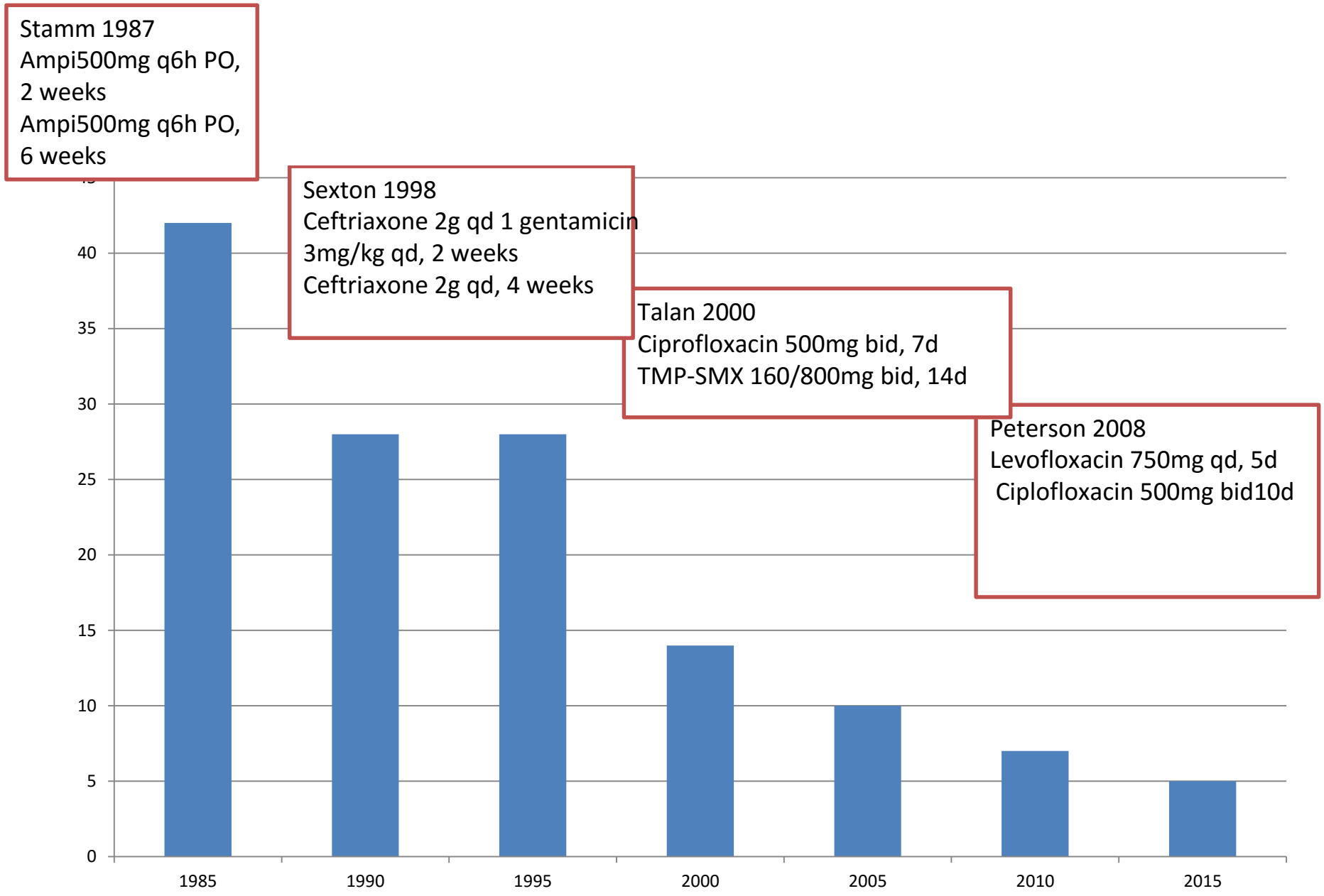


Figure Legend:

Probability of survival is for the 60 days after ventilator-assistedpneumonia onset as a function of the duration of antibiotic administration.


Stamm 1987
Ampi500mg q6h PO, 2 weeks
Ampi500mg q6h PO, 6 weeks
Sexton 1998
Ceftriaxone 2g qd 1 gentamicin 3mg/kg qd, 2 weeks
Ceftriaxone 2g qd, 4 weeks
Talan 2000
Ciprofloxacin 500mg bid, 7d
TMP-SMX 160/800mg bid, 14d
Peterson 2008
Levofloxacin 750mg qd, 5d
Ciplofloxacin 500mg bid10d
40
35
30
25
20
15
10
5
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1985
1990
1995
2000
2005
2010
2015

The NEW ENGLAND JOURNAL of MEDICINE

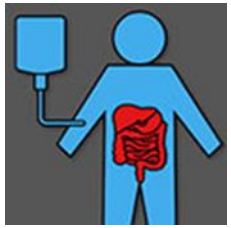
ORIGINAL ARTICLE

Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection

R.G. Sawyer, J.A. Claridge, A.B. Nathens, O.D. Rotstein, T.M. Duane, H.L. Evans, C.H. Cook, P.J. O'Neill, J.E. Mazuski, R. Askari, M.A. Wilson, L.M. Napolitano, N. Namias, P.R. Miller, E.P. Dellinger, C.M. Watson, R. Coimbra, D.L. Dent, S.F. Lowry,* C.S. Cocanour, M.A. West, K.L. Banton, W.G. Cheadle, P.A. Lipsett, C.A. Guidry, and K. Popovsky

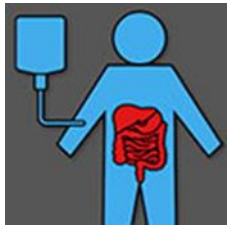
- control group: until 2±1 calendar days after the first day that the patient had
  - a maximum temperature of less than 38.0°C for 1 whole calendar day,
  - less than 11,000 peripheral white cells per cubic millimeter,
  - and the ability to meet more than half their nutritional needs enterally. A maximum of 10 days of therapy was allowed
- Study group: 4 days.

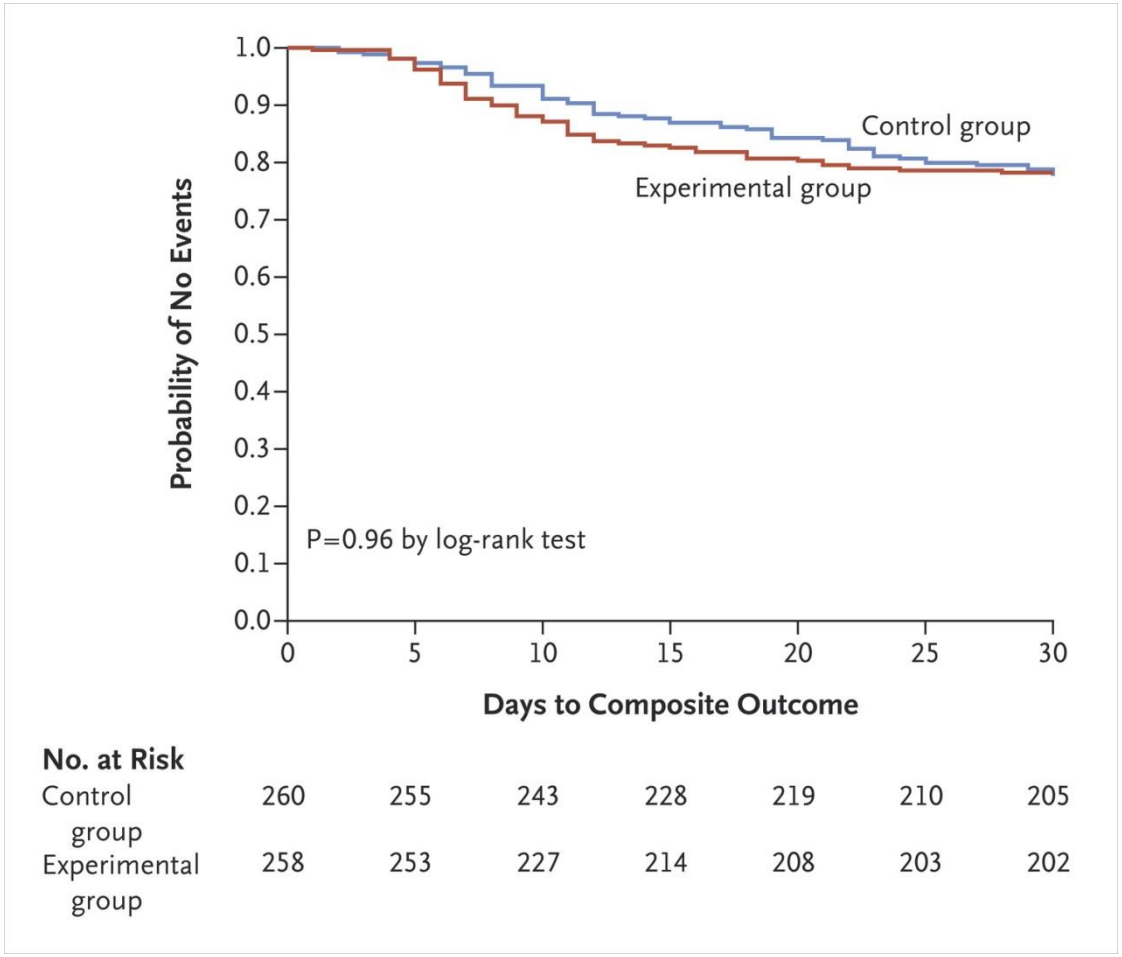
STOP IT



- The median duration of antimicrobial treatment was:
  - 4.0 days (interquartile range, 4.0 to 5.0) in the experimental group
  - 8.0 days (interquartile range, 5.0 to 10.0), control group
- The composite primary end point of surgical-site infection, recurrent intraabdominal infection, or death occurred in:
  - experimental group : 56 of 257 patients (21.8%),
  - control group :58 of 260 patients (22.3%)
  - (absolute difference, −0.5 percentage point, 95% confidence interval [CI], −7.0 to 8.0; P=0.92) (

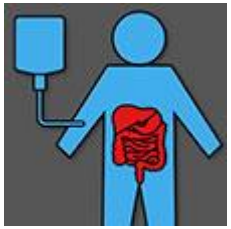
STOP IT





No. at Risk

Control group	260	255	243	228	219	210	205
Experimental group	258	253	227	214	208	203	202



Duración en infección piel y partes blandas

FDA guías para ensayos clínicos en piel:

- ABSSSI (exc. Pie diabético, fascitis necrosante, infección UPP). Etiología staph/strepto, las otras entidades, polimicrobianas, BGN…
- Evaluación de la respuesta clínica a las 48-72 horas: reducción > 20% de la lesión.

Introducción de linezolid y dalbavancina

Early clinical assessment of response to treatment of skin and soft-tissue infections: how can it help clinicians? Perspectives from Europe. Nathwani D, Dryden M, Garau J. Int J Antimicrob Agents. 2016 May 25

VI. Do Strategies to Encourage Prescriber-Led Review of Appropriateness of Antibiotic Regimens, in the Absence of Direct Input From an Antibiotic Stewardship Team, Improve Antibiotic Prescribing?

Recommendation

6. We suggest the use of strategies (eg, antibiotic time-outs, stop orders) to encourage prescribers to perform routine review of antibiotic regimens to improve antibiotic prescribing (weak recommendation, low-quality evidence).

Comment: Published data on prescriber-led antibiotic review are limited, but successful programs appear to require a methodology that includes persuasive or enforced prompting. Without such a mechanism, these interventions are likely to have minimal impact.

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PCT in ICU patients

- 4507 ICU patients were randomly assigned to the procalcitonin-guided group (761) or to standard-of-care (785).
- In the procalcitonin-guided group, a non-binding advice to discontinue antibiotics was provided if procalcitonin concentration had decreased by 80% or more of its peak value or to 0·5 µg/L or lower.
- Median duration of treatment was:
  - 5 days (3–9) in the procalcitonin-guided group
  - 7 days (4–11) in the standard-of-care group
  - (between-group absolute difference 1·22, 0·65–1·78, p<0·0001).

Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. Lancet Infect Dis. 2016 Feb 29.

PROA HUSE

Mantener tratamiento			5.192	47,45%
Modificar tratamiento				
Ajustar a las guías del hospital	1.032	31,27%		
Ajustar dosis/intervalo	761	23,06%		
Realizar desescalada	746	22,60%		
Suspender algún antibiótico	401	12,15%		
Añadir algún antibiótico	218	6,36%		
Realizar terapia secuencial	142	4,30%		
Total modificar			3.300	30,16%
Suspender tratamiento				
Tratamiento completado	1.220	71,90%		
Tratamiento no indicado	476	28,06%		
Total suspender			1.696	15,50%
Parada automática de profilaxis			753	6.88%
Total			10.941	100%

PROA HUSE

Total recomendación (n)	Aceptado	No aceptado	No deducible
Suspender tratamiento (1.696)	912	746	38
Tratamiento NO INDICADO(476)	197 (41,38%)	265 (55,67%)	14 (2,94%)
Tratamiento COMPLETADO(1.220)	715 (58,6%)	481 (39,4%)	24 (1,96%)
Modificar tratamiento (3.300)	1.704	1.413	183
Ajustar a las guías hospital (1032)	367 (35,52%)	617 (59,82%)	48 (4,64%)
Ajustar dosis/intervalo (761)	493 (64,86%)	209 (27,5%)	58 (7,63%)
Realizar desescalada (746)	386 (51,74%)	314 (42,09%)	46 (6,16%)
Suspender algún antibiótico (401)	230 (57,35%)	157 (39,15%)	14 (3,49%)
Añadir algún antibiótico (218)	134 (61,46%)	73 (33,48%)	11 (5,04%)
Realizar terapia secuencial (142)	93 (65,49%)	43 (30,28%)	6 (4,22%)

Conclusiones

¿Qué hacer para disminuir la duración de los tratamientos antibióticos en mi hospital?

- Guías con recomendaciones claras y concisas de duración.
- Ayudas a la prescripción:
  - Toda la profilaxis pautada con duración e identificada
  - Obligatoriedad de pautar fecha de fin o time-out
- Auditoría prospectiva de las prescripciones largas: ¿>7 días?
- Uso protocolizado de procalcitonina en determinadas infecciones.