

Y A-T-IL UNE PLACE POUR
UNE DUREE DE
TRAITEMENT
RACCOURCIE DANS LES
PNEUMONIES
COMMUNAUTAIRES

JNI Marseille

2008

PNEUMONIES COMMUNAUTAIRES – ANTIBIOTHERAPIE INITIALE (PROBABILISTE) et MORTALITE

- L'antibiothérapie initiale est un facteur pronostic appartenant au domaine de l'organisation du soin (donc accessible à modification et plus facile à évaluer).

→ **ATB initiale inefficace augmente la mortalité à 30 jours :**
- OR 4,7 (IC 95 % 2,5 – 8,5)

Leroy O et al ; Intensive Care Med 1995

→ **ATB initiale dans les 4 à 8 H suivant l'admission diminue la mortalité à 30 jours :**
- OR 0,85 (IC 95 % 0,75 - 0,96)

Meehan TP et al ; JAMA 1997, Houck PM et al ; Arch Intern Med 2004

- Conséquences probables sur des indicateurs autres que la mortalité (complications – durée d'hospitalisation – délais de récupération..)

DUREE DE TRAITEMENT DES PNEUMONIES COMMUNAUTAIRES

Organisation	Durée recommandée de traitement
IDSA / ATS 2007	Durée de Tt minimale: 5 jours (niveau de preuve I), apyrexie depuis 48 à 72 h et pas plus d'un signe d'instabilité avant arrêt du tt (niveau de preuve II). (recommandation modérée)
ERS / ESCMID 2005	Durée appropriée non établie Durée habituelle 7 à 10 jours (sécurité inconnue pour des durées inférieures) Bactéries intra cellulaires comme <i>L.pneumophila</i> : au moins 14 jours. (grade C4)
SPILF 2006	La durée classique du traitement est de 7 à 14 jours (10 jours en moyenne). Les nouvelles molécules (kétolides, FQ anti pneumococciques) permettent de diminuer cette durée.

Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults

A Randomized Trial

Jean Chastre, MD

Michel Wolff, MD

Jean-Yves Fagon, MD

Sylvie Chevret, MD

Franck Thomas, MD

Delphine Wermert, MD

Eva Clementi, MD

Jesus Gonzalez, MD

Dominique Jusserand, MD

Pierre Asfar, MD

Dominique Perrin, MD

Fabienne Fieux, MD

Sylvie Aubas, MD

for the PneumA Trial Group

Context The optimal duration of antimicrobial treatment for ventilator-associated pneumonia (VAP) is unknown. Shortening the length of treatment may help to contain the emergence of multiresistant bacteria in the intensive care unit (ICU).

Objective To determine whether 8 days is as effective as 15 days of antibiotic treatment of patients with microbiologically proven VAP.

Design, Setting, and Participants Prospective, randomized, double-blind (until day 8) clinical trial conducted in 51 French ICUs. A total of 401 patients diagnosed as having developed VAP by quantitative culture results of bronchoscopic specimens and who had received initial appropriate empirical antimicrobial therapy were enrolled between May 1999 and June 2002.

Intervention A total of 197 patients were randomly assigned to receive 8 days and 204 to receive 15 days of therapy with an antibiotic regimen selected by the treating physician.

Main Outcome Measures Primary outcome measures—death from any cause, microbiologically documented pulmonary infection recurrence, and antibiotic-free days—were assessed 28 days after VAP onset and analyzed on an intent-to-treat basis.

Results Compared with patients treated for 15 days, those treated for 8 days had neither excess mortality (18.8% vs 17.2%; difference, 1.6%; 90% confidence interval [CI], -3.7% to 6.9%) nor more recurrent infections (28.9% vs 26.0%; difference,

CONTEXTE DES ESSAIS CLINIQUES DANS LES PNEUMONIES COMMUNAUTAIRES

- ❑ Populations / lieux de prise en charge très hétérogènes (ambulatoires / hospitalisées / soins intensifs)
 - ❑ Diagnostic clinique = probabilité
 - ❑ Paramètres microbiologiques (initiaux / suivi) : rares à exceptionnels ❑ analyses d'échecs / corrélations clinico-microbiologiques problématiques
 - ❑ Traitement probabiliste
 - ❑ Hétérogénéité du moment de prise en charge par rapport au début de l'infection
- complexité de mise en place des essais d'intervention

DUREE DE TRAITEMENT DES PNEUMONIES COMMUNAUTAIRES

- Guérison = absence de rechute
- Stabilité clinique (réponse clinique favorable) = « contrôle de l'infection »

Contrôle de l'infection est sous l'influence de nombreux facteurs

HÔTE

Comorbidités
Défenses locales et générales
(clairance bactérienne)

MICROBIENS

Virulence
Inoculum
Susceptibilité ATB

MALADIE

Extension locale/générale
Complications
Délai avant prise en charge

Tt ATB

Activité anti microbienne
Propriétés PK / PD

DUREE DE TRAITEMENT DES PNEUMONIES COMMUNAUTAIRES

- ❑ Individualisation de la durée de traitement
(même problématique que relais IV / PO, durée de séjour...etc..)
- ❑ Nécessité d'indicateurs de stabilité clinique / contrôle de l'infection
- ❑ Relations indicateurs de stabilité clinique et :
 - évolution / événements / complications
 - facteurs liés à stabilité clinique
- ❑ Essais cliniques interventionnels :
 - durée « usuelle » VS durée dépendante des indicateurs

**INDICATEURS CLINIQUES
ET / OU BIOLOGIQUES DU
CONTRÔLE DE L'INFECTION**

Table 10. Criteria for clinical stability.

Temperature $\leq 37.8^{\circ}\text{C}$

Heart rate ≤ 100 beats/min

Respiratory rate ≤ 24 breaths/min

Systolic blood pressure ≥ 90 mm Hg

Arterial oxygen saturation $\geq 90\%$ or $\text{pO}_2 \geq 60$ mm Hg on room air

Ability to maintain oral intake^a

Normal mental status^a

NOTE. Criteria are from [268, 274, 294]. pO_2 , oxygen partial pressure.

^a Important for discharge or oral switch decision but not necessarily for determination of nonresponse.

Time to Clinical Stability in Patients Hospitalized With Community-Acquired Pneumonia

Implications for Practice Guidelines

Ethan A. Halm, MD, MPH; Michael J. Fine, MD, MSc; Thomas J. Marrie, MD; Christopher M. Coley, MD;

Wishwa N. Kapoor, MD, MPH; D. Scott Obrosky, MS; Daniel E. Singer, MD

JAMA, 1998;279:1452-57

Table 3.—Effect of Different Definitions of Stability and Initial Disease Severity on Time to Overall Clinical Stability (N = 610)*

Definition	Definition of Stability			Pneumonia Severity Index Risk Class, d							
				Class I-III		Class IV		Class V		All Patients	
	Temperature, °C (°F)	O ₂ Saturation, %	Respiratory Rate Breaths/min	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range
A	≤38.5 (101)	≥90	≤24	3	2-4	3	2-7	5	3-9	3	2-5
B	≤37.8 (100)	≥90	≤24	3	2-5	4	2-7	6	3-9	3	2-6
C	≤37.2 (99)	≥92	≤24	4	3-7	6	3-9	7	4-11	5	3-8
D	≤37.2 (99)	≥92	≤20	6	3-12	7	3-16	10	6-17	6	4-13
E	≤37.2 (99)	≥94	≤20	6	4-15	9	4-17	13	7-17	7	4-17

*All definitions of stability include heart rate ≤100 beats/min, systolic blood pressure ≥90 mm Hg, ability to eat, and baseline mental status. The day of admission is day 1. For each definition, the time to stability is the first day that all 5 vital signs, ability to eat, and mental status were stable. The definition of stable oxygenation is oxygen saturation at least equal to the specified value or PaO₂ ≥60 mm Hg. Pneumonia Severity Index¹⁴ risk classes I through III are low risk; class IV is moderate risk; and class V is high risk. Time to stability was longer for patients in classes IV and V compared with patients in classes I through III (*P* < .001). There were no differences between classes I, II, and III.

Table 4.—Risk of Admission to a Special Care Unit Before and After Reaching Stability*

Definition	Definition of Stability			Admission to a Special Care Unit (N = 91)	
	Temperature, °C (°F)	O ₂ Saturation, %	Respiratory Rate, Breaths/min	Before Stable, No. (%)	After Stable, No. (%)
A	≤38.3 (101)	≥90	≤24	85 (14)	6 (1)
B	≤37.8 (100)	≥90	≤24	85 (14)	6 (1)
C	≤37.2 (99)	≥92	≤24	87 (14)	4 (0.6)
D	≤37.2 (99)	≥92	≤20	88 (15)	3 (0.5)
E	≤37.2 (99)	≥94	≤20	89 (15)	2 (0.3)

*All definitions of vital sign stability include criteria of heart rate ≤100 beats/min, systolic blood pressure ≥90 mm Hg, ability to eat, and baseline mental status. Special care units include intensive care units, coronary care units, and telemetry monitoring units.

Reaching Stability in Community-Acquired Pneumonia: The Effects of the Severity of Disease, Treatment, and the Characteristics of Patients

Rosario Menéndez,¹ Antoni Torres,³ Felipe Rodríguez de Castro,⁵ Rafael Zalacaín,⁶ Javier Aspa,⁷ Juan J. Martín Villasclaras,⁹ Luis Borderías,¹⁰ José M. Benítez Moya,¹¹ Juan Ruiz-Manzano,¹² José Blanquer,² Diego Pérez,² Carmen Puzo,⁴ Fernando Sánchez-Gascón,¹³ José Gallardo,¹⁴ Carlos J. Álvarez,⁹ and Luis Molinos,¹⁵ for the Neumofail Group

¹Servicio de Neumología, Hospital Universitario La Fe, and ²Hospital Clínico, Valencia, ³Instituto de Neumología y Alergia, Hospital Clínic, and ⁴Hospital San Pablo, Barcelona, ⁵Hospital Dr Negrín, Las Palmas de Gran Canaria, ⁶Hospital de Cruces, Bilbao, ⁷Hospital de la Princesa and ⁸Hospital 12 de Octubre, Madrid, ⁹Hospital Carlos Haya, Málaga, ¹⁰Hospital San Jorge, Huesca, ¹¹Hospital Virgen de la Macarena, Sevilla, ¹²Hospital Germans Trias i Pujol, Badalona, ¹³Hospital General Universitario, Murcia, ¹⁴Hospital General, Guadalajara, and ¹⁵Hospital Ntra Sra de Covadonga, Oviedo, Spain

CID, 2004;39:1783-90

- Prospective, multicentrique, Espagne, 15 hôpitaux
- 1145 patients adultes, Fine I-III: 58 %, IV-V: 42 %
- Dg microbiologique: 18,3 %, échecs: 10,8 %, décès: 5,6 %
- Exclus: Immuno déprimés (Cancer en cours de Tt, neutropénie, CD4 < 500....)
- Stabilité clinique définie selon critères de Halm et al. ($\theta \leq 37,2^{\circ}\text{C}$ vs $37,8^{\circ}\text{C}$)

Table 4. Results of the 2 multivariate Cox studies on the predictors of clinical stability

Independent variable	First Cox model, initial variables		Second Cox model, initial and evolutive variables	
	HR ^a (95% CI)	P	HR ^a (95% CI)	P
Dyspnea				
Yes	0.76 (0.66–0.87)	.0001	0.79 (0.69–0.91)	.0009
No	1.0 (referent)		1.0 (referent)	
Confusion				
Yes	0.66 (0.52–0.83)	.0005	0.61 (0.48–0.97)	<.0001
No	1.0 (referent)		1.0 (referent)	
Chronic bronchitis				
Yes	...		0.81 (0.70–0.94)	.005
No	...		1.0 (referent)	
Pleural effusion				
Yes	0.67 (0.51–0.90)	.007	...	
No	1.0 (referent)		...	
Multilobed CAP				
Yes	0.72 (0.62–0.84)	.0001	0.84 (0.72–0.98)	.027
No	1.0 (referent)		...	
Risk class^b				
I–II	1.0 (referent)		1.0 (referent)	
III–V	0.73 (0.63–0.84)	.0001	0.73 (0.63–0.85)	<.0001
Adherence to guidelines				
Yes	1.22 (1.04–1.44)	.01	...	
No	1.0 (referent)		...	
Treatment failure				
Yes	...		0.31 (0.25–0.40)	<.0001
No	...		1.0 (referent)	
Cardiac complications				
Yes	...		0.66 (0.52–0.84)	.0001
No	...		1.0 (referent)	
Respiratory complications				
Yes	...		0.77 (0.61–0.98)	.039
No	...		1.0 (referent)	
Empyema				
Yes	...		0.57 (0.36–0.90)	.017
No	...		1.0 (referent)	
ICU admission				
Yes	...		0.57 (0.42–0.77)	.0003
No	...		1.0 (referent)	

NOTE. CAP, community-acquired pneumonia; HR, hazard ratio; ICU, intensive care unit.
^a HR of clinical stability. The probability of reaching clinical stability is higher when the HR is >1 and lower when the HR is <1.
^b Risk class of Fine et al. [12].

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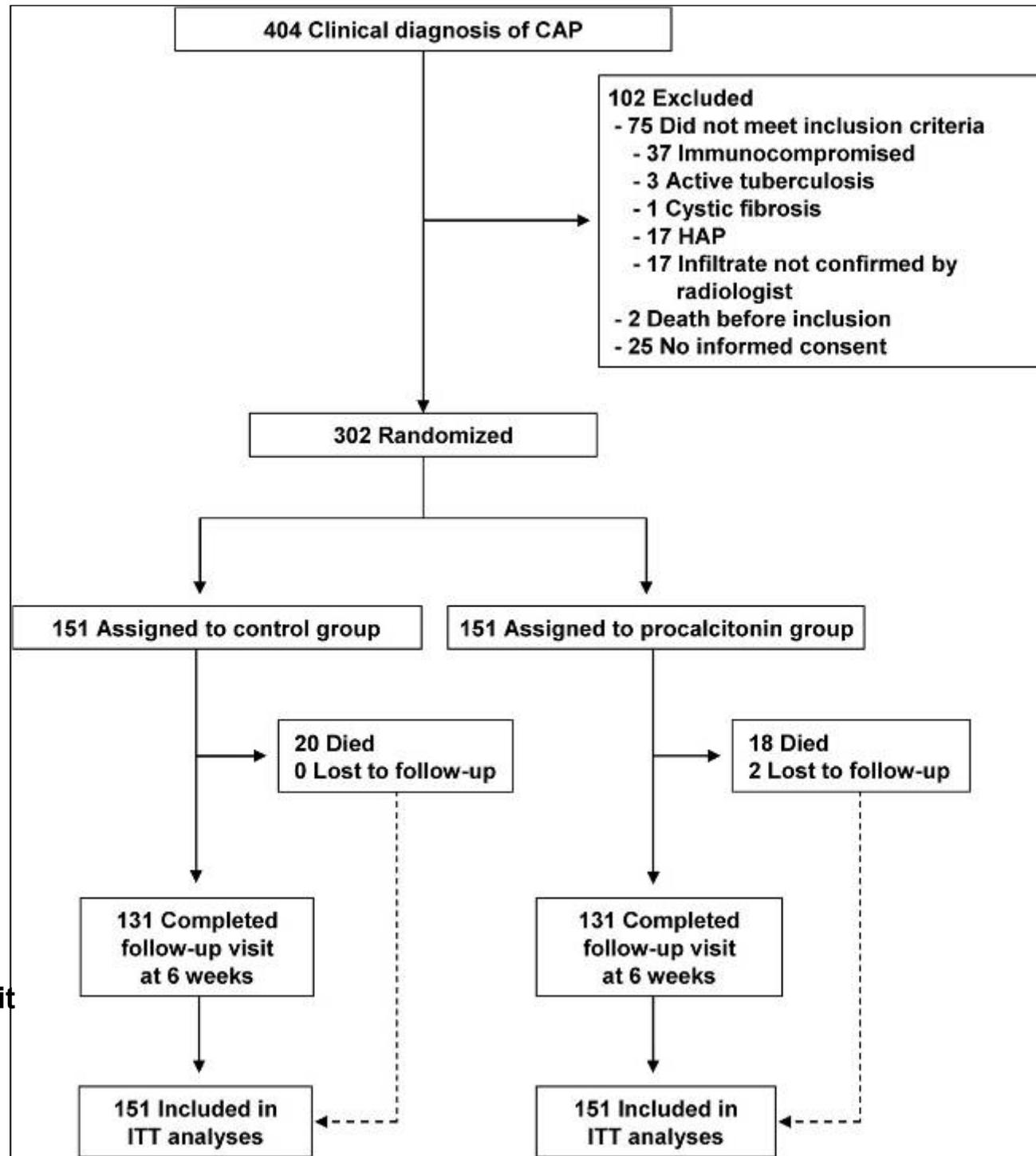
Procalcitonin Guidance of Antibiotic Therapy in Community-acquired Pneumonia

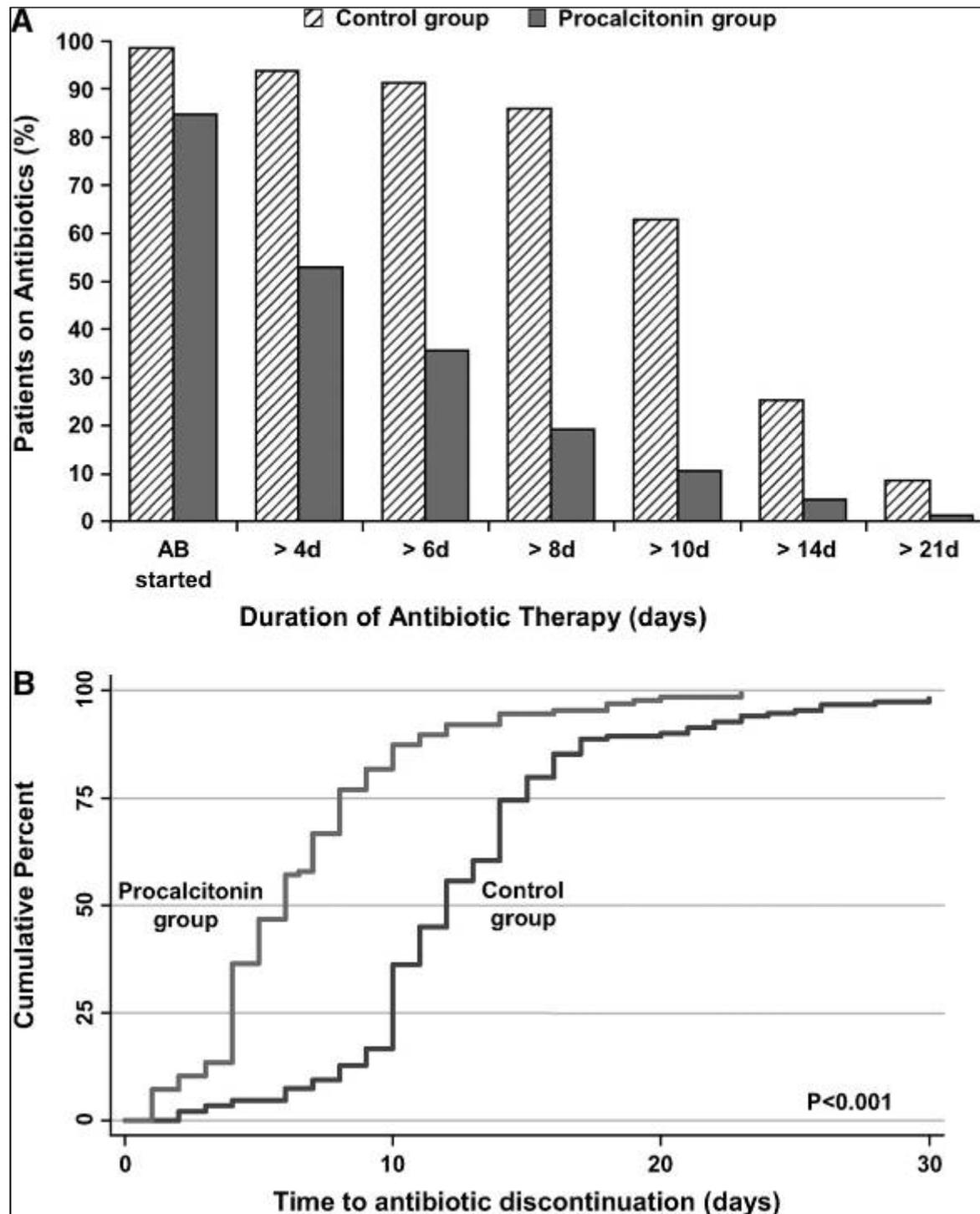
A Randomized Trial

Mirjam Christ-Crain, Dalana Stolz, Roland Bingisser, Christian Müller, David Miedinger, Peter R. Huber, Werner Zimmerli, Stephan Harbarth, Michael Tamm, and Beat Müller

Departments of Internal Medicine, Endocrinology, Pneumology, Emergency Medicine, and Clinical Chemistry, University Hospital, Basel; Medical University Clinic, Kantonsspital, Liestal; and Division of Hospital Epidemiology, University Hospital, Geneva, Switzerland

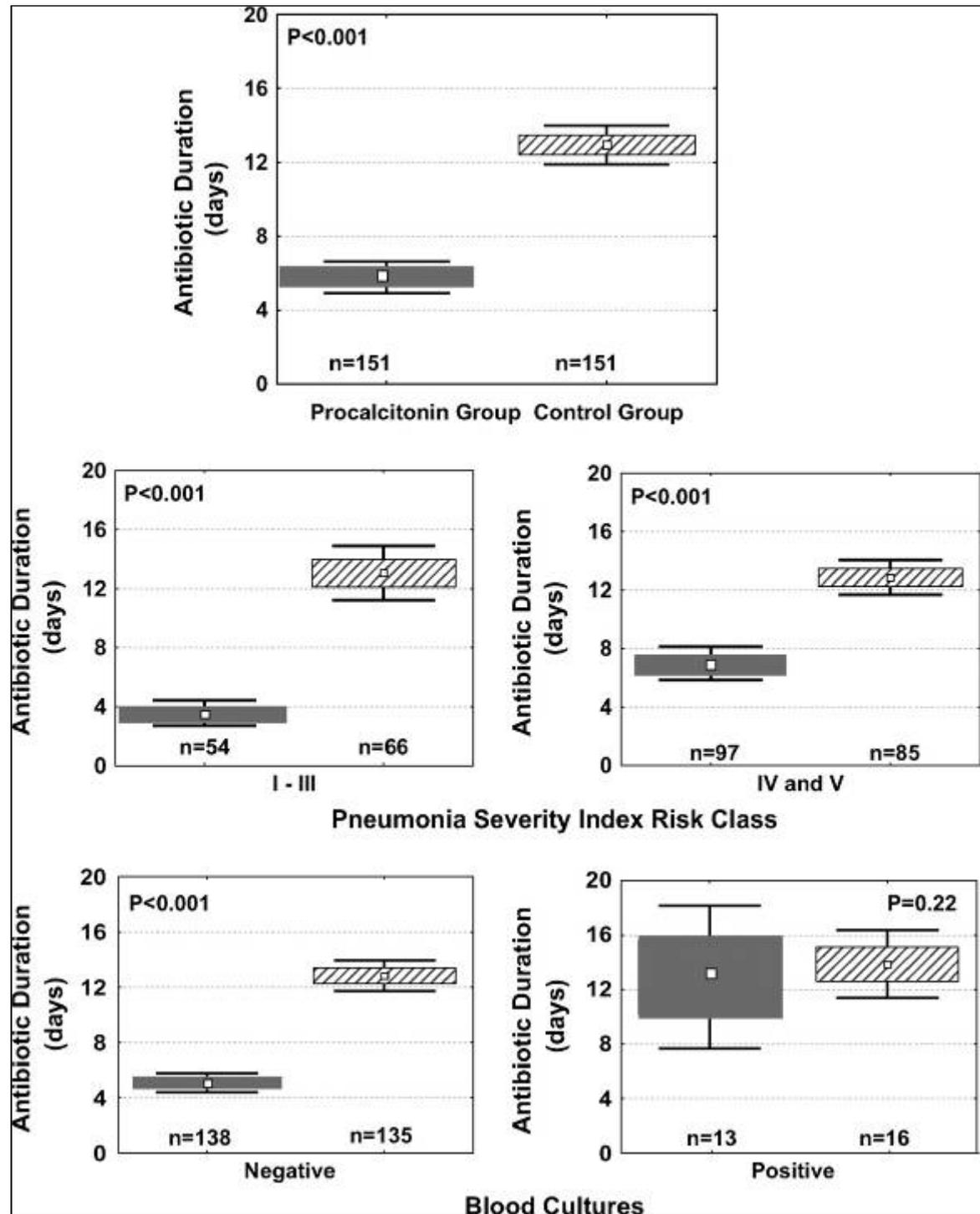
Am J Respir Crit Care Med 2006;174:84-93





Am J Respir Crit
Care Med
2006;174:84-93

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Care Med
2006;174:84-93



TRAITEMENT RACCOURCI DES PNEUMONIES COMMUNAUTAIRES POINTS CLES

- ❑ Sélection des patients**
- ❑ Indicateurs cliniques (ou biologiques) validés de contrôle de l'infection**
- ❑ Traitement probabiliste adapté (recommandations) au profil de sélection des patients**

LES ESSAIS CLINIQUES

Treatment of lobar pneumonia in Papua New Guinea: short course chemotherapy with penicillin or chloramphenicol

G. H. Rée* and M. Davis†

*Goroka Base Hospital, Goroka, Eastern Highlands Province,
Papua New Guinea*

Summary

In an attempt to reduce the costs of treatment we treated 203 patients with clinical lobar pneumonia either with penicillin or chloramphenicol for periods of up to 24 hours after remission of fever (mean 2.4 days). The results show that for patients with moderately severe pneumonia short-course treatment is as effective as the more traditional treatment. Patients with severe pneumonia may respond to such treatment but require careful evaluation before stopping treatment.

Crystalline penicillin		Chloramphenicol	
4 mega units per day until 24 hours after defervescence of fever followed by:		1.5g per day orally until 24 hours after defervescence of fever followed by:	
No further treatment	Procaine penicillin 1.2 mega units i.m. daily until discharge	No further treatment	Chloramphenicol 1.5g daily until discharge

Present addresses:

* Hospital for tropical Diseases, 4 St Pancras Way, London NW1.

† Madang General Hospital, Yomba, Madang Province, PNG.

0163-4453/83/010029+04 \$02.00/0

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Rée GH et al, Journal of infection 1983

Table I

	Penicillin		Chloramphenicol		Total
	Standard	SCC	Standard	SCC	
Total patients	52	52	48	51	203
Male	32	30	23	27	112
Females	20	22	25	24	91
Severe	14	19	13	15	61
Deaths	1	2	1	0	4
Days in hospital*	6.7	6.8	5.6	6.5	6.4
	±3.4	±4.1	±3.6	±2.7	±3.4
Previous treatment	4	2	6	10	22
Duration of treatment (days)	6.2‡	2.1‡	5.3§	2.8§	
	±2.69	±1.20	±2.95	±1.41	

* Mean of hospital stay in days \pm 1 SD.

† No significant difference between standard and SCC ($P > 0.05$) or between penicillin and chloramphenicol ($P > 0.05$).

‡ Difference is statistically significant ($t = 9.816$, $P < 0.01$).

§ Difference is statistically significant ($t = 5.37$, $P < 0.01$).

- Apperix = 3j & 6 groups.

RP

One-day treatment for lobar pneumonia

D. R. SUTTON, A. C. B. WICKS, and LINDSAY DAVIDSON

Department of Medicine, University College of Rhodesia

An investigation was undertaken to discover whether a single intramuscular dose of long-acting (or mixed long-acting and crystalline) penicillin or a single day's therapy with oral penicillin was satisfactory treatment for lobar pneumonia. These treatments were compared with standard hospital oral and injection therapies. All the experimental treatment regimes were found to be satisfactory. They provide justification for treating lobar pneumonia on an out-patient basis in order to save hospital admissions.

One-day treatment for lobar pneumonia

TABLE III
RESULTS OF TREATMENT

	Treatment Group							Total
	A	B	C	D	E	F	G	
No. of patients	20	28	20	23	19	19	21	150
Radiological and clinical resolution	19	27	18	20	18	18	19	139
Failures (see text)	1	1	2	3	1	1	2	11
Complications								
Effusions	0	0	0	1	1	0	1	3
Pleural thickening	1	1	0	0	0	0	0	2
Deaths	0	0	1	0	0	0	0	1
Days for temperature to return to normal and remain normal (mean ± S.D.)	3.1 ± 1.6	2.6 ± 0.9	3.4 ± 1.7	3.2 ± 1.3	2.6 ± 1.6	2.9 ± 1.7	2.6 ± 1.6	

apart from residual sputum production. Three penicillin regimens were compared with standard hospital oral and injection therapies.

DUREE DE TRAITEMENT DES PNEUMONIES COMMUNAUTAIRES ESSAIS CLINIQUES

Auteur Année Promoteur	Essai	Critère principal	Patients	Microbio Comorbidité Décès	Résultats	Indicateur clinique OK AMM OK Reco
Dunbar CID 2003 Ortho Mc Neil	Levo 750 od / 5j vs Levo 500 od/10j R,DA,C,Ninf 70 centres USA	PP succès clinique J 7 à 14j post ↓ Tt	ITT 256 vs 272 77 à 70%PP PSI I-III 86%- 82% PSI IV 14%-18% 53± 17 ans	PP pneumo ECBC:42/390 Hémocs:14 Atypiques: 131 Comorbidités ? Décès ?	92,4% vs 91,1%	NON NON * NON
Tellier G JAC 2004 Aventis	Teli 800 od/5j vs 800 od / 7j vs Clari 500 bid/10j R,DA,C,EQ 77 centres	PP succès clinique J17-21 post début de Tt	187 vs 191 vs 181 PSI I-III 93%,93%,94% Age m:42 ans >65: 15 à 20%	PP pneumo ECBC:80/466 Hémocs:26 Comorbidités ? Décès:0,8%	89,3%vs 88,8% vs 91,8%	NON OUI OUI

* Lévoﬂoxacine 750 mg: pas d'AMM en France

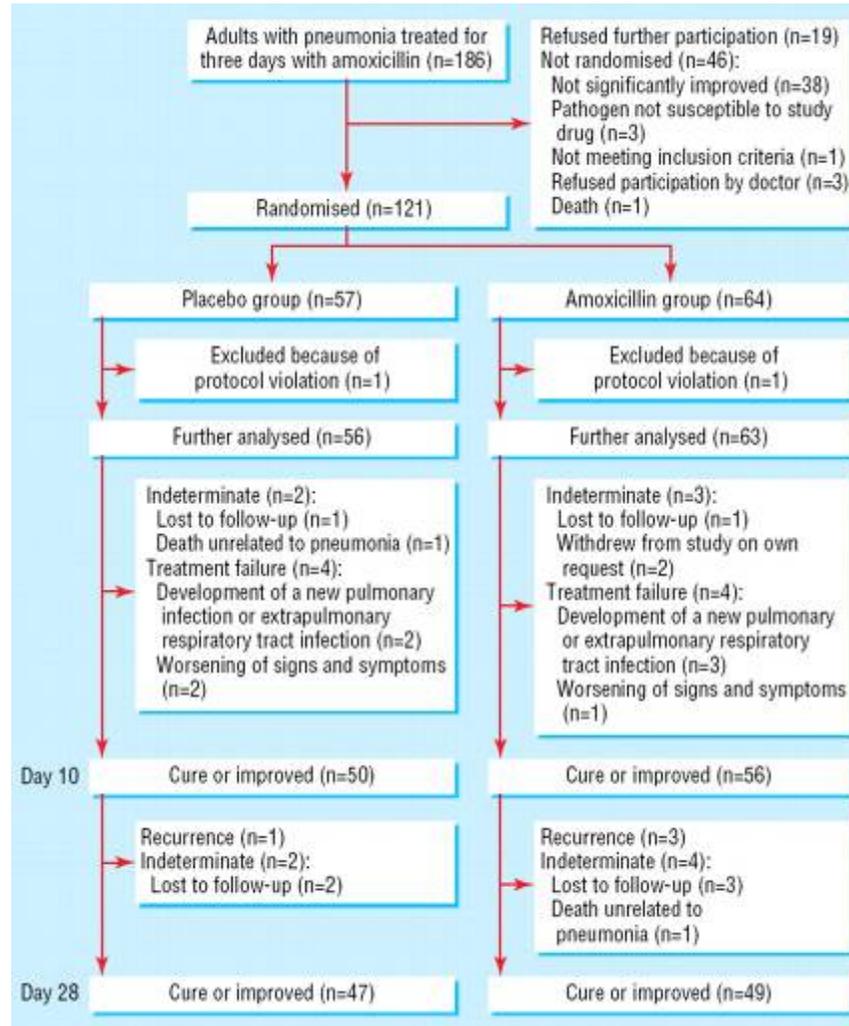
Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study

Rachida el Moussaoui, Corianne A J M de Borgie, Peterhans van den Broek, Willem N Hustinx, Paul Bresser, Guido E L van den Berk, Jan-Werner Poley, Bob van den Berg, Frans H Krouwels, Marc J M Bonten, Carla Weenink, Patrick M M Bossuyt, Peter Speelman, Brent C Opmeer, Jan M Prins

BMJ 2006;332:1355

- prospective, double aveugle, contrôlée non infériorité contre placebo
- multicentrique, Hollande, 2000-2003, adultes hospitalisés PSI \leq 110
- exclus: immuno déprimés, hospitalisation récente, nursing home, PaO₂ \leq 50, empyème, suspicion de déglutition, atypique, Klebsielle, staphylococoque.
- indicateur: score clinique (4 points - respiratoire / 6 points - général)
- Tt empirique Amoxicilline IV – si réponse clinique à 72h, randomisation Amox 750 mg PO tid VS placebo, durée 5 jours.
- 186 patients inclus, 121 randomisés. 70 % PSI I-III. Pneumocoque n=36 (31%). 14 hémocs +

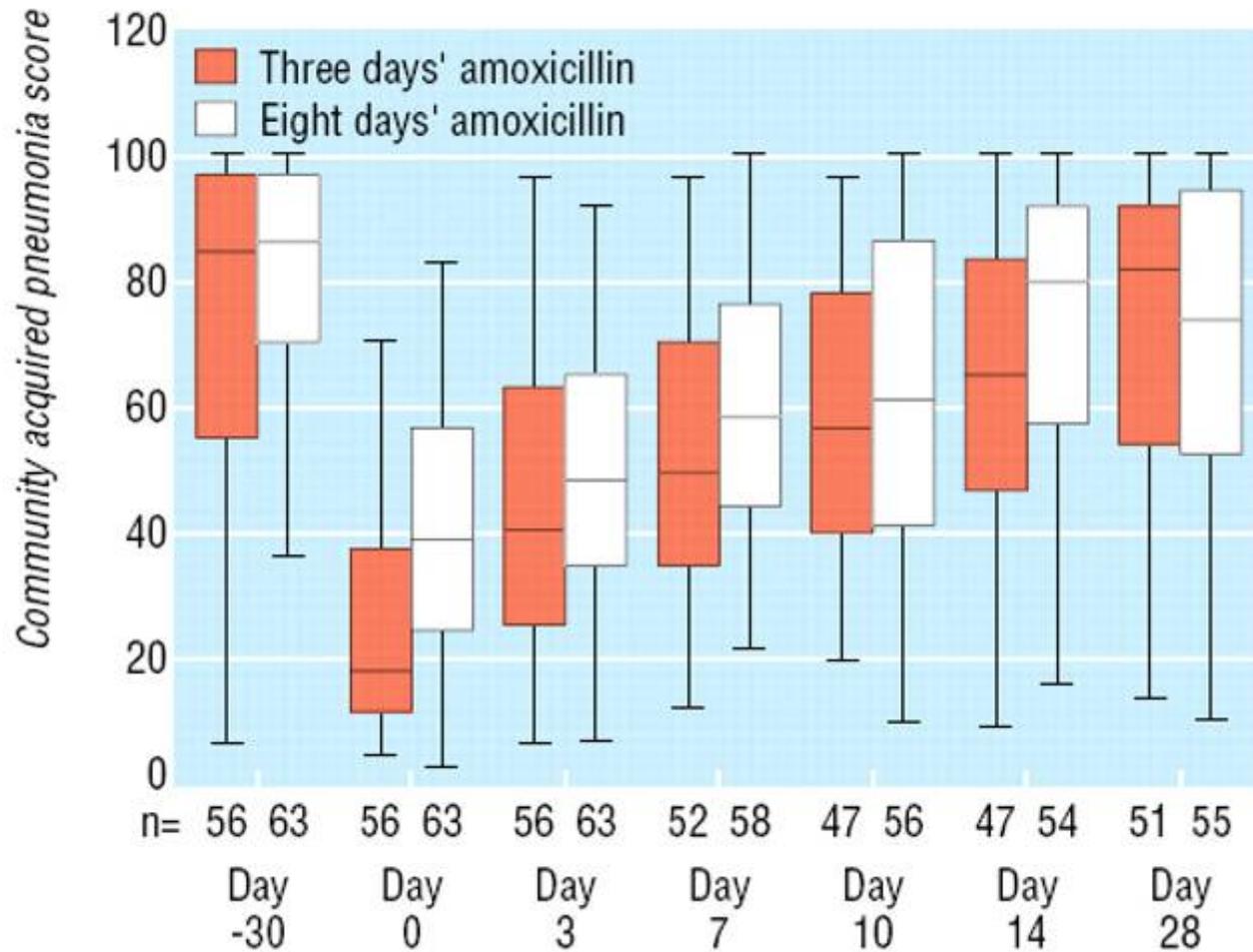
Fig 1 Trial profile



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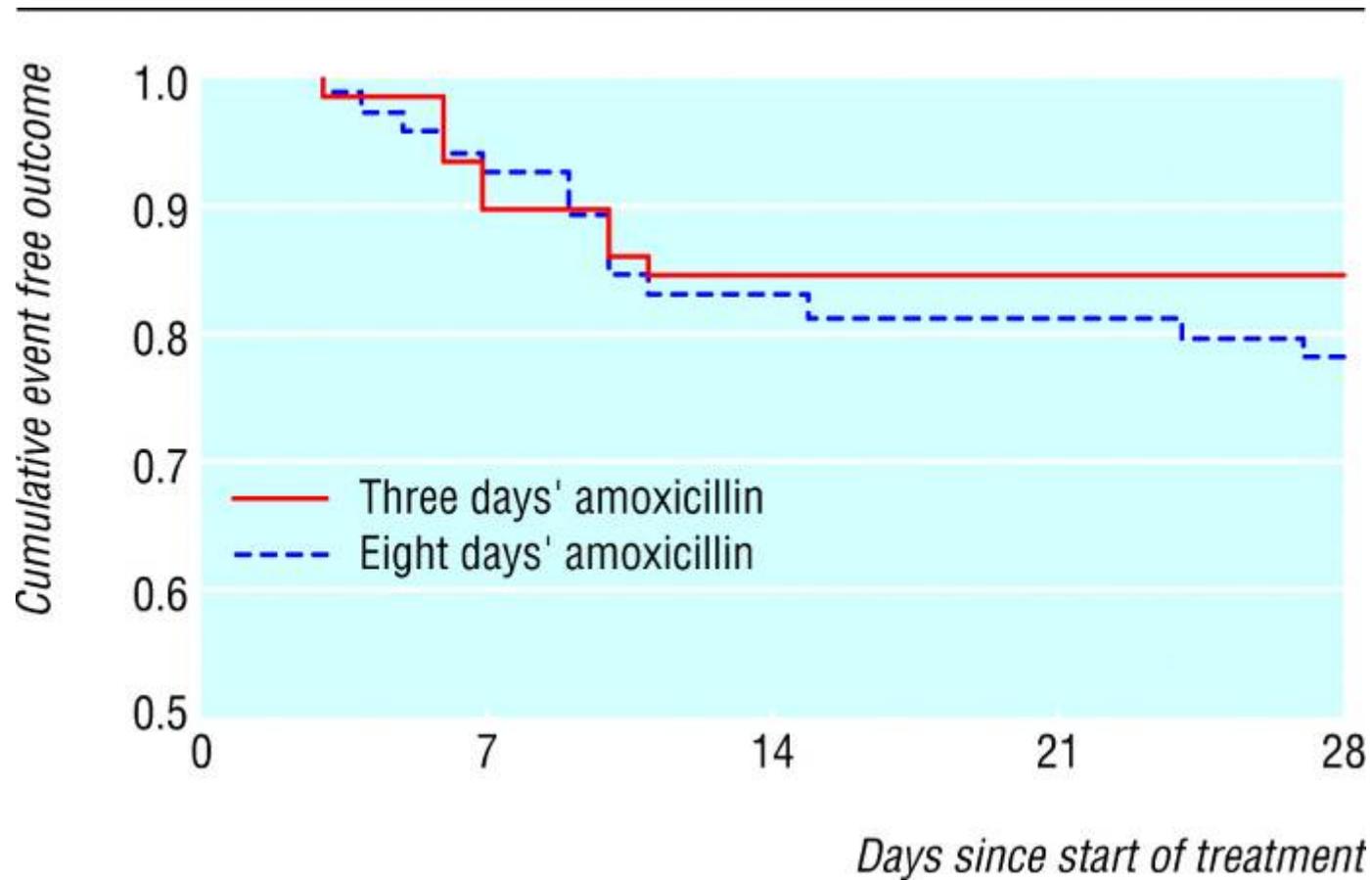
Fig 2 Community acquired pneumonia scores (medians, interquartile ranges, 10th to 90th centiles) during treatment and follow-up. Day -30=score before pneumonia; day 0=start of treatment; day 10=test of cure; day 28=end of follow-up



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**Fig 3 Proportion of patients considered clinical successes in intention to treat population.
Day 3=day of randomisation**

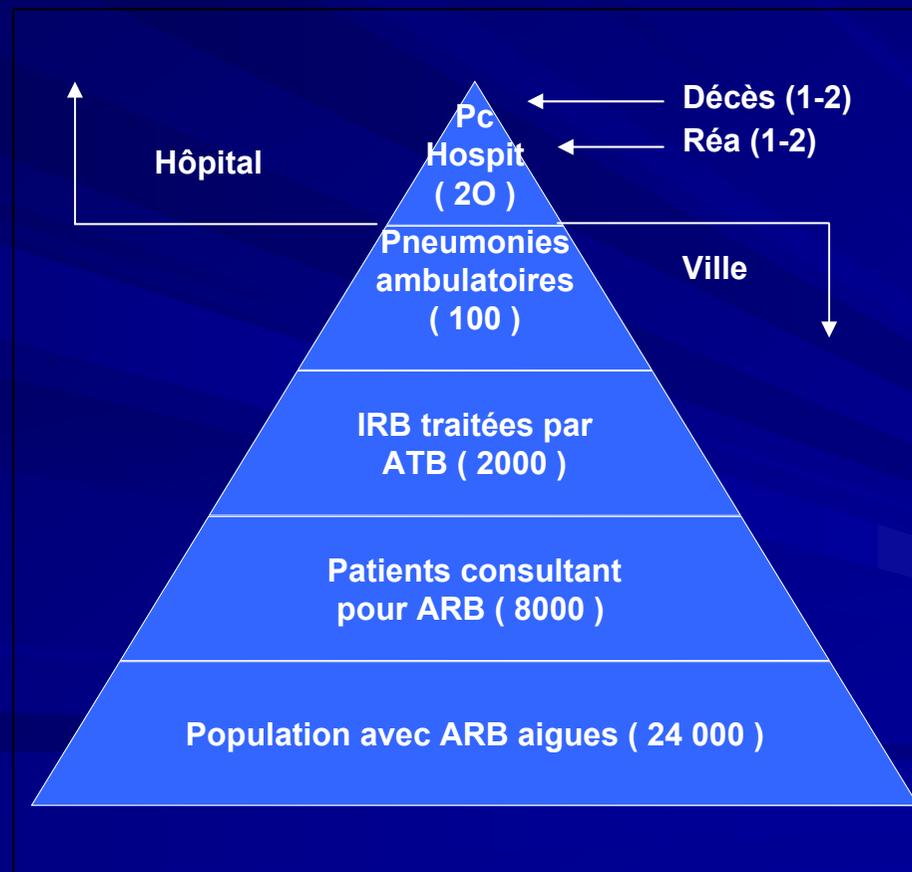


el Moussaoui, R. et al. BMJ 2006;332:1355

TRAITEMENT RACCOURCI DES PNEUMONIES COMMUNAUTAIRES

CONCLUSIONS

Approche scientifique complexe



AFFECTIONS RESPIRATOIRES BASSES (ARB), INFECTIONS RESPIRATOIRES BASSES (IRB),
PNEUMONIES COMMUNAUTAIRES (Pc). Macfarlane Thorax 2000.

TRAITEMENT RACCOURCI DES PNEUMONIES COMMUNAUTAIRES CONCLUSIONS

□ Pc « de ville » (ambulatoires):

- quantitativement les plus importantes, les moins sévères, les plus aptes à recevoir un tt court.
- Pb: noyées dans IRB, indicateurs de contrôle de l'infection difficiles à appliquer.
- chez patients sélectionnés; Télithromycine 5j ou Amox 3j à confirmer
- priorité plutôt au bénéfice collectif (réduction globale de la prescription) qu'individuel.

□ Pc hospitalisées:

- population hétérogène, mais facile à décrire, la meilleure pour développer les essais (indicateurs applicables, suivi possible, etc...)
- intérêt potentiel des FQ anti pneumo (↓ durée de séjour...T2A...)
- validité externe importante

□ Pc Réanimation:

- population infime, terrain expérimental pour recherche clinique / biologique
- validité externe limitée

TRAITEMENT RACCOURCI DES PNEUMONIES COMMUNAUTAIRES CONCLUSIONS

**DUREE DE TRAITEMENT QUI
PEUT ET DOIT ETRE
RACCOURCIE SANS RISQUE**

- TRAITEMENT NON JUSTIFIE

- TRAITEMENT INEFFICACE