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Pneumonie aigue communautaire et bon usage des antibiotiques

Aurélien Dinh

Infectiologie

Hôpitaux Universitaires Paris Ile de France Ouest

Conflits d'intérêts

- PHRC national 2013
- PHRC national 2016

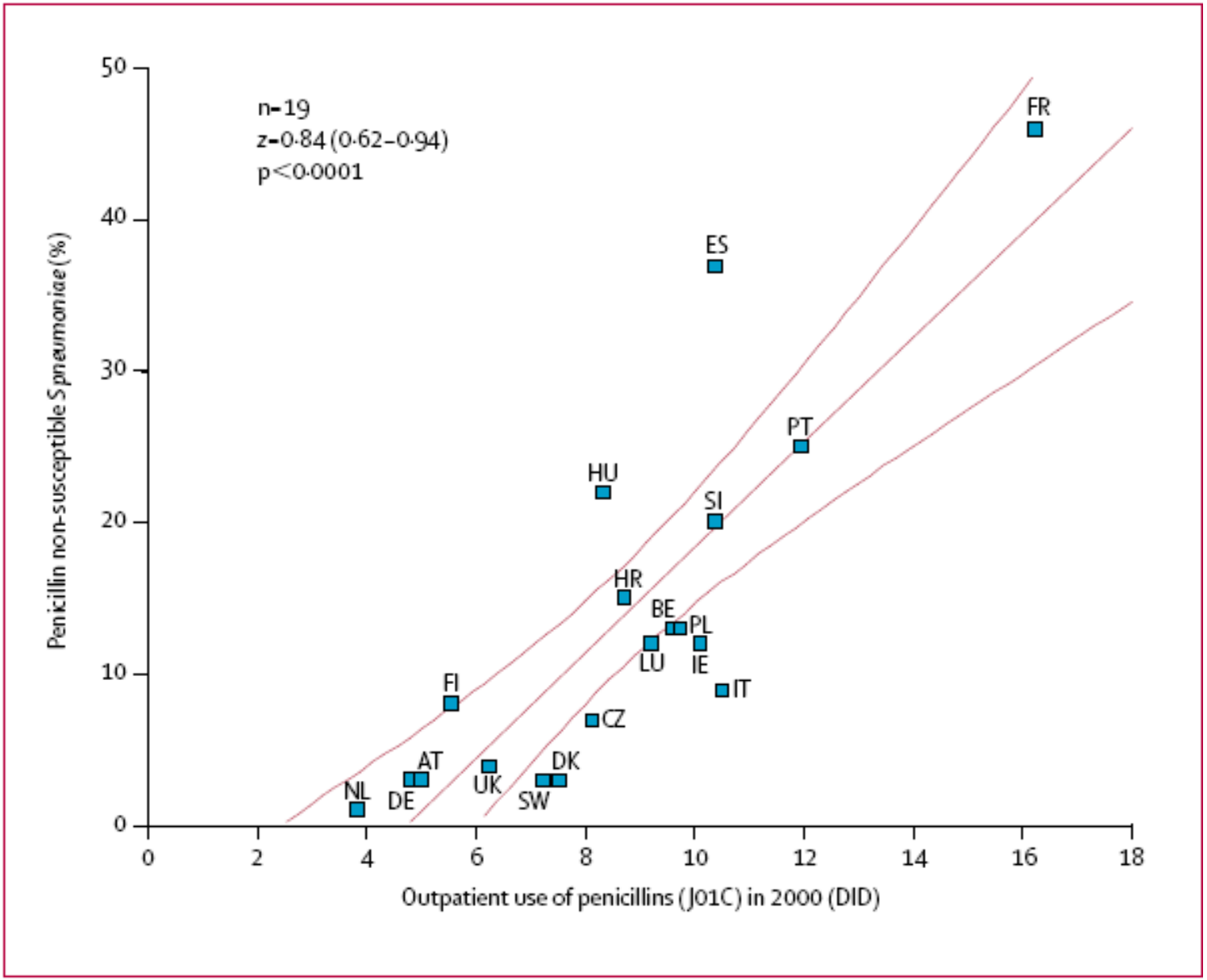


Figure 6: **Correlation between penicillin use and prevalence of penicillin non-susceptible *S pneumoniae***
AT, Austria; BE, Belgium; HR, Croatia; CZ, Czech Republic; DK, Denmark; FI, Finland; FR, France; DE, Germany; HU, Hungary; IE, Ireland; IT, Italy; LU, Luxembourg; NL, The Netherlands; PL, Poland; PT, Portugal; SI, Slovenia; ES, Spain; UK, England only.

H. Goosens
Lancet 2005

Antibiotic-Resistant Bugs in the 21st Century
A Clinical Super-Challenge

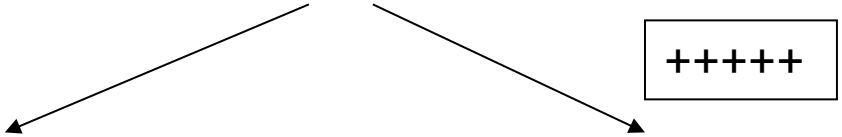
N ENGL J MED 360;5 NEJM.ORG JANUARY 29, 2009

Cesar A. Arias, M.D., Ph.D., and Barbara E. Murray, M.D.

Multidrug-Resistant Bacterial Organisms Causing Major Clinical Problems.*

Organism and Antibiotic Resistance	Common Mechanism of Resistance	Recent, Resurrected, and Future Antimicrobial Agents with Potential Clinical Use
Hospital-associated MRSA†		
Vancomycin (both VISA and VRSA)	Thickening of cell wall (not fully elucidated); change in the last amino acid of peptidoglycan precursors	Linezolid, quinupristin–dalfopristin, daptomycin, tigecycline, ceftobiprole, ceftaroline, dalbavancin, telavancin, oritavancin, iclaprim
Daptomycin	Associated with changes in cell wall and cell membrane (not fully elucidated)	Linezolid, quinupristin–dalfopristin, tigecycline, ceftobiprole, ceftaroline, dalbavancin, telavancin, oritavancin, iclaprim
Linezolid	Mutations in the 23S ribosomal RNA genes; rarely, acquisition of a methyltransferase gene (*cfr*)	Daptomycin, quinupristin–dalfopristin, tigecycline, ceftobiprole, ceftaroline, dalbavancin, telavancin, oritavancin, iclaprim
Vancomycin-resistant *Enterococcus faecium*‡		
Ampicillin (common)	Mutation and overexpression of *pbp5*	Linezolid, quinupristin–dalfopristin, daptomycin, tigecycline
High-level resistance to aminoglycosides	Acquisition of aminoglycoside-modifying enzymes; ribosomal mutations (streptomycin)	No alternative for a reliable bactericidal effect alone or in combination
Linezolid	Mutations in the 23S ribosomal RNA genes	Quinupristin–dalfopristin, daptomycin, tigecycline
Daptomycin	Unknown	Linezolid, quinupristin–dalfopristin, tigecycline
Quinupristin–dalfopristin	Enzymes that inactivate quinupristin–dalfopristin, target modification	Daptomycin, linezolid, tigecycline
Escherichia coli, klebsiella species, and enterobacter species§		
Oxyimino-cephalosporins (ceftriaxone, cefotaxime, ceftazidime, and cefepime)	Extended-spectrum β-lactamases (includes hyperproduction of the AmpC enzymes by Enterobacteriaceae family)	Carbapenems, tigecycline
Carbapenems	Production of carbapenemases, decreased permeability	Polymyxins, tigecycline
Acinetobacter species¶		
Carbapenems	Decreased permeability, increased efflux, and production of carbapenemases	Polymyxins
Pseudomonas aeruginosa¶		
Carbapenems	Decreased permeability, increased efflux, and production of carbapenemases	Polymyxins

Mécanisme d'émergences de résistances



- **Direct :** Émergence de résistance au site infectieux
  - **Une seule espèce**
  - **Faible nombre de bactéries**
  - **Ne touche que les patients réellement infectés**
  - **Un seul mécanisme de résistance**

- **Indirecte :** émergence de résistance au niveau de la flore commensale (cutanée, digestive)
  - **Plusieurs espèces**
  - **Grand nombre de bactéries**
  - **Mécanismes de résistance multiple**
  - **Touche tous les patients mêmes non traités**

Moyens de lutte

- Réduire **le nombre de prescription** ! Ex : campagne « les ATB c'est pas automatique »
- Réduire **la durée de prescription**
- Mais **ne pas réduire la dose**: moindre efficacité>>persistance de l'agent pathogène>>développement de résistance

En pratique

- 10 pts X 10 j = 100 DDJ
- 8 pts X 10j = 80 DDJ
- 10 pts X 8 j = 80 DDJ aussi…!
- Les 20% de DDJ « gagnées » ne sont peut-être pas équivalentes…

D’après Pr Antoine Andremont, Laboratoire de bactéiologie, CHU Claude Bernard Bichat Paris 7

Effets des volumes de consommation d'ATB sur la résistance bactérienne

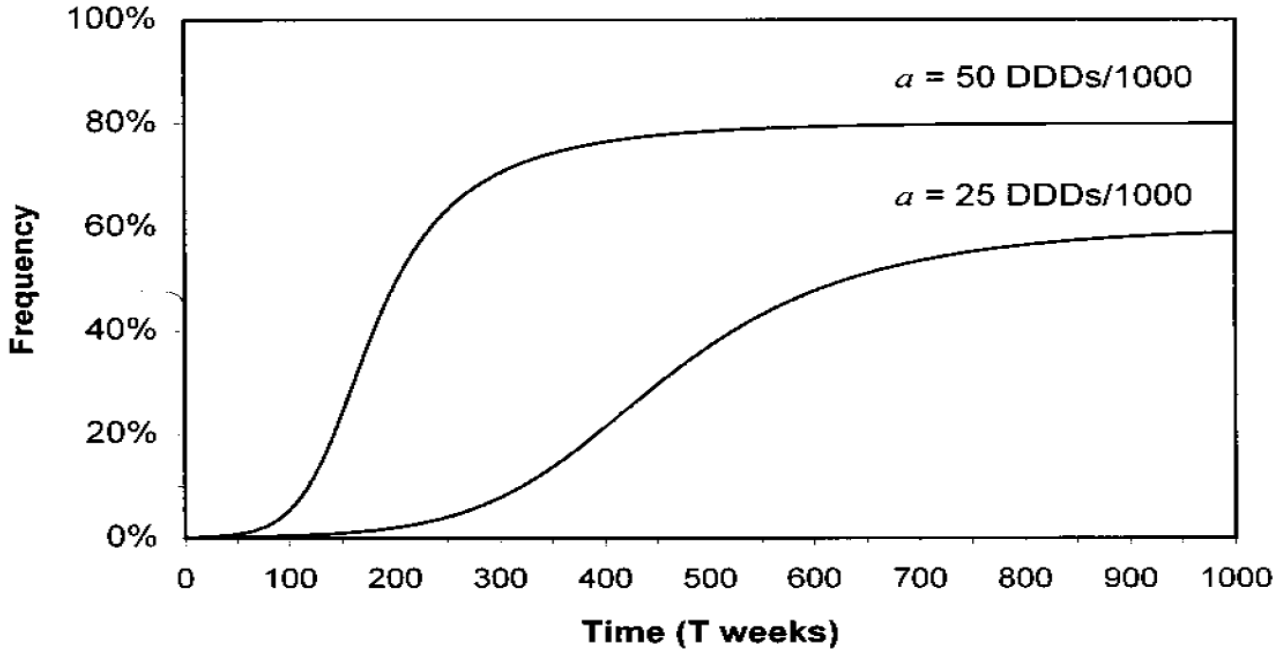
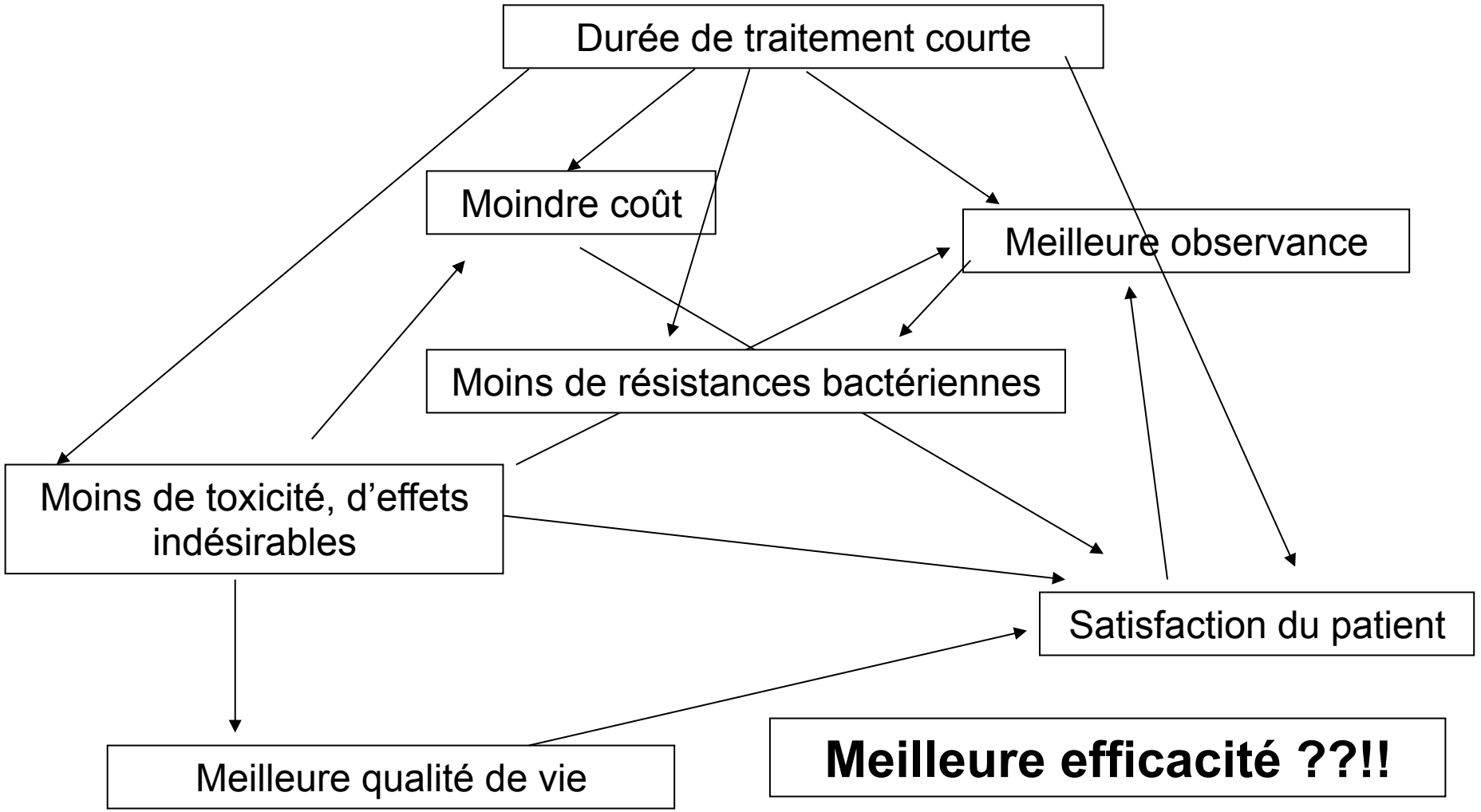


FIG. 1. Change in the frequency of resistance p_t after frequency-dependent selection in which antibiotic consumption falls as resistance rises ($w_S(q_t) = 1 - aq_t$, $w_R = 0.99$, and $p_0 = 10^{-3}$).

Austin et al. PNAs 1999

Intérêt d'une durée courte pour une même efficacité !!



D'après Li JZ. Am Med J 2007

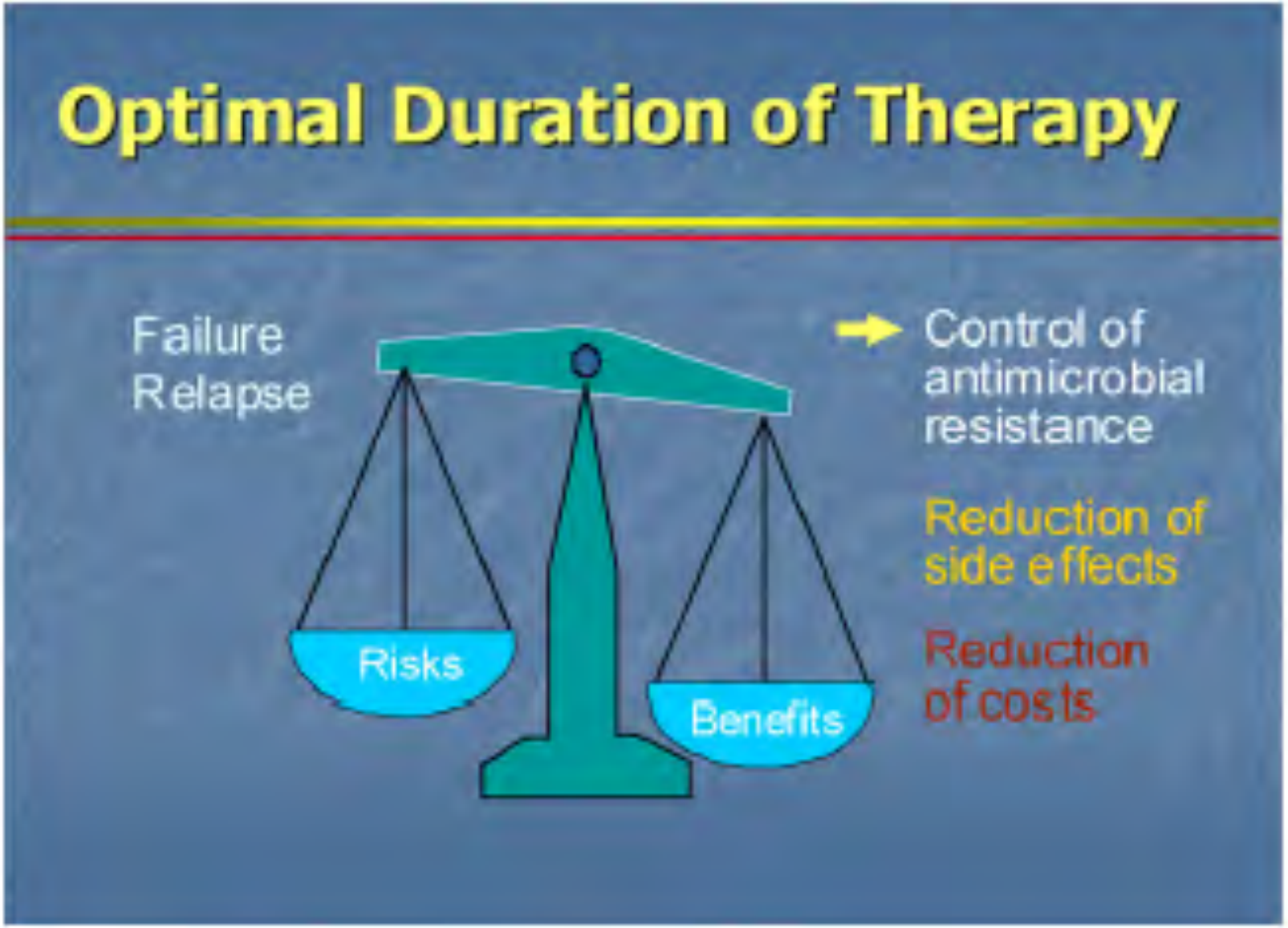
FDR de portage de pneumocoque péni R

	OR	95% CI	p
Oral β-lactam during the preceeding 30 d	3.0	1.1-8.3	0.03
Low dosage (below recommendation)	5.9	2.1-16.7	0.002
Drug duration (>5 d)	3.5	1.3-9.8	0.02

Guillemot D, JAMA 1998

« Treatment duration: so common, so complex »

T. Hooton



Rubinstein E. Int J Antimicrob Agents. 2007 Nov;30 Suppl 1:S76-9

MISE AU POINT

Antibiothérapie par voie générale dans les infections respiratoires basses de l'adulte
Pneumonie aiguë communautaire
Exacerbations de Bronchopneumopathie Chronique Obstructive

« La durée de traitement antibiotique des PAC est classiquement de 7 à 14 jours (10 jours en moyenne) »

IDSA/ATS guidelines (Mandell et al. CID 2007)

Patients with CAP should be treated for a minimum of **5 days**.
The recommended duration for patients with **good clinical response** within the first 2-3 d of therapy is 5 to 7 days total

NICE recommendations :
5 day course of antibiotic therapy for patients with low severity CAP;
Consider a **7-10** day course of antibiotic therapy for patients with moderate **and high severity** CAP.

DUREE DE TRAITEMENT DES PNEUMONIES COMMUNAUTAIRES

Organisation	Durée recommandée de traitement
IDSA 2003	***S.pneumoniae* : tt poursuivi 72 h après apyrexie** ***S.aureus, P.aeruginosa*, K.sp, anaérobies et bactéries atypiques : Tt ≥ 2 semaines**
CIDS / CTS 2000	**1 à 2 semaines, selon la réponse du patient**
ATS 2001	***S.pneumoniae* et autres bactéries: 7-10 jours** **Atypiques: Tt peut nécessiter 10 à 14 jours** **Nouveaux ATB peuvent raccourcir à 5-7 jours pour patients ambulatoires**
BTS 2001	**Pathogène non identifié: 7-10 jours** **Legionella sp: 14-21 jours** **Atypiques: 14 jours** **S.pneumoniae: 7 jours** **Staph, entérobactéries: 14-21 jours**

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 *L.pneumophila*: 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.

Should Patients With VAP Receive 7 Days or 8–15 Days of Antibiotic Therapy? Recommendation

- For patients with VAP, we recommend a 7-day course of antimicrobial therapy rather than a longer duration (strong recommendation, moderate-quality evidence).

- Remarks: There exist situations in which a shorter or longer duration of antibiotics may be indicated, depending upon the rate of improvement of clinical, radiologic, and laboratory parameters.

Management of Adults With HAP/VAP • CID 2016

Les essais cliniques

Auteurs	Caractéristique des études	Indications	Durées de traitement et posologies	Efficacité
Moussaoui et al.(24) (BMJ 2006)	121 patients, Non infériorité, Double aveugle, Randomisée, Contre placebo, Multicentrique	PAC de l'adulte	Amoxicilline 3j vs 8j :	Non infériorité
Uzun et al (25) (J. Chemother. 1994)	25 patients, prospective de cohorte, non comparative	PAC de l'adulte	Azithromycine 1500mg sur 3j	Efficace
Ree et al. (26) (J. Infect. 1983)	203 patients, prospective randomisée, contrôlée	PAC lobaire de l'adulte	Penicillin vs chloramphenicol pdt 2,4 j en moyenne	Non infériorité
Hoepelman et al. (27) (Int J of Antimicrob. Agent 1998)	144 patients	Infections respiratoires basses de l'adulte	Azthromycine 3j vs augmentin 10j	Non infériorité
Shorr et al.(28) (Clin Ther 2005)	177 patients, Double aveugle, Randomisée, Contrôlée, Multicentrique,	PAC chez patient de 65 ans et plus	Lévofloxacine 750 mg/ j pdt 5j vs 500 mg/j pdt 10 j	Non infériorité
Shorr et al. (29) (Respir Med 2006)	528 patients, Double aveugle, Randomisée, Contrôlée, Multicentrique,	PAC sévères hospitalisées (Fine III/IV)	Lévofloxacine 750 mg/ j pdt 5j vs 500 mg/j pdt 10 j	Non infériorité
O'Doherty B. et al. (30) (Eur J Clin Microbiol Infect Dis 1998)	203 patients, Randomisée, Multi centrique	PAC de l'adulte	Azithromycine 3j vs Chlarythromycine 10j	Non infériorité
MASCOT (31) (Lancet 2002)	2 000 patients, Non infériorité, Double aveugle, Randomisée, Contre placebo, Multi centrique	PAC non sévères de l'enfant (2 à 59 mois)	Amoxicilline 3j vs 5j PO	Non infériorité
Awasthi et al (32) (BMJ 2004)	3283 patients, Non infériorité Double aveugle, Randomisée, Contre placebo Multi centrique	PAC non sévères de l'enfant	Amoxicilline 3j vs 5j	Non infériorité
Awunor-Renner C. (36) (Ann Trop Med Parasitol. 1979)	73 patients	PAC de l'adulte	Durée moyenne 2,5j	Efficace
Kinasewitz G, Wood RG. (37) (Eur J Clin Microbiol Infect Dis. 1991)	71 patients, randomisée, double aveugle, Multicentrique	PAC de l'adulte	Azithromycine 250 mg/j pdt 5j vs cefaclor 1500mg/j pdt 10 j	Non infériorité

« A new concept ? »

Un concept nouveau ?

The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 122, No. 18 — CHICAGO, ILLINOIS — AUGUST 28, 1943

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PENICILLIN IN THE TREATMENT OF INFECTIONS

A REPORT OF 500 CASES

STATEMENT BY THE COMMITTEE ON CHEMOTHERAPEUTIC AND OTHER AGENTS, DIVISION OF MEDICAL SCIENCES, NATIONAL RESEARCH COUNCIL

CHESTER S. KEEFER, M.D., BOSTON, CHAIRMAN; FRANCIS G. BLAKE, M.D., NEW HAVEN, CONN.; E. KENNERLY MARSHALL JR., M.D., BALTIMORE; JOHN S. LOCKWOOD, M.D., PHILADELPHIA, AND W. BARRY WOOD JR., M.D., ST. LOUIS.

patients with pneumococcal pneumonia, stated, "It is plain from the reported cases that...many patients have recovered on less than 100,000 units given over a period of two to three days." Dawson and Hobby [23], in their 1944 report on treating

The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 124, No. 10 — CHICAGO, ILLINOIS — MARCH 4, 1944

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THE CLINICAL USE OF PENICILLIN

OBSERVATIONS IN ONE HUNDRED CASES

MARTIN HENRY DAWSON, M.D.
AND
GLADYS L. HOBBY, PH.D.
NEW YORK

"In general, the results were satisfactory with doses of 10,000 units every four hours for one and a half to two days."

Keefer CS *et al.* JAMA 1943
Dawson MH & Hobby GL JAMA 1944

Thorax (1970), 25, 241.

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.

TABLE III

RESULTS OF TREATMENT

	Treatment Group							
	A	B	C	D	E	F	G	Total
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 [illegible] penicillin as a mixture of [illegible]

Merci à Patrick Petitpretz

Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults (Review)

Pugh R, Grant C, Cooke RPD, Dempsey G

Authors' conclusions

We conclude that for patients with VAP not due to NF-GNB, a short fixed-course (seven or eight days) antibiotic therapy may be more appropriate than a prolonged course (10 to 15 days). Use of an individualised strategy (incorporating clinical features or serum procalcitonin) appears to safely reduce duration of antibiotic therapy for VAP.

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Méta analyse

- De 1980 à 2006 (Li JZ Am Med J 2007)
- Seuil à 7j
- Meilleure efficacité d'un traitement court ?

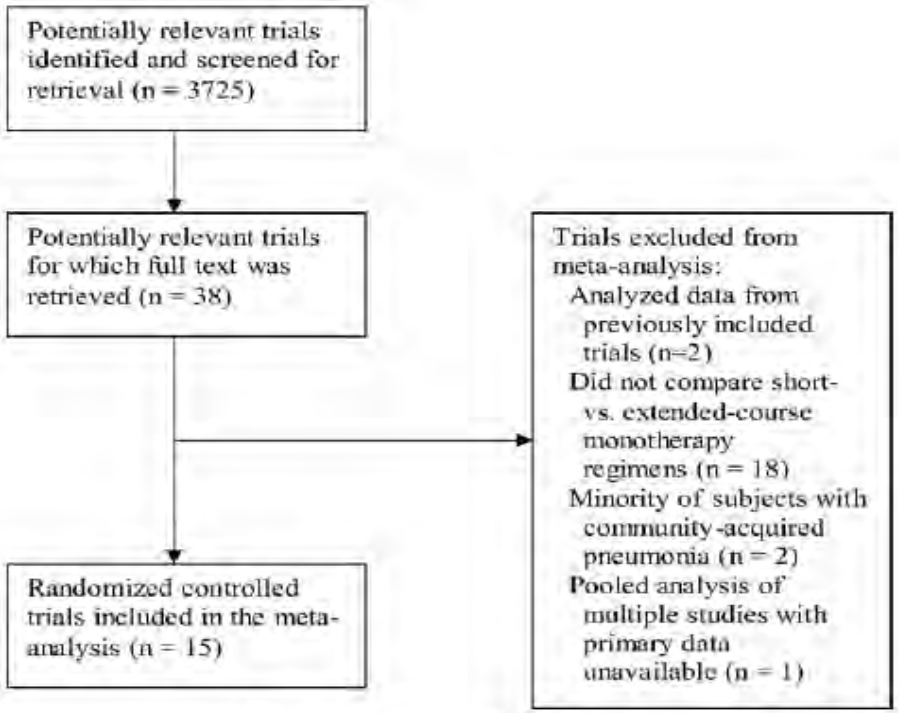

Figure 1 Study flow diagram.

Risque d'échec en fonction de la durée

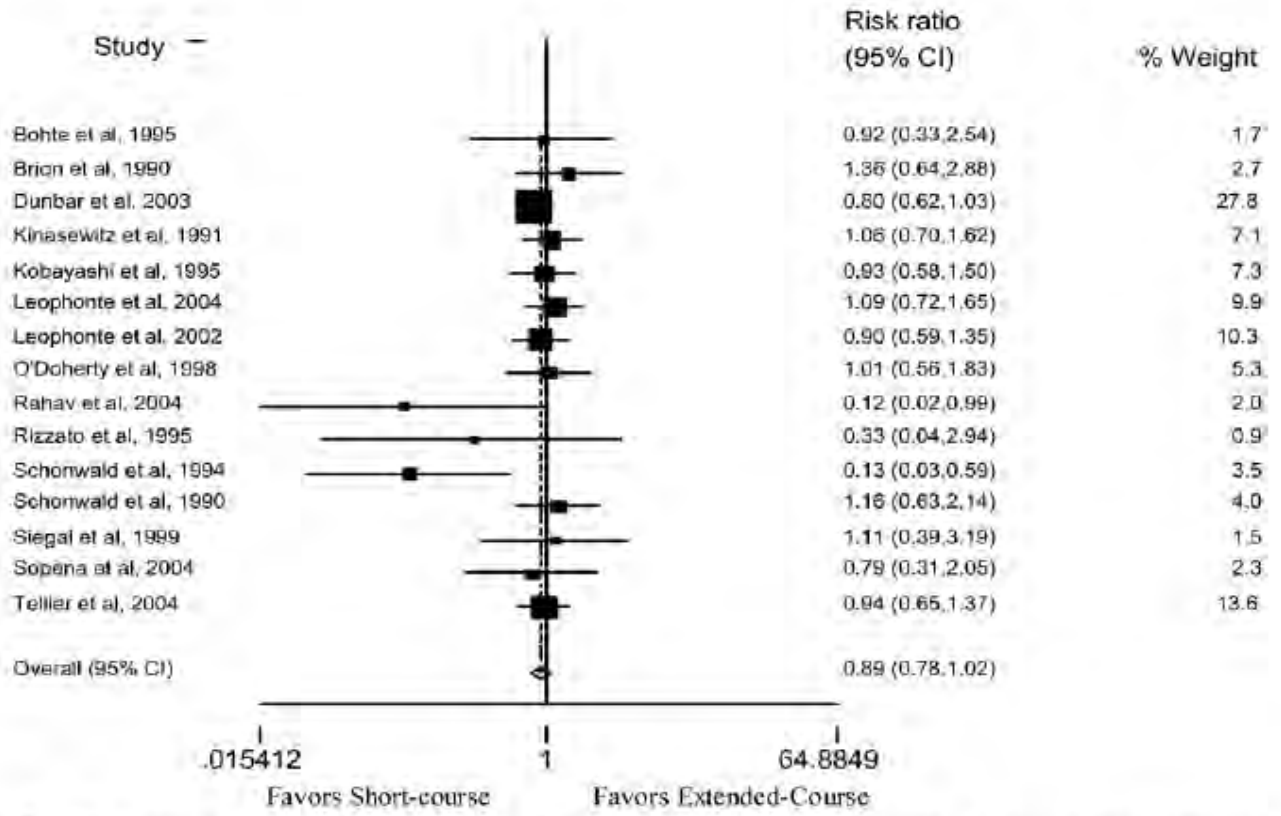

Figure 2 Relative risk of clinical failure with short-course versus extended course antibiotic regimens.

Mortalité en fonction de la durée

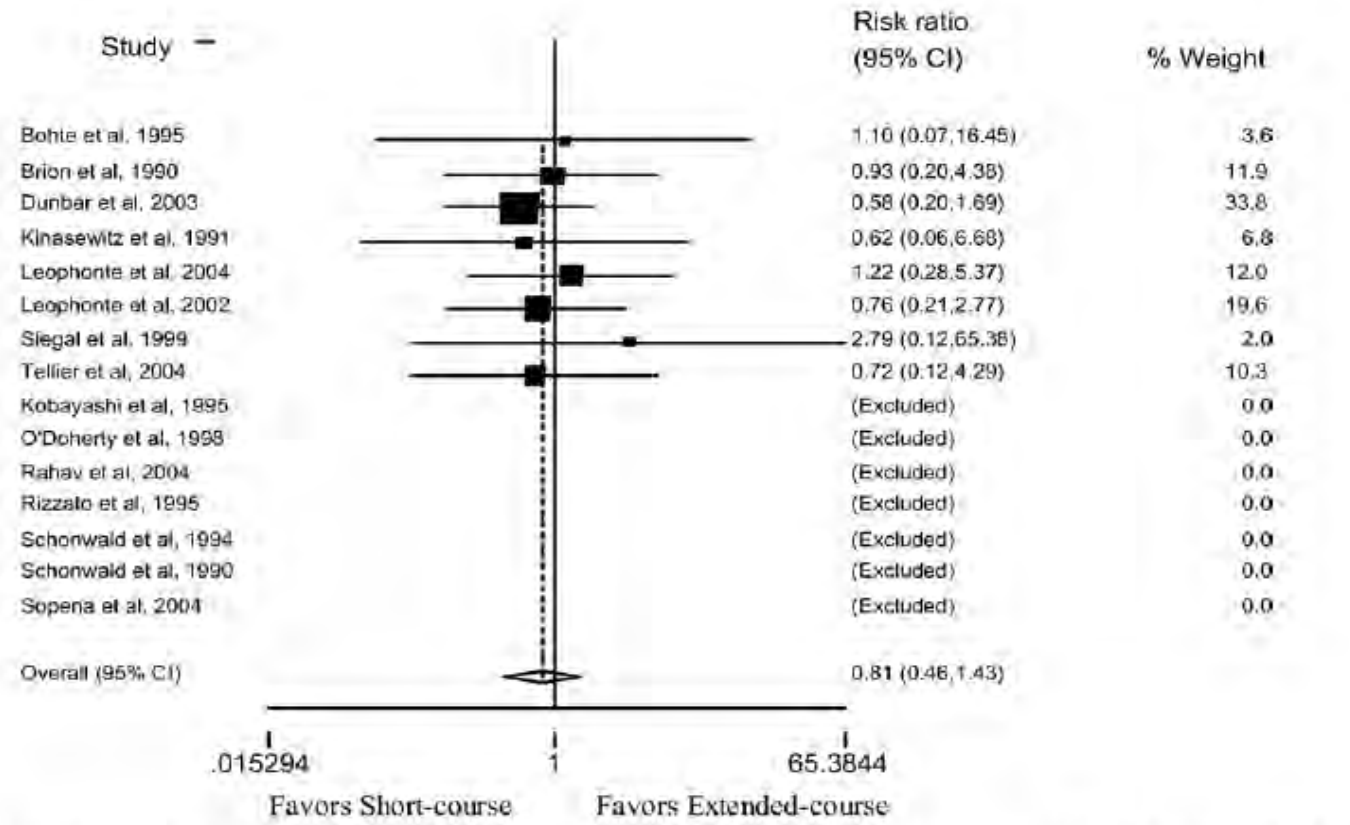

Figure 3 Relative risk of mortality with short-course versus extended-course antibiotic regimens. (The relative risk of mortality could not be calculated in 7 studies due to the lack of deaths in both arms).

HAS (avril 2008)

- « L'antibiothérapie curative ne dépasse généralement pas **une semaine**.
- En effet, beaucoup d'infections ne nécessitent pas une antibiothérapie d'une durée plus longue.
- Une antibiothérapie prolongée expose à un bénéfice/risque défavorable (résistances bactériennes augmentées, toxicité accrue).
- De plus, des traitements plus courts ont été validés dans des situations bien définies. »

PNP sévères

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

Outcome

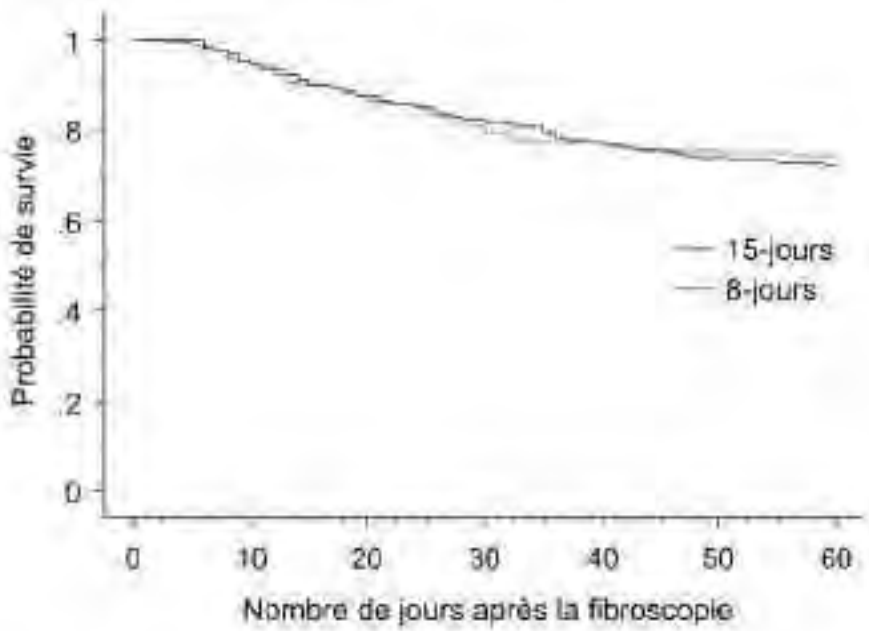

Fig. 2. Probabilité de survie (courbes de Kaplan-Meier) en fonction de la durée de traitement antibiotique (8 vs 15 jours) d'une pneumonie acquise sous ventilation mécanique [16].

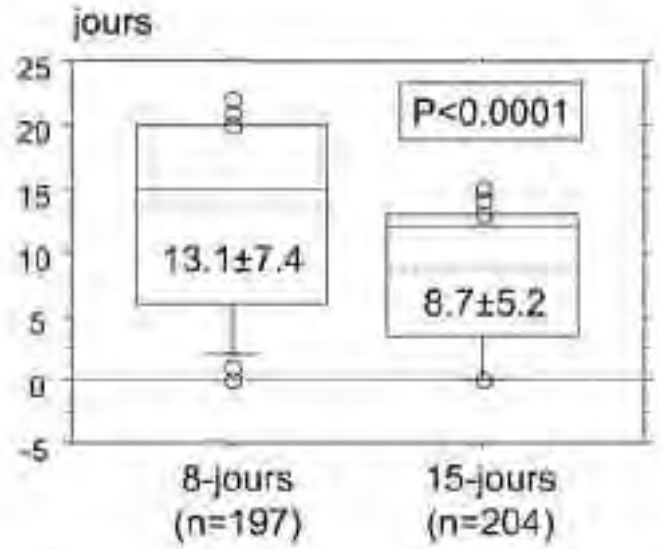

Fig. 3. Nombre de jours vivant sans antibiotique en fonction de la durée de traitement antibiotique d'une pneumonie acquise sous ventilation mécanique (d'après [16]).

PNP communautaires

Research

BMJ

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

El Moussaoui, BMJ 2006.

Méthodologie

- Prospective, double aveugle, contrôlée non infériorité contre placebo
- Multicentrique, Hollande, 2000-2003, adultes hospitalisés PSI ≤ 110
- Exclus: immuno déprimés, hospitalisation récente, nursing home, PaO2 ≤ 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

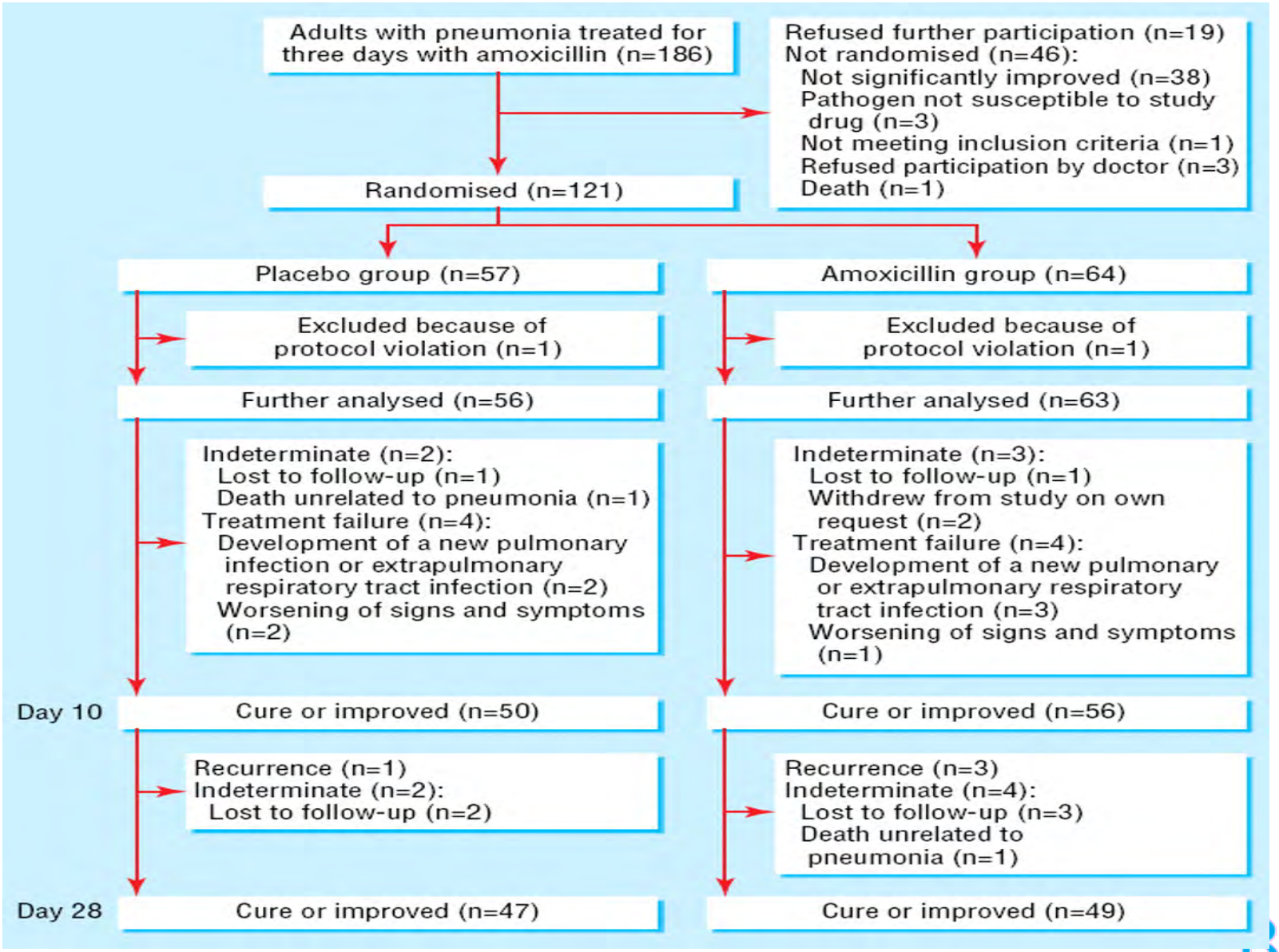

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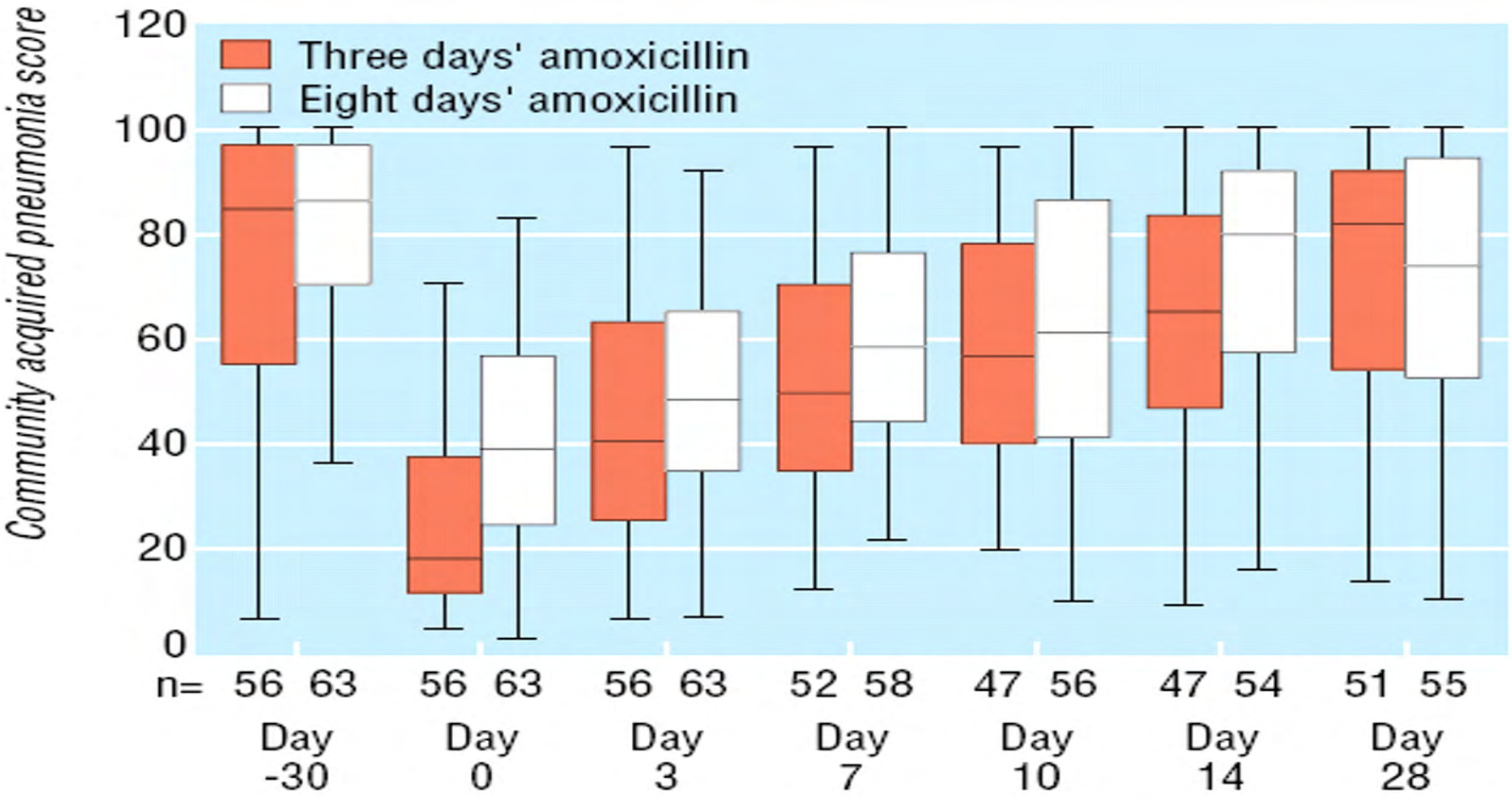
Fig 2 Community acquired pneumonia scores (medians, interquartile ranges, 10th to 90th centiles) during treatment and follow-up. Day -30=score before pneumonia; day 0=start of treatment; day 10=test of cure; day 28=end of follow-up



BMJ

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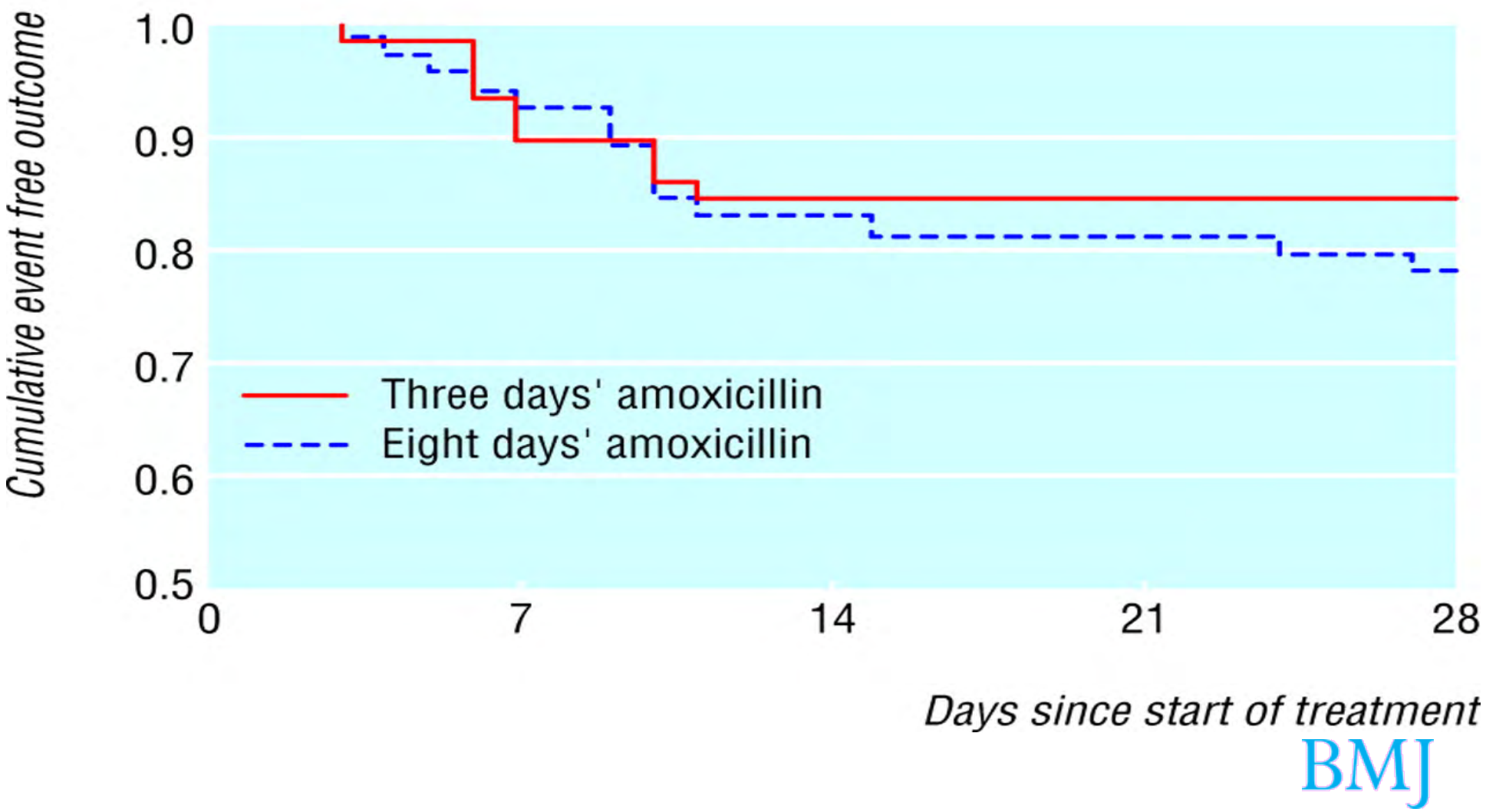
Fig 3 Proportion of patients considered clinical successes in intention to treat population. Day 3=day of randomisation



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Peut-on traiter les pneumonies aiguës communautaires hospitalisées par 3 jours de β-lactamines ?

A. Dinh*[1], J. Dumoulin[2], C. Duran[1], B. Davido[1], A. Lagrange[1], D. Benhamou[3], M. C. Dombret[4], B. Renaud[5], Y. E. Claessens[6], J. Labarère[7], B. Philippe[8], J. F. Boitiaux[8], J. P. Bedos[9], J. Ropers[10], T. Chinet[2], A. C. Crémieux[1,11]

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UNIVERSITÉ DE VERSAILLES ST-QUENTIN-EN-YVELINES

Essai Pneumonie Traitement Court (PTC)

PHRC national 12-202.0496

- **Hypothèse** : antibiothérapie de 3 jours est suffisante chez les patients avec une PAC répondant à 3 jours de C3G ou amoxicilline-acide clavulanique

- **Méthode** :
  - Essai multicentrique (20 centres),
  - Contrôlé, randomisé vs placebo (double aveugle)
  - De non infériorité,
  - 2 groupes parallèles,
  - Comparant 2 durées de traitement : 3j *vs.* 8j

Critères d'inclusion

- **Age > 18 ans**
- Ayant consulté en urgence 3 jours avant
- **Admis pour PAC**

J0
  - **1 des signes** : dyspnée, toux, exp. muco-pur., foyer de crépitants
  - \+ T> **38**°C
  - \+ Nouvel **infiltrat** à la RX

- **Ayant répondu à 3 jours de TT** par C3G ou amox-clav.

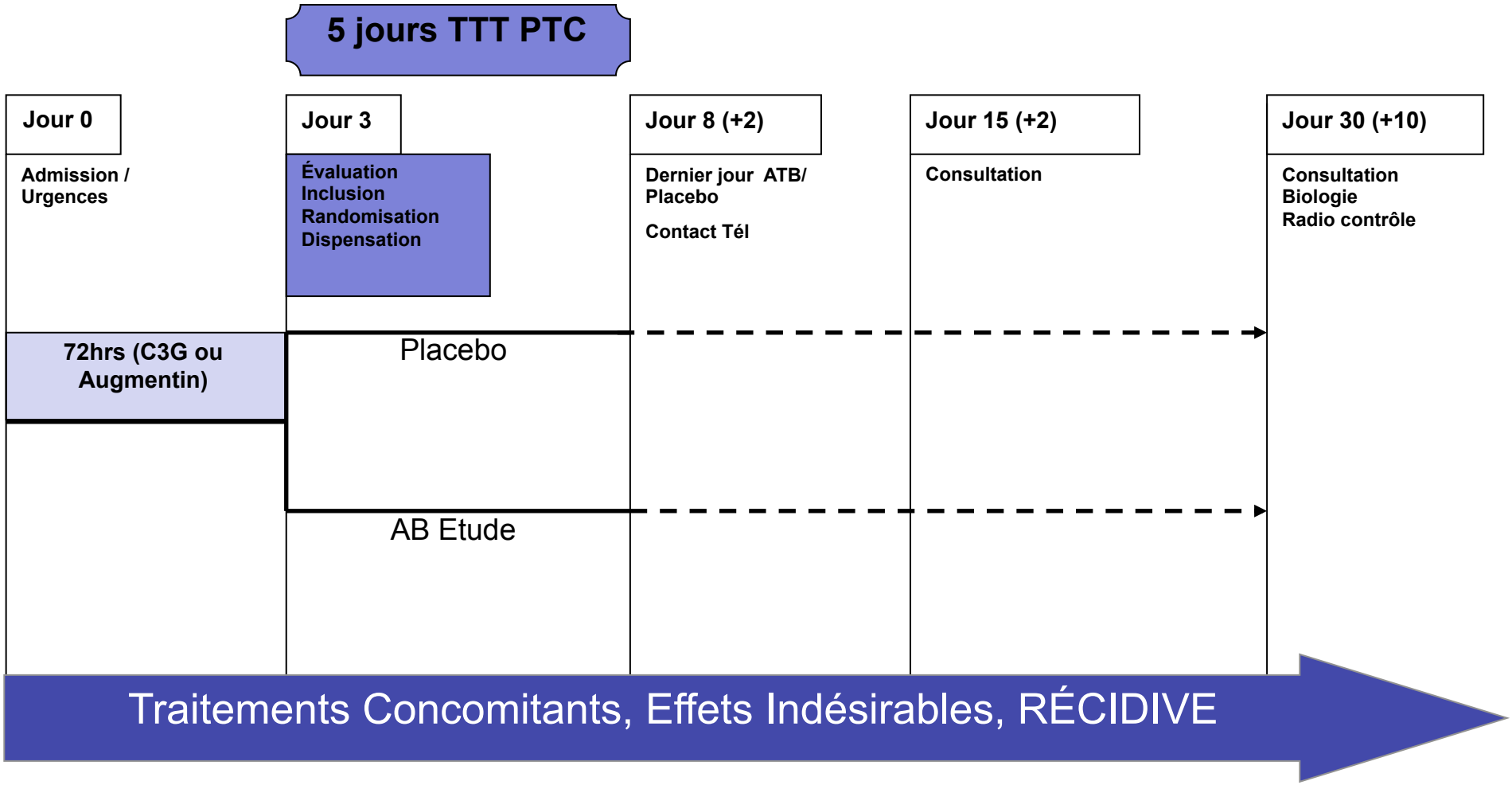
J3
  - T ≤ 37,8°C
  - \+ Critères de stabilité IDSA
    - FC < 100/min et
    - FR < 24c/min)
    - SaO2 ≥ 90% (mode oxygénation normale préalable PAC)
    - Pa Systolique ≥ 90 mmHg

- Apte à prendre un traitement oral

Critères de non inclusion

- PAC sévère ou compliquée
- Légionellose suspectée ou confirmée
- Pneumonies liées aux soins
- Suspicion de pneumopathie d'inhalation
- Infection intercurrente requérant un traitement antibiotique
- Terrain immunodéprimé connu
- Antibiothérapie préalable de plus de 24 h avant la consultation aux urgences
- Bithérapie (1 dose de macrolides ou de FQ autorisée)
- Clairance de la créatinine < à 30ml/min
- Antécédents d'ictères/Atteinte hépatique liés à l'amox/ac.clav
- Antécédent d'hypersensibilité à une β-lactamine
- Femmes enceintes
- Allaitement
- Espérance de vie < 1 mois
- Patient sous tutelle ou sans couverture sociale
- Personnes sans domicile fixe

Schéma de l'étude



Critère de jugement principal

- **Guérison** définie à J15 par association de :
  - Apyrexie (température corporelle < 37,8°C)
  - Disparition ou amélioration des signes cliniques suivants s'ils étaient initialement présents :
    - dyspnée,
    - toux,
    - expectorations muco-purulentes,
    - foyer de crépitants
  - Sans antibiothérapie additionnelle depuis J8

Objectifs secondaires

- Comparer **l'efficacité clinique à J30**
- Comparer la **survenue d'EI** lié au traitement antibiotique
- Comparer la **durée d'hospitalisation**
- Comparer la **satisfaction globale** des patients à J30
- Comparer la **reprise de l'activité** professionnelle et des activités habituelles à J30

Résultats (1/2)

- Aujourd'hui (30/11) : **284 inclusions**
- Patients : âge moy 68.5 ±18.8 ans, sexe ratio 1.5 (M/F)
- Principaux antécédents :

Principales comorbidités	**%**
BPCO	24
Insuffisance cardiaque	21
Diabète	20
Maladie vasculaire cérébrale	9
Pathologie rénale	6
Néoplasie	2
Pathologie hépatique	2

Résultats (2/2)

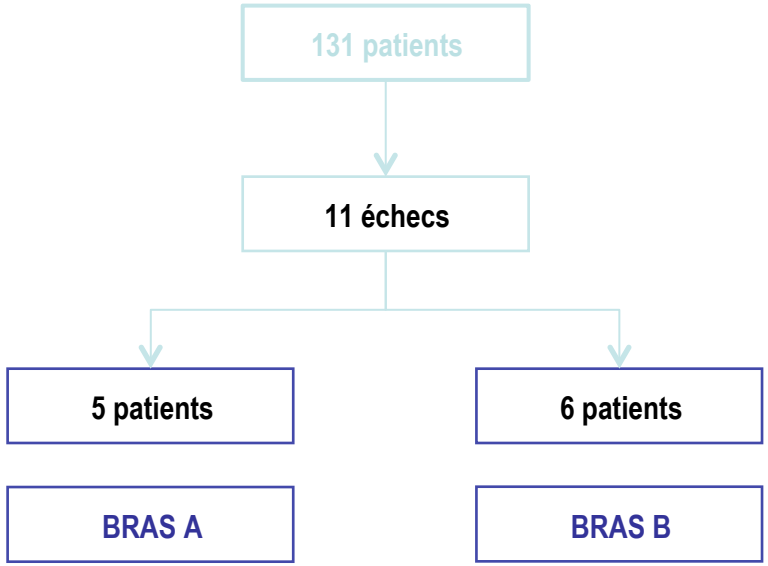
- Durée moyenne séjour : 6,2 jours
- Principal évènement indésirable : diarrhées (n=24), dont 1 infection à *Clostridium difficile*
- **33 EIG** (18 patients), **3 décès**.

Evènements indésirables graves	**N**
Récidive pneumonie	14
Superinfection	2
Insuffisance cardiaque	3
Néoplasie	2
Infection intercurrente	2
Allergie	2
VIH	I

Evènements indésirables graves	**N**
AVC	I
Deshydratation	I
Hépatite	1
Péricardite	1
Crise d'asthme	1
Douleurs lombaires	1
Lithiase rénale	1

Comité Indépendant de Surveillance

- Révision des 131 premiers patients inclus : 19 ont présenté un EIG et 3 sont décédés.
- Taux de guérison global : 91,6%
  - avec 11 échecs dont 2 décès,
  - répartis entre les deux bras de l'étude (6/5).
- Le comité indépendant a conclu à la sécurité de l'essai et à sa poursuite.



Discussion

- Population **âgée avec comorbidités** correspondant aux données de la littérature (PAC hospitalisés)
- 3j *vs* 8j : R. El Moussaoui *et al.* (BMJ 2006) >> patients **jeunes,** PAC **peu grave**
- PAC **bactérienne ?**
- Rapidité de la **réponse au traitement** antibiotique : élément essentiel pronostique de la durée nécessaire

Conclusion

Vers une durée individualisée ?

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Duration of Antibiotic Treatment in Community-Acquired Pneumonia
A Multicenter Randomized Clinical Trial

Ane Uranga, MD; Pedro P. España, MD; Amaia Bilbao, MSc, PhD; Jose María Quintana, MD, PhD; Ignacio Arriaga, MD; Maider Intxausti, MD; Jose Luis Lobo, MD, PhD; Laura Tomás, MD; Jesus Camino, MD; Juan Nuñez, MD; Alberto Capelastegui, MD, PhD

Essai de non infériorité

Multicentrique (4 hôpitaux)
2012-2013

312 patients

Randomisation à J5
- Arrêt à 48h d'obtention des critères de stabilité
- Arrêt selon clinicien en charge

Objectif :
- Guérison clinique J10 et J30
- QdV CAP J5 et J10 (questionnaire 18 items : 0-90)

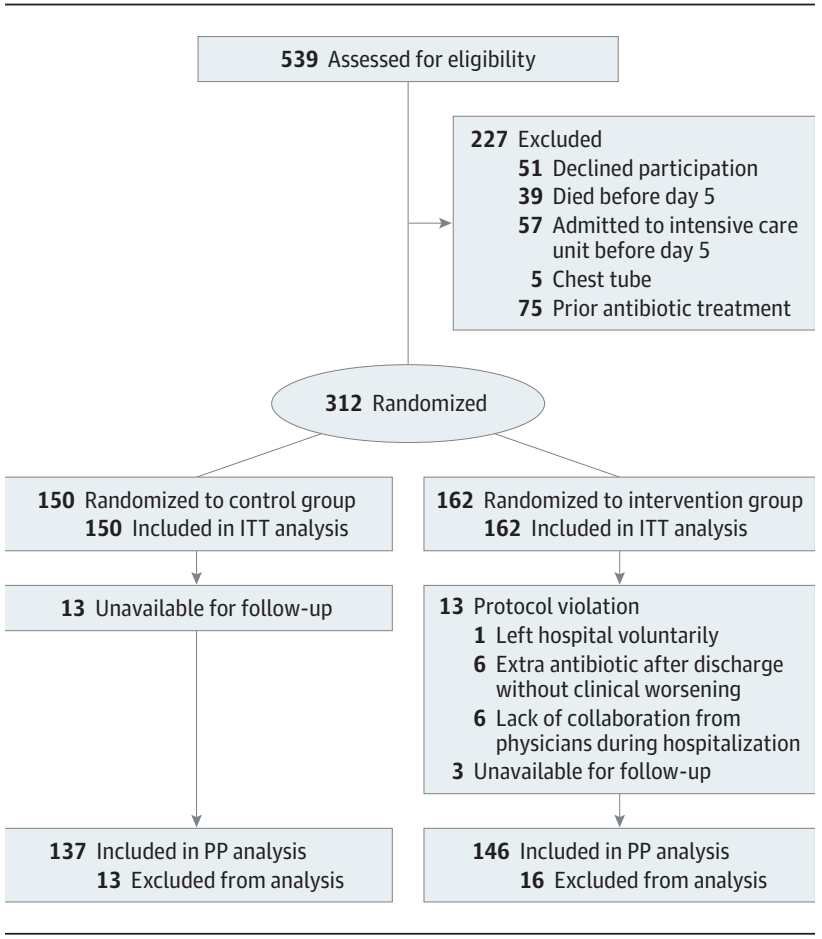


Table 1. Baseline Characteristics of Study Participants[a]

Characteristic	Control Group (n = 150)	Intervention Group (n = 162)
Age, mean (SD), y	66.2 (17.9)	64.7 (18.7)
Sex		
Male	95 (63.3)	101 (62.3)
Female	55 (36.7)	61 (37.7)
Tobacco		
Current smoker	32 (21.3)	36 (22.6)
Never smoker	68 (45.3)	71 (44.7)
Former smoker	50 (33.3)	52 (32.7)
Alcohol consumption (yes)	24 (16.1)	17 (10.5)
Comorbidities		
Liver disease	4 (2.7)	4 (2.5)
Heart disease	38 (25.3)	39 (24.1)
Congestive heart failure	14 (9.3)	12 (7.4)
Cerebrovascular disease	16 (10.7)	9 (5.6)
Renal disease	12 (8.0)	12 (7.4)
COPD	21 (14)	27 (16.7)
Diabetes	25 (16.7)	21 (13.0)
Charlson Comorbidity Index, median (IQR)	1 (0-2)	1 (0-2)
Charlson Comorbidity Index, categorized		
0	61 (40.7)	70 (43.2)
1	37 (24.7)	47 (29.0)
>1	52 (34.7)	45 (27.8)
Katz Index, mean (SD)[b]	0.6 (1.6)	0.4 (1.3)
PSI class		
I-III	89 (59.3)	102 (63.0)
IV-V	61 (40.7)	60 (37.0)
PSI score, mean (SD)	83.7 (33.7)	81.8 (33.8)

Eligibility

Patients ≥ 18 years old, hospitalized with a diagnosis of CAP. Pneumonia is defined as pulmonary infiltrate on chest X-ray not seen previously plus at least one symptom compatible with pneumonia such as cough, fever, dyspnea, and/or chest pain.

ATB :

- 80% des patients traités par FQ

- 10% beta lactamines +ML

Durée de traitement

Table 4. Results for Secondary Study Outcomes in the Per-Protocol Analysis[a]

Outcome	Control Group (n = 137)	Intervention Group (n = 146)	*P* Value
Time, median (IQR), d			
Taking antibiotics	10 (10-11)	5 (5-6.5)	<.001
Not taking antibiotics	21 (10-27)	25 (5-32)	.001
Taking intravenous antibiotics	2 (1-4)	3 (2-4)	.22
Until clinical improvement	12 (8-18)	12 (7-15)	.41
Return to normal activity	18 (9-25)	15 (10-21)	.36
Radiographic resolution at day 30	93 (73.2)	112 (81.2)	.12
In-hospital mortality	2 (1.5)	3 (2.1)	>.99
30-d Mortality	3 (2.2)	3 (2.1)	>.99
Recurrence by day 30	6 (4.4)	4 (2.8)	.53
Readmission by day 30	9 (6.6)	2 (1.4)	.02
In-hospital complications			
Pleural effusion	10 (7.3)	5 (3.4)	.15
Treatment failure[b]	2 (1.5)	3 (2.1)	>.99
Respiratory failure[c]	26 (19.0)	31 (21.2)	.64
Severe sepsis[d]	7 (5.1)	8 (5.5)	.89
Renal failure[e]	5 (3.7)	6 (4.1)	.85
ICU admission	2 (1.5)	1 (0.7)	.61
Use of invasive mechanical ventilation	2 (1.5)	1 (0.7)	.61
Use of noninvasive mechanical ventilation	3 (2.2)	2 (1.4)	.67
Need for vasopressors	2 (1.5)	3 (2.1)	>.99
Antibiotic adverse effects by day 30	18 (13.1)	17 (11.7)	.72
Time with antibiotic adverse effects, mean (SD), d	3 (2.8)	1.7 (2.1)	.24
Length of hospital stay, mean (SD), d	5.5 (2.3)	5.7 (2.8)	.69

Abbreviations: ICU, intensive care unit; IQR, interquartile range; radiographic progression of pneumonia or the appearance of a new infectious

Outcome

Table 2. Results for the Primary Study Outcomes

Outcome	Control Group	Intervention Group	*P* Value
Intent-to-Treat Analysis			
Total No. of participants	150	162	
Clinical success, No. (%)[a]			
At day 10	71 (48.6)	90 (56.3)	.18
At day 30	132 (88.6)	147 (91.9)	.33
CAP symptom questionnaire score, mean (SD)[b]			
At day 5	24.7 (11.4)	27.2 (12.5)	.10
At day 10	18.6 (9.0)	17.9 (7.6)	.69
Per-Protocol Analysis			
Total No. of participants	137	146	
Clinical success, No. (%)[a]			
At day 10	67 (50.4)	86 (59.7)	.12
At day 30	126 (92.7)	136 (94.4)	.54
CAP symptom questionnaire score, mean (SD)[b]			
At day 5	24.3 (11.4)	26.6 (12.1)	.16
At day 10	18.1 (8.5)	17.6 (7.4)	.81

EDITORIAL

The New Antibiotic Mantra—"Shorter Is Better"

Brad Spellberg, MD

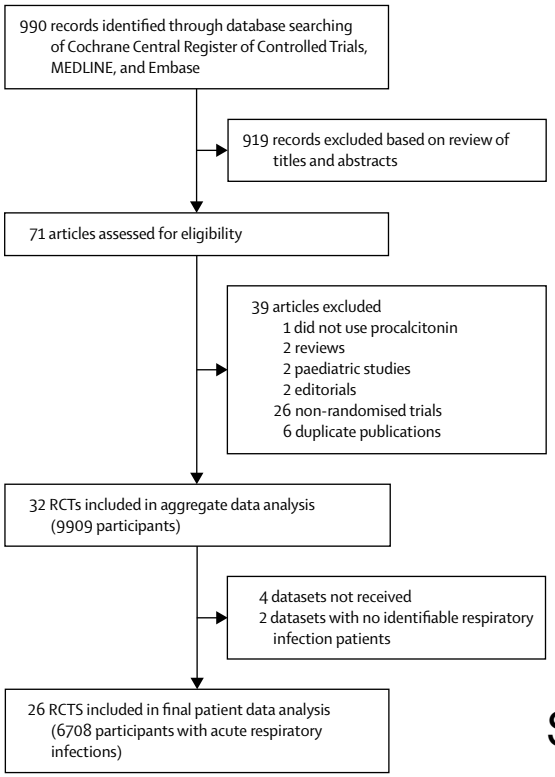
Of course, the ultimate goal is to customize duration of therapy to the patient's response. So what should we do when patients are given a prescription for a fixed duration of therapy and their symptoms resolve before they complete the course?

Here we need to change the dogma: patients should no longer be told to keep taking the antibiotic. Patients should be told that if their symptoms resolve before completing the antibiotic they should communicate with their physician to determine if they can stop therapy early. Health care professionals should be encouraged to allow patients to stop antibiotic treatment as early as possible on resolution of symptoms of infection. Ultimately, we should replace the old dogma of continuing therapy past resolution of symptoms with a new, evidence-based dogma of "shorter is better."

PCT ?

Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis

Philipp Schuetz, Yannick Wirz*, Ramon Sager*, Mirjam Christ-Crain, Daiana Stolz, Michael Tamm, Lila Bouadma, Charles E Luyt, Michel Wolff, Jean Chastre, Florence Tubach, Kristina B Kristoffersen, Olaf Burkhardt, Tobias Welte, Stefan Schroeder, Vandack Nobre, Long Wei, Heiner C Bucher, Djillali Annane, Konrad Reinhart, Ann R Falsey, Angela Branche, Pierre Damas, Maarten Nijsten, Dylan W de Lange, Rodrigo O Deliberato, Carolina F Oliveira, Vera Maravić-Stojković, Alessia Verduri, Bianca Beghé, Bin Cao, Yahya Shehabi, Jens-Ulrik S Jensen, Caspar Corti, Jos A H van Oers, Albertus Beishuizen, Armand R J Girbes, Evelien de Jong, Matthias Briel*, Beat Mueller*



Schuetz *et al.* Lancet 2017

	Control (n=3372)	Procalcitonin group (n=3336)
Age, years	61·2 (18·4)	60·7 (18·8)
Sex		
Men	1910 (57%)	1898 (57%)
Women	1462 (43%)	1438 (43%)
Clinical setting		
Primary care	501 (15%)	507 (15%)
Emergency department	1638 (49%)	1615 (48%)
ICU	1233 (37%)	1214 (36%)
Primary diagnosis		
Total upper acute respiratory infection	280 (8%)	292 (9%)
Common cold	156 (5%)	149 (4%)
Rhino-sinusitis, otitis	67 (2%)	73 (2%)
Pharyngitis, tonsillitis	46 (1%)	61 (2%)
Total lower acute respiratory infection	3092 (92%)	3044 (91%)
Community-acquired pneumonia	1468 (44%)	1442 (43%)
Hospital-acquired pneumonia	262 (8%)	243 (7%)
Ventilator-associated pneumonia	186 (6%)	194 (6%)
Acute bronchitis	287 (9%)	257 (8%)
Exacerbation of COPD	631 (19%)	621 (19%)
Exacerbation of asthma	127 (4%)	143 (4%)
Other lower acute respiratory infection	131 (4%)	144 (4%)
Procalcitonin dose on enrolment		
Data available	2590 (77%)	3171 (95%)
<0·1 µg/L	921 (36%)	981 (31%)
0·1–0·25 µg/L	521 (20%)	608 (19%)
>0·25–0·5 µg/L	308 (12%)	383 (12%)
>0·5–2·0 µg/L	358 (14%)	520 (16%)
>2·0 µg/L	482 (19%)	679 (21%)

Data are mean (SD) or n (%). ICU=intensive care unit. COPD=chronic obstructive pulmonary disease.

Résultats

	Control (n=3372)	Procalcitonin group (n=3336)	Adjusted OR (95% CI)*, p value	$p_{interaction}$
Overall				
30-day mortality	336 (10%)	286 (9%)	0·83 (0·7 to 0·99), p=0·037	..
Treatment failure	841 (25%)	768 (23%)	0·90 (0·80 to 1·01), p=0·068	..
Length of ICU stay, days	13·3 (16·0)	13·7 (17·2)	0·39 (–0·81 to 1·58), p=0·524	..
Length of hospital stay, days	13·7 (20·6)	13·4 (18·4)	–0·19 (–0·96 to 0·58), p=0·626	..
Antibiotic-related side-effects	336/1521 (22%)	247/1513 (16%)	0·68 (0·57 to 0·82), p<0·0001	..

	Control (n=3372)	Procalcitonin group (n=3336)	Adjusted OR or difference (95% CI), p value*	$p_{interaction}$
Overall				
Initiation of antibiotics	2894 (86%)	2351 (70%)	0·27 (0·24 to 0·32), p<0·0001	..
Duration of antibiotics, days†	9·4 (6·2)	8·0 (6·5)	–1·83 (–2·15 to –1·5), p<0·0001	..
Total exposure of antibiotics, days‡	8·1 (6·6)	5·7 (6·6)	–2·43 (–2·71 to –2·15), p<0·0001	..

Schuetz *et al.* Lancet 2017

PHRC-N-16-0618

AIR

Antibiothérapie des Infections Respiratoires
Antibiotic therapy In Respiratory tract infections

A controlled randomized, open label, multicenter, non-inferiority trial evaluating an individualized antibiotic treatment duration strategy based on patient clinical response for community acquired pneumonia in community setting

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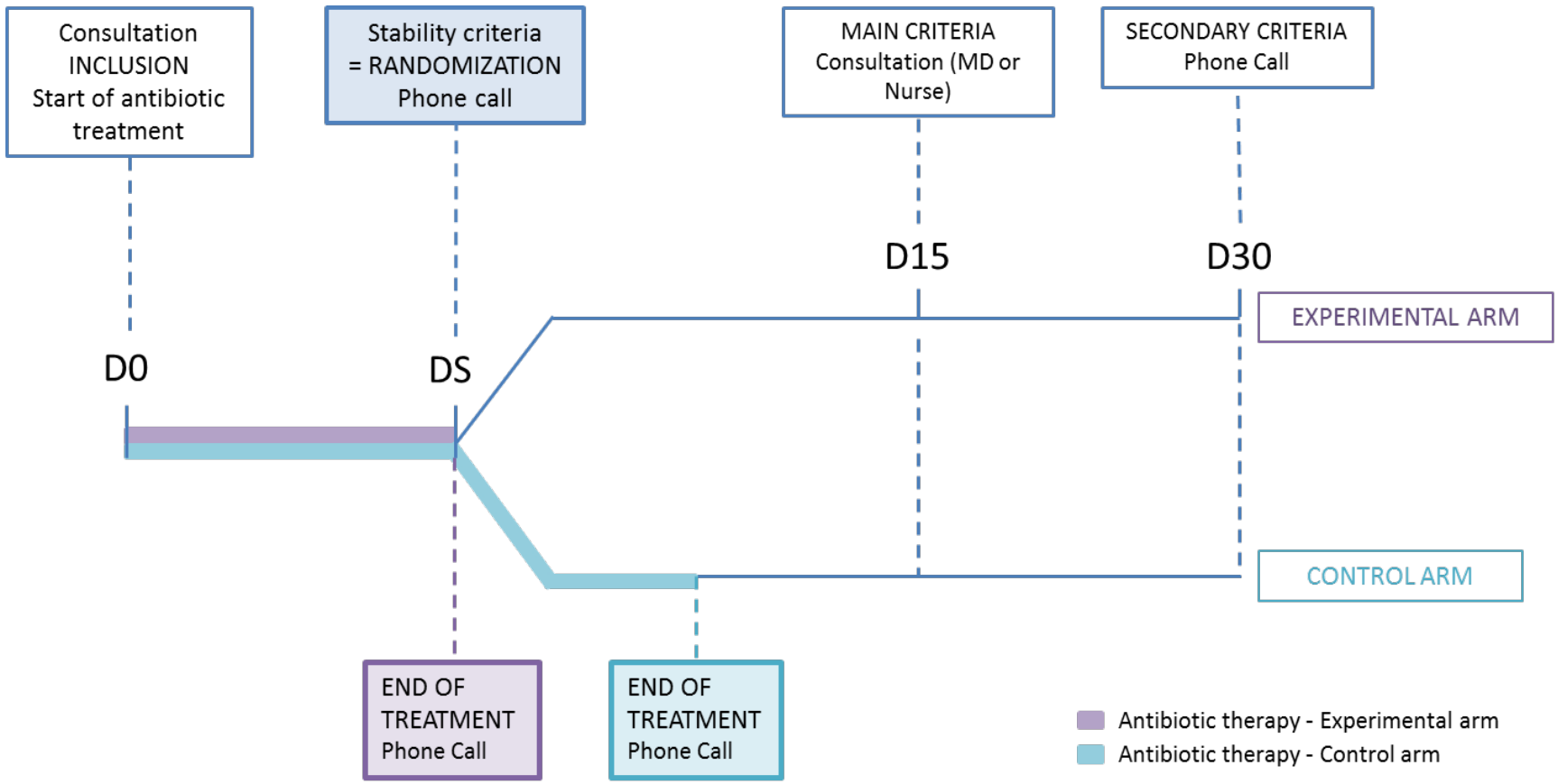
Study design



Outils connectés

Journal of Antimicrobial Chemotherapy Advance Access published September 10, 2013

J Antimicrob Chemother
doi:10.1093/jac/dkt362

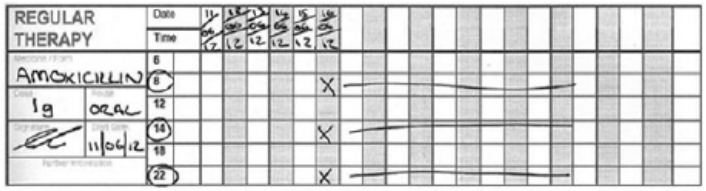
Journal of Antimicrobial Chemotherapy

A multidisciplinary intervention to reduce antibiotic duration in lower respiratory tract infections

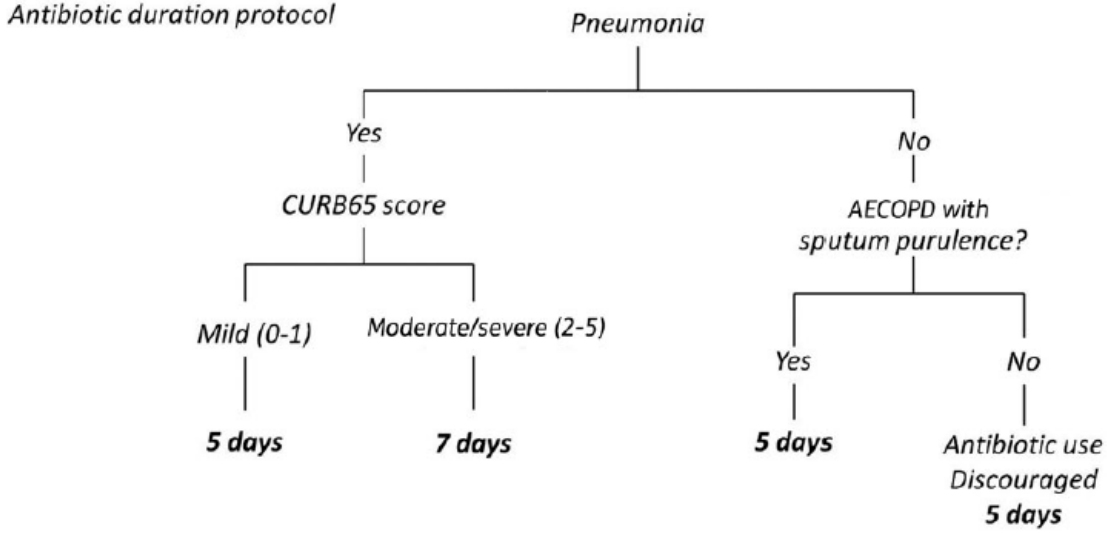
Colin Murray†, Arlene Shaw†, Matthew Lloyd, Robin P. Smith, Thomas C. Fardon, Stuart Schembri and James D. Chalmers*

Study design

Automatic stop dates



Antibiotic duration protocol



On a encore du travail

Title: Duration of Antibiotic Use among Adults with Uncomplicated Community-Acquired Pneumonia Requiring Hospitalization in the United States

- Etude rétrospective

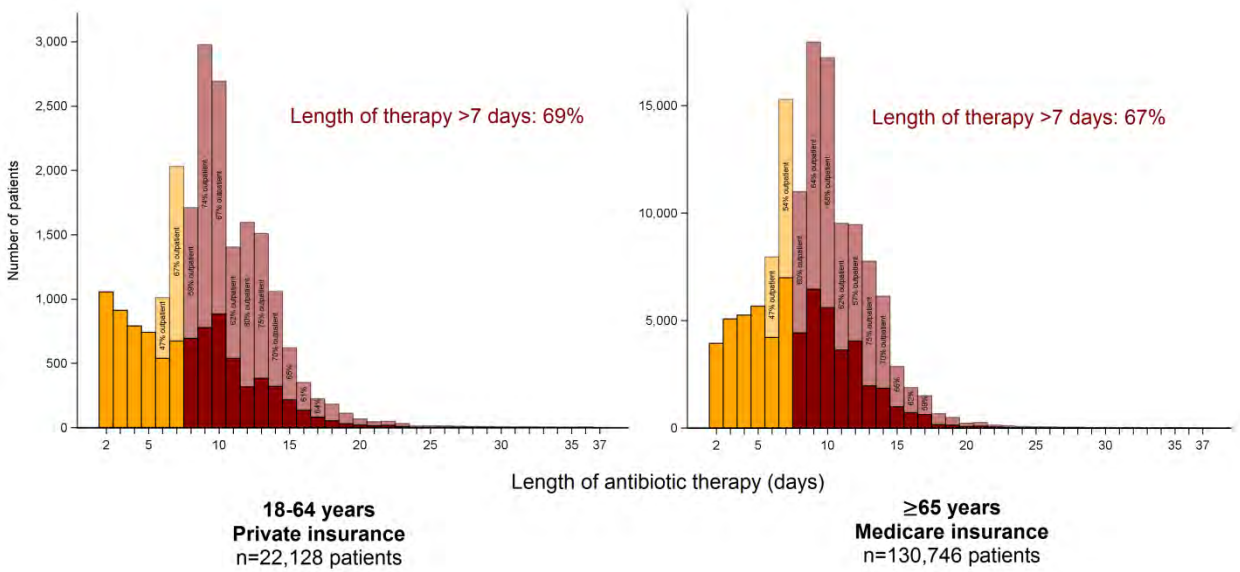
- Base de donnée informatique hospitalière (2012-2013)

- PAC simple

- 22 128 patients

- Durée moyenne 9,5j

70%>7j



Yi *et al*. CID 2017

On n’a pas parlé de …

- Diagnostic : scanner ?
- Viral *vs.* bactérien
- Mono/bithérapie
- Vaccination
- Intérêt des corticoïdes

MERCI DE VOTRE ATTENTION

Remerciements

Ambroise Paré, Boulogne-Billancourt : ATTAL-BEHAR Julie, BEAUNE Sebastien, BLIVET Sandra, CHINET Thierry, CUDENNEC Tristan, DUMOULIN Jennifer, DUPONT Caroline, GIRAUT Violaine, GREFFE Ségolène, GRENET Julie, GUYOT Caroline, LABRUNE Sylvie, MOULIAS Sophie, NALINE Charlotte, ROUVEIX Elisabeth, SAHUT-D'IZARN Marine, SEFSSAFI Abel, TEILLET Laurent, TRAD Salim

CH Annecy : BRU Jean-Pierre, GAILLAT Jacques, GAUTIER Vincent, JANSSEN Cecile, PAGANI Leonardo, VITRAT Virginie

CH Argenteuil : ABDERRAHMANE Malika, CAMUSET Juliette, LEGALL Catherine, LONGUET-FLANDRES Pascale, MENN Anne-Marie

Beaujon, Clichy : DE LASTOURS Victoire, PREVOST Gwenolée

Bicêtre : BURDET Charles, DERRADJI Ouda, ESCAUT Lelia, HINGLAIS Etienne, LEBRAS Philippe, LEFEVRE Edouard, NOAILLON Mathilde, RABIER Pauline, RAPHAEL Maurice, TEICHER Elina, VERNY Christiane, VITTECOQ Daniel, WYPLOSZ Benjamin

Bichât : BEN HAYOUN Michèle, BRUN-VEZINET Françoise, CASALINO Enrique, CHOQUET Christophe, DOMBRET Marie-Christine, DUVAL Xavier, JOLY Véronique, LESCURE Xavier, POGLIAGHI Manuela, RIOUX Christophe, YAZDANPANAH Yazdan

CHI Créteil : BARROS Elsa, BEGGA Belinda, BOUKOBZA Sébastien, BOUREDJI Houria, CHOUAHI Imad, DELACROIX Isabelle, FROISSART Antoine, GARRAIT Valérie, NGWEM Elsa, PHLIPPOTEAU Catherine, SALEHABADI Sepehr, TOPER Cécile, VINAS Florent

CHU Grenoble : AMSILLI Marie, EPAULARD Olivier, PAVESE Patricia, PIERRE Isabelle, STAHL Jean-Paul

Foch, Suresnes : AULAGNIER Jérôme, CELERIER Julie, COJOCARIU Roxana, KAHN Jean-Emmanuel, MATHIEU Emmanuel, RACHLINE Charlotte, SENE Thomas, THIERRY Christelle

Lariboisière : APARICIO Caroline, DELCEY Veronique, LOPES Amanda, MORGAND Marjolaine, SELLIER Pierre, SIMONEAU Guy

Melun : CHAKVETADZE Catherine, DIAMANTIS Sylvain, GAUTHIER Arnaud, JIDAR Kaoutar, JOURDAIN Béatrice, MARIE Elisabeth, POSTAL Pâques Marie-Joelle

CH Pontoise : BOITIAUX Jean-Francois, DESCHAMPS Patrick, DEVAUD Edouard, PHILIPPE Bruno

Raymond Poincaré : CALIN Ruxandra-Oana, CHROBOCZEK Tomasz, DAVIDO Benjamin, DE TRUCHIS Pierre, HANACHI Mouna, LAGRANGE Aurore, MAKHLOUFI Sabrina, MELLON Guillaume, SALOMON Jérôme, SENARD Olivia

CHU Rennes : REVEST Matthieu, TATTEVIN Pierre

CHU Rouen : BENHAMOU Daniel, CHAPUZET Claire, CHAUFFREY Laure, ETIENNE Manuel, JOLY Luc-Marie, OBSTOY Bérengère, SALAUN Mathieu, THIBERVILLE Luc, TILLON Julie

Saint-Antoine : BOLLENS Diane, BOTTERO Julie, CAMPA Pauline, COSQUERIC Gäelle, LEFEBVRE Bénédicte, OUAZENE Zineb, PACANOWSKI Jérôme, PATERON Dominique, THOMAS Caroline, VALIN Nadia

CH Saint-Denis : COMPAIN Caroline, CORDEL Hugues, DOUMENC Benoit, FOIS Elena, GAMBIER Nicolas, KHUONG Marie-Aude, PASQUALONI Elisa, POUPARD Marie

VOUS AVEZ AIMÉ LA PCT ?

Vous adorerez PTC !

ETUDE PTC

NEWSLETTER JANVIER 2016

Dans une galaxie proche, très proche, l'étude PTC a réussi à inclure 160 patients, soit plus de 50% de l'effectif total.

Pour pouvoir atteindre nos objectifs, nous devons inclure 13 patients par mois.

Donc, ne passez pas du côté obscur de la Force : raccourcissez la durée de traitement antibiotique !!!

QUE LA FORCE D'INCLURE SOIT AVEC VOUS !!!

« Dans PTC tu incluras et 3 jours d'antibiotiques tu prescriras ! »
Yoda

PNEUMONIE TRAITEMENT COURT

ETUDE PTC SAISON 2

WINTER IS LEAVING BUT...

FLU SEASON IS COMING

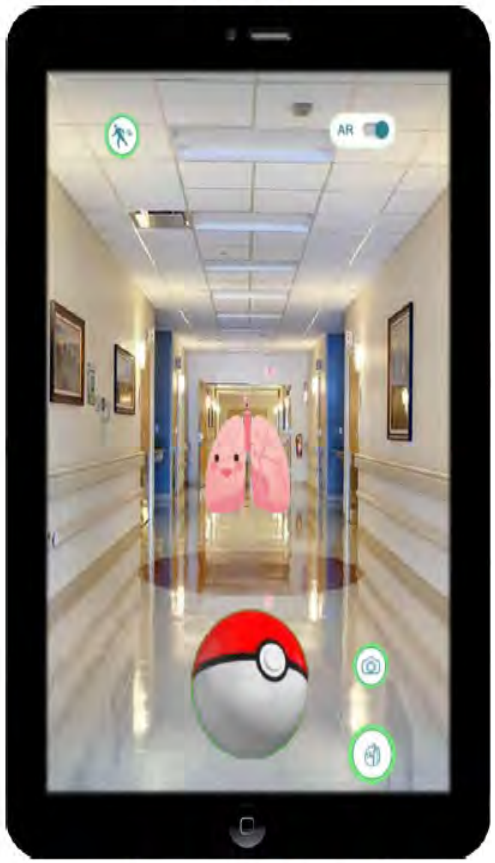
Étude PTC GO

Devenez Chasseurs de PTC !!

Comment ? C'est très simple !

1) Trouvez votre potentiel PTC

2) Capturez-le !!



Vous avez jusqu'à Octobre 2017 !!!

PTC = 198 patients !!

Qui hospitaliser ?

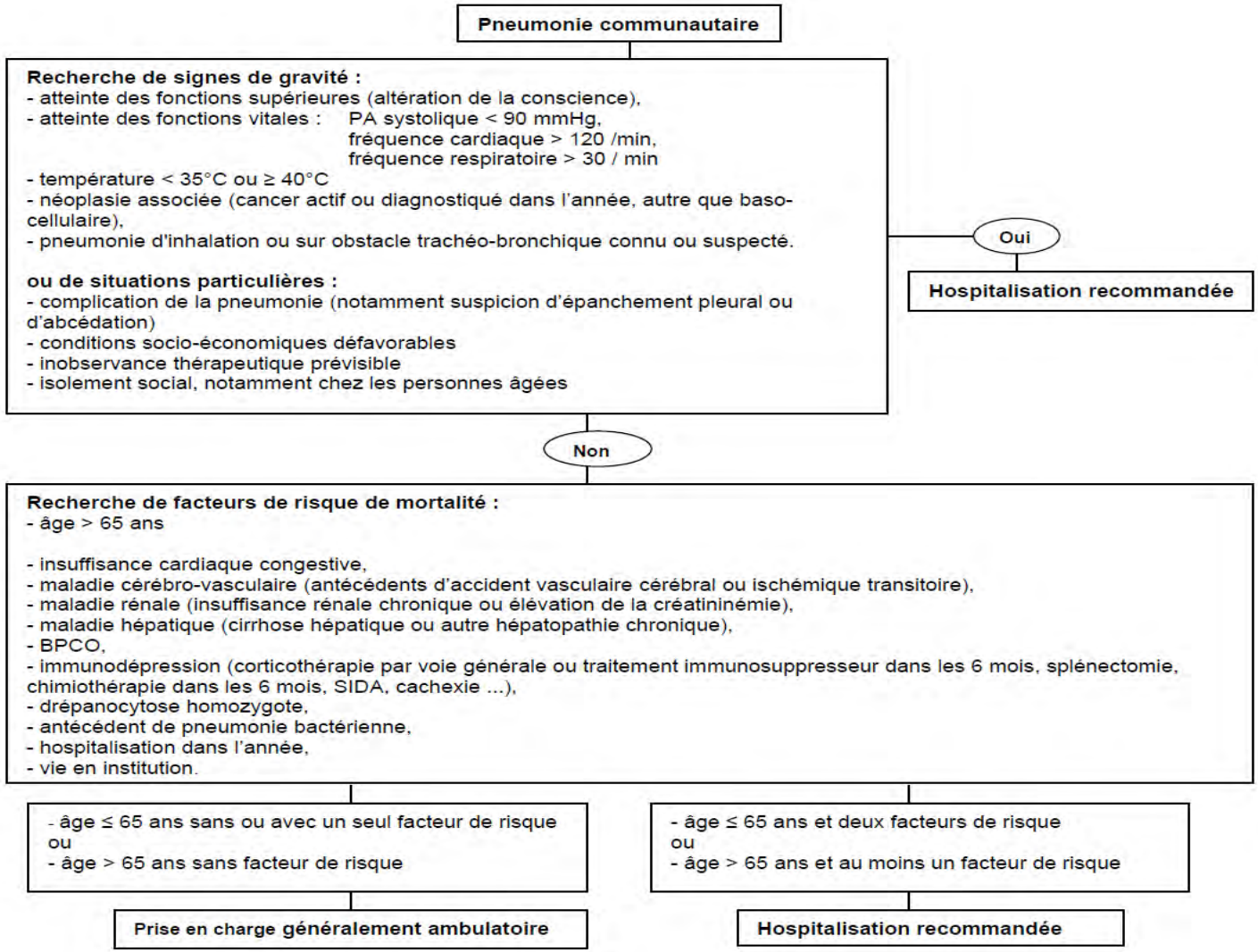


Tableau 4 : *Antibiothérapie probabiliste des Pneumonies Aiguës Communautaires non graves, hospitalisées (service d'urgence ou de médecine), situation générale*

	Premier choix	**Echec à 48 h**
Arguments en faveur du pneumocoque (pneumocoque fortement suspecté ou documenté) [4]		
Sujet jeune, sujet âgé ou sujet avec co-morbidité(s)	**Amoxicilline**	***Réévaluation***
Pas d'argument en faveur du pneumocoque		
	Premier choix	**Echec des Bêta-lactamines à 48 h**
Sujet jeune	Amoxicilline	Association à un macrolide ou substitution par FQAP (lévofloxacine)[1]
	ou pristinamycine ou télithromycine [2]	***Réévaluation***
*Sujet âgé**	Amoxicilline/acide clavulanique	Association à un macrolide
Sujet avec co-morbidité(s)	ou céfotaxime ou ceftriaxone ou FQAP (lévofloxacine)[1]	ou substitution par FQAP (lévofloxacine)[1] ***Réévaluation***

bleau 5 : *Antibiothérapie probabiliste des Pneumonies Aiguës Communautaires graves (Unité de Soins ensifs ou réanimation)*

Sujet jeune, sujet âgé, sujet avec co-morbidité(s)	C3G (céfotaxime IV ou ceftriaxone IV) + macrolide IV ou FQAP (lévofloxacine)[1]
Facteurs de risques de *Pseudomonas* : bronchectasies, mucoviscidose, antécédents d'exacerbations de BPCO dues à *P. aeruginosa*	Bêta-lactamine anti-*Pseudomonas* [2] : - pipéracilline/tazobactam - ou céfépime - ou carbapénème [3] : - *imipénème/cilastatine* - *ou méropénème* - *ou doripénème* + aminoside (amikacine ou tobramycine) au maximum 5 jours + antibiotique actif sur les bactéries intracellulaires : macrolide IV ou FQAP IV (lévofloxacine)[1]

- Bithérapie pour qui ?
- Corticoïdes quand ? Comment ?
- Durée de traitement ?

Annals of Internal Medicine

REVIEW

Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia

A Systematic Review and Meta-analysis

Background: Community-acquired pneumonia (CAP) is common and often severe.

Purpose: To examine the effect of adjunctive corticosteroid therapy on mortality, morbidity, and duration of hospitalization in patients with CAP.

Data Sources: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials through 24 May 2015.

Study Selection: Randomized trials of systemic corticosteroids in hospitalized adults with CAP.

Data Extraction: Two reviewers independently extracted study data and assessed risk of bias. Quality of evidence was assessed with the Grading of Recommendations Assessment, Development and Evaluation system by consensus among the authors.

Data Synthesis: The median age was typically in the 60s, and approximately 60% of patients were male. Adjunctive corticosteroids were associated with possible reductions in all-cause mortality (12 trials; 1974 patients; risk ratio [RR], 0.67 [95% CI, 0.45 to 1.01]; risk difference [RD], 2.8%; moderate certainty), need for mechanical ventilation (5 trials; 1060 patients; RR, 0.45 [CI, 0.26 to 0.79]; RD, 5.0%; moderate certainty), and the acute respiratory distress syndrome (4 trials; 945 patients; RR, 0.24 [CI, 0.10 to 0.56]; RD, 6.2%; moderate certainty). They also decreased time to clinical stability (5 trials; 1180 patients; mean difference, −1.22 days [CI, −2.08 to −0.35 days]; high certainty) and duration of hospitalization (6 trials; 1499 patients; mean difference, −1.00 day [CI, −1.79 to −0.21 days]; high certainty). Adjunctive corticosteroids increased frequency of hyperglycemia requiring treatment (6 trials; 1534 patients; RR, 1.49 [CI, 1.01 to 2.19]; RD, 3.5%; high certainty) but did not increase frequency of gastrointestinal hemorrhage.

Limitations: There were few events and trials for many outcomes. Trials often excluded patients at high risk for adverse events.

Conclusion: For hospitalized adults with CAP, systemic corticosteroid therapy may reduce mortality by approximately 3%, need for mechanical ventilation by approximately 5%, and hospital stay by approximately 1 day.

Primary Funding Source: None.

Ann Intern Med. doi:10.7326/M15-0715 www.annals.org

For author affiliations, see end of text.

This article was published online first at www.annals.org on 11 August 2015.

Revue de la littérature par 2 reviewers indépendants
Résultats
Âge moyen 60 ans
60% H
CTC associée avec réduction de la mortalité (3%)
De la VM (5%)
SDRA
Diminution délai avant stabilité
Durée hospitalisation (-1j)
Augmentation glycémie
Pas d'hémorragie

Figure 1. Effect of corticosteroids on all-cause mortality in patients hospitalized with community-acquired pneumonia, by severity of pneumonia.

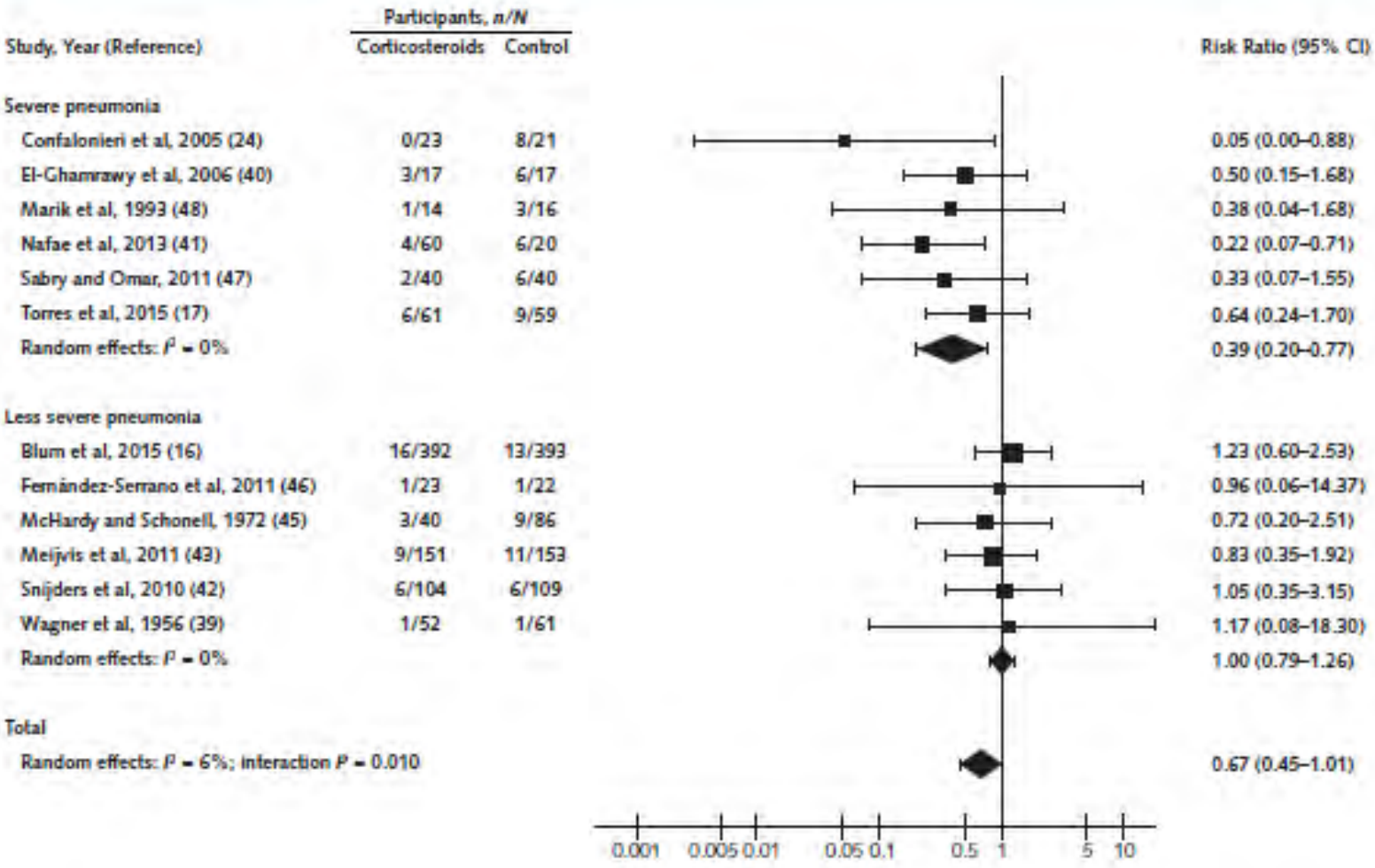


Figure 2. Effect of corticosteroids on need for mechanical ventilation in patients hospitalized with community-acquired pneumonia, by severity of pneumonia.

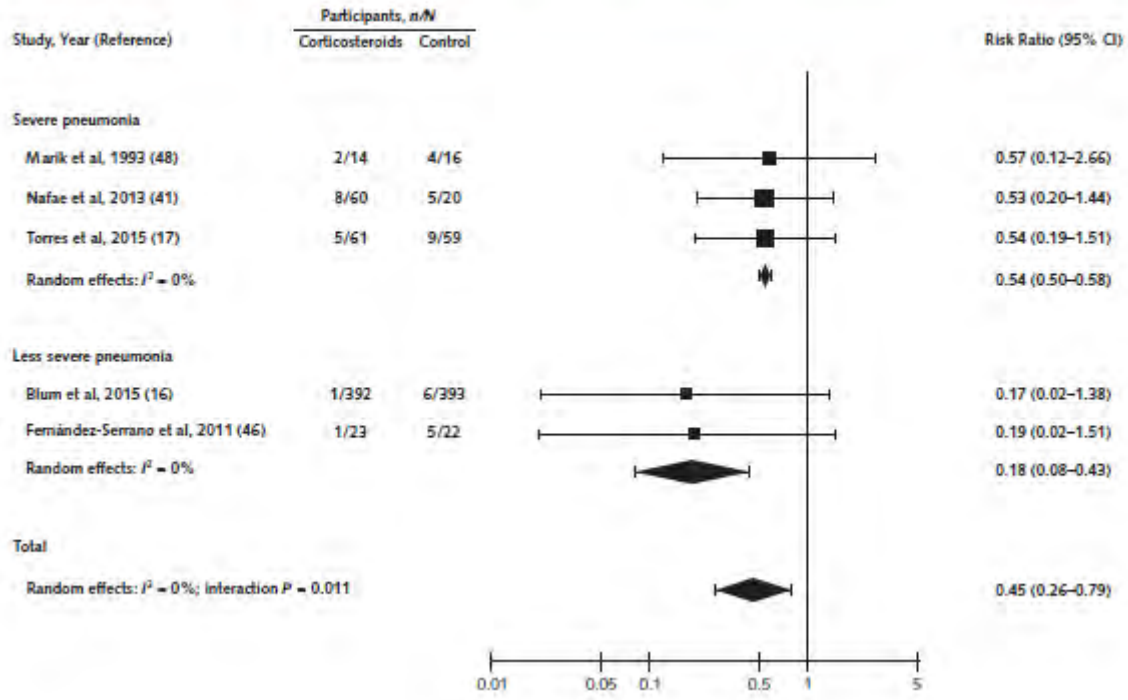


Figure 3. Effect of corticosteroids on development of the acute respiratory distress syndrome in patients hospitalized with community-acquired pneumonia.

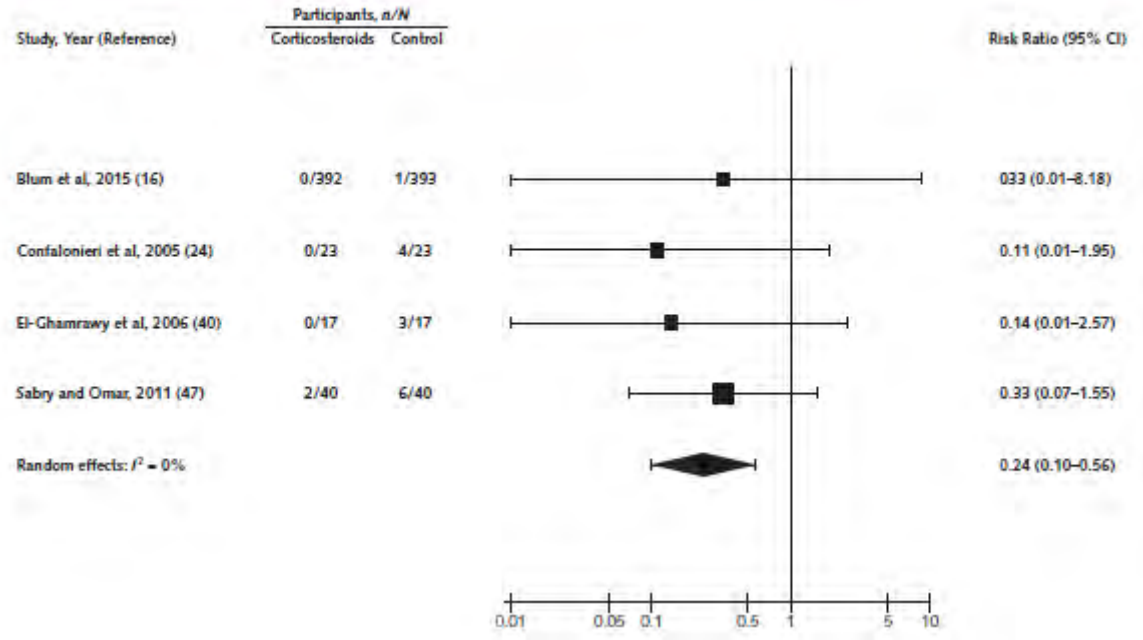
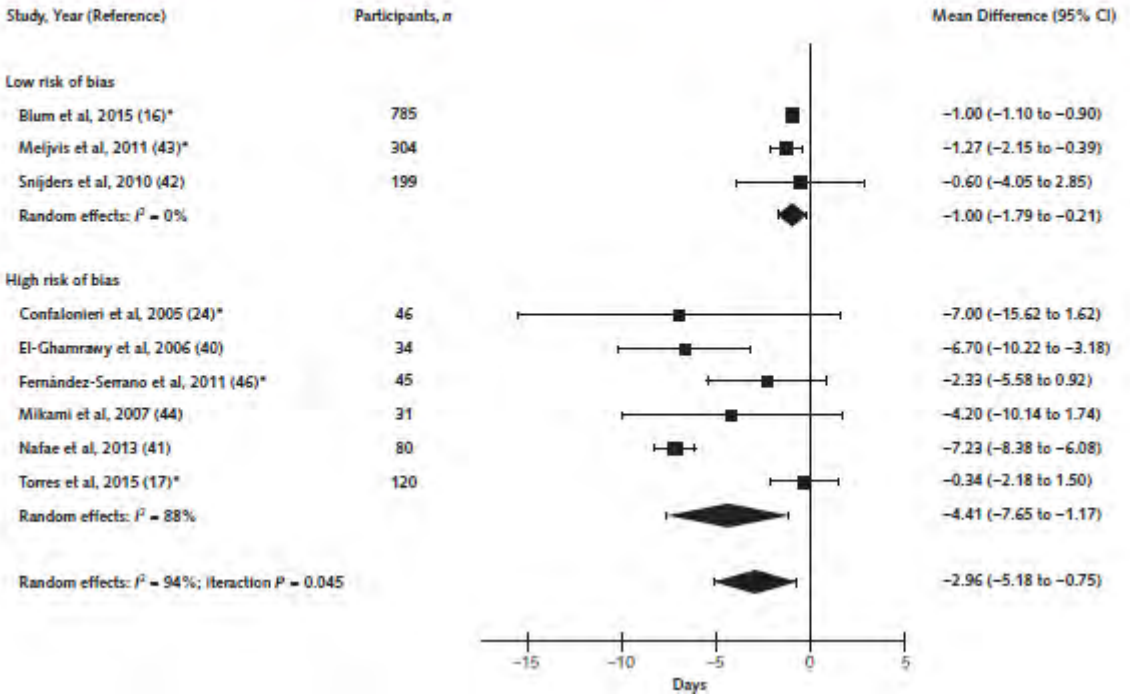


Figure 4. Effect of corticosteroids on duration of hospitalization in patients with community-acquired pneumonia, by study risk of bias.



Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial

Claudine Angela Blum, Nicole Nigro*, Matthias Briel, Philipp Schuetz, Elke Ullmer, Isabelle Suter-Widmer, Bettina Winzeler, Roland Bingisser, Hanno Elsaesser, Daniel Drozdov, Birsen Arici, Sandrine Andrea Urwyler, Julie Refardt, Philip Tarr, Sebastian Wirz, Robert Thomann, Christine Baumgartner, Hervé Duplain, Dieter Burki, Werner Zimmerli, Nicolas Rodondi, Beat Mueller, Mirjam Christ-Crain*

Summary

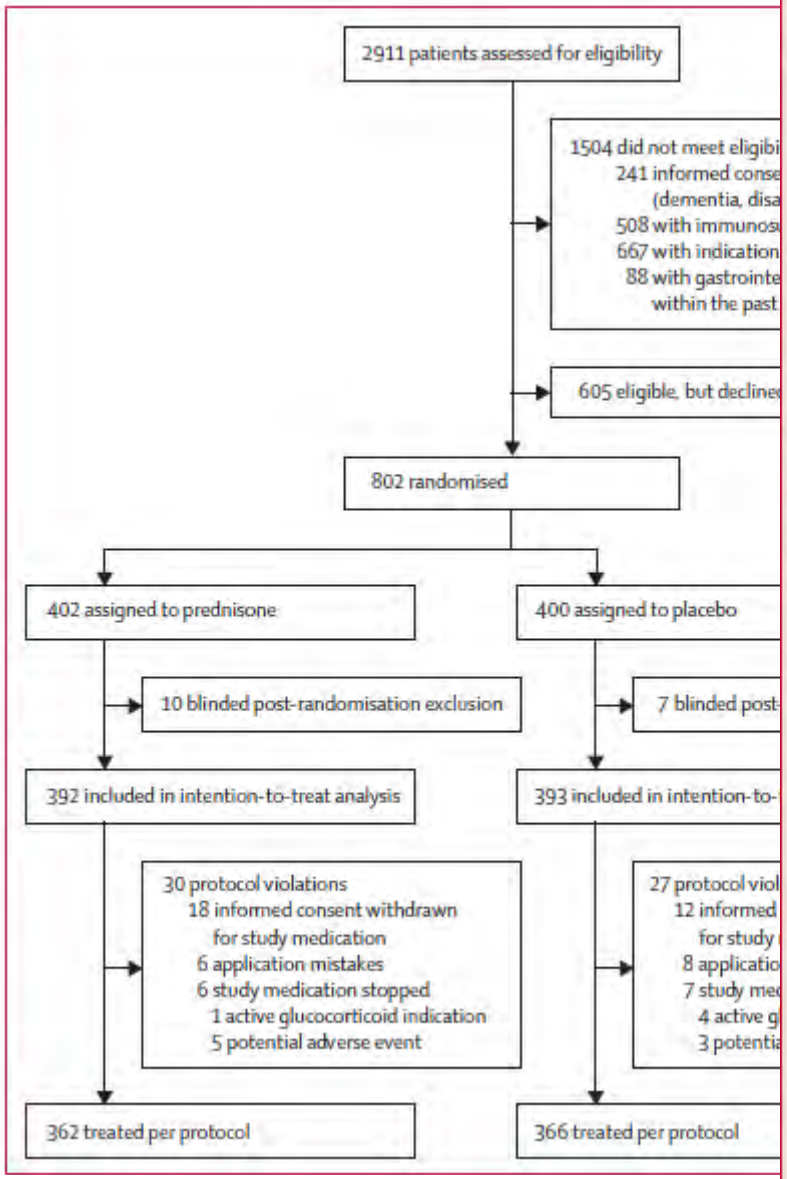
Background Clinical trials yielded conflicting data about the benefit of adding systemic corticosteroids for treatment of community-acquired pneumonia. We assessed whether short-term corticosteroid treatment reduces time to clinical stability in patients admitted to hospital for community-acquired pneumonia.

Methods In this double-blind, multicentre, randomised, placebo-controlled trial, we recruited patients aged 18 years or older with community-acquired pneumonia from seven tertiary care hospitals in Switzerland within 24 h of presentation. Patients were randomly assigned (1:1 ratio) to receive either prednisone 50 mg daily for 7 days or placebo. The computer-generated randomisation was done with variable block sizes of four to six and stratified by study centre. The primary endpoint was time to clinical stability defined as time (days) until stable vital signs for at least 24 h, and analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00973154.

Findings From Dec 1, 2009, to May 21, 2014, of 2911 patients assessed for eligibility, 785 patients were randomly assigned to either the prednisone group (n=392) or the placebo group (n=393). Median time to clinical stability was shorter in the prednisone group (3·0 days, IQR 2·5–3·4) than in the placebo group (4·4 days, 4·0–5·0; hazard ratio [HR] 1·33, 95% CI 1·15–1·50, p<0·0001). Pneumonia-associated complications until day 30 did not differ between groups (11 [3%] in the prednisone group and 22 [6%] in the placebo group; odds ratio [OR] 0·49 [95% CI 0·23–1·02]; p=0·056). The prednisone group had a higher incidence of in-hospital hyperglycaemia needing insulin treatment (76 [19%] *vs* 43 [11%]; OR 1·96, 95% CI 1·31–2·93, p=0·0010). Other adverse events compatible with corticosteroid use were rare and similar in both groups.

Interpretation Prednisone treatment for 7 days in patients with community-acquired pneumonia admitted to hospital shortens time to clinical stability without an increase in complications. This finding is relevant from a patient perspective and an important determinant of hospital costs and efficiency.

www.thelancet.com Published online January 19, 2015 http://dx.doi.org/10.1016/S0140-6736(14)62447-8



	Prednisone (n=392)	Placebo (n=393)
General characteristics		
Age, years	74 (61–83)	73 (61–82)
Male sex	241 (61%)	246 (63%)
Clinical variables		
Days with symptoms	4·0 (2·0–7·0)	4·0 (2·0–7·0)
Temperature (°C)	37·6 (37·0–38·2)	37·6 (37·0–38·2)
Systolic blood pressure (mm Hg)	124 (110–140)	123 (110–140)
Heart rate (beats per min)	84 (74–95)	82 (72–96)
Respiratory rate (breaths per min)	20 (18–24)	20 (18–24)
SaO_2 (%)	95 (92–96)	94 (92–97)
Bacteraemia	39 (10%)	48 (12%)
Confusion	22 (6%)	29 (7%)
CAP score (points)*	43 (30–60)	46 (29–63)
Laboratory values		
Procalcitonin (ng/mL)	0·52 (0·18–2·51)	0·50 (0·17–2·63)
C-reactive protein (mg/L)	159 (80·3–245)	164 (79·1–250)
White-blood-cell count (cells per µL)	12 200 (8900–15 800)	11 900 (8700–15 600)
Glucose (fasting morning, mmol/L)	6·3 (5·4–7·8)	6·5 (5·8–7·7)
PSI score†		
PSI class I	47 (12%)	45 (11%)
PSI class II	72 (18%)	69 (18%)
PSI class III	71 (18%)	95 (24%)
PSI class IV	148 (38%)	132 (34%)
PSI class V	54 (14%)	52 (13%)
Total PSI score (points)	93 (63–115)	86 (65–110)
Comorbidities		
Diabetes mellitus (any type)	77 (20%)	78 (20%)
Insulin treatment	44 (11%)	35 (9%)
Chronic obstructive pulmonary disease	73 (19%)	60 (15%)
Heart failure	80 (20%)	62 (16%)
Cerebrovascular disease	38 (10%)	31 (8%)
Renal insufficiency	125 (32%)	126 (32%)
Neoplastic disease	29 (7%)	25 (6%)
Liver disease	17 (4%)	12 (3%)
Co-infections‡	45 (11%)	46 (12%)
Antibiotic pretreatment	84 (21%)	95 (24%)

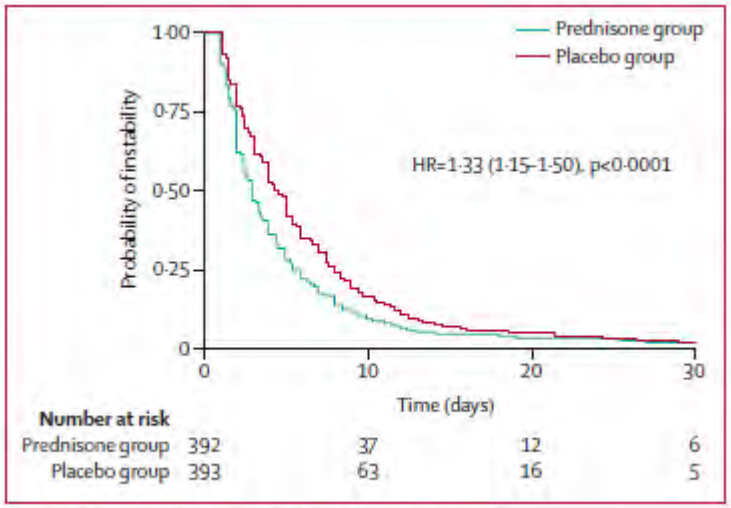


Figure 2: Kaplan-Meier-curve of time to clinical stability

	Prednisone (n=392)	Placebo (n=393)	Regression analysis	
			HR, OR, or difference (95% CI)	p value
Primary endpoint				
Intention-to-treat: time to clinical stability, days	3·0 (2·5–3·4)	4·4 (4·0–5·0)	HR 1·33 (1·15 to 1·50)	<0·0001
Per-protocol: time to clinical stability, days	3·0 (2·5–3·2)	4·4 (4·0–5·0)	HR 1·35 (1·16 to 1·56)	<0·0001
Secondary endpoints				
Time to effective hospital discharge, days	6·0 (6·0–7·0)	7·0 (7·0–8·0)	HR 1·19 (1·04 to 1·38)	0·012
Recurrent pneumonia	23 (6%)	18 (5%)	OR 1·30 (0·69 to 2·44)	0·42
Re-admission to hospital	32 (9%)	28 (8%)	OR 1·14 (0·67 to 1·93)	0·64
ICU admission	16 (4%)	22 (6%)	OR 0·72 (0·37 to 1·39)	0·32
Time to ICU admission, days	1 (1–1)	1 (1–1)	HR 0·73 (0·38 to 1·38)	0·33
Time in ICU, days	3 (2–4)	3 (1–12)	Difference –0·2 days (–8·7 to 8·2)	0·96
Death from any cause	16 (4%)	13 (3%)	OR 1·24 (0·59 to 2·62)	0·57
Time to death, days	8·0 (3·0–22·0)	9·0 (2·0–12·0)	HR 1·23 (0·59 to 2·55)	0·59
Total duration of antibiotic treatment, days	9·0 (7·0–11·0)	9·0 (7·0–12·0)	Difference –0·47 days (–1·21 to 0·27 days)	0·22
Intravenous antibiotic treatment, days	4·0 (3·0–6·0)	5·0 (3·0–7·0)	Difference –0·89 days (–1·57 to –0·20) days)	0·011
CAP score* at day 5, points	59 (41–78)	58 (40–74)	Difference 1·00 (–5·23 to 7·23)	0·75
CAP score* at day 30, points	83 (67–88)	84 (72–89)	Difference –1·00 (–4·38 to 2·38)	0·56

ORIGINAL ARTICLE

Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults

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BACKGROUND

The choice of empirical antibiotic treatment for patients with clinically suspected community-acquired pneumonia (CAP) who are admitted to non–intensive care unit (ICU) hospital wards is complicated by the limited availability of evidence. We compared strategies of empirical treatment (allowing deviations for medical reasons) with beta-lactam monotherapy, beta-lactam–macrolide combination therapy, or fluoroquinolone monotherapy.

METHODS

In a cluster-randomized, crossover trial with strategies rotated in 4-month periods, we tested the noninferiority of the beta-lactam strategy to the beta-lactam–macrolide and fluoroquinolone strategies with respect to 90-day mortality, in an intention-to-treat analysis, using a noninferiority margin of 3 percentage points and a two-sided 90% confidence interval.

RESULTS

A total of 656 patients were included during the beta-lactam strategy periods, 739 during the beta-lactam–macrolide strategy periods, and 888 during the fluoroquinolone strategy periods, with rates of adherence to the strategy of 93.0%, 88.0%, and 92.7%, respectively. The median age of the patients was 70 years. The crude 90-day mortality was 9.0% (59 patients), 11.1% (82 patients), and 8.8% (78 patients), respectively, during these strategy periods. In the intention-to-treat analysis, the risk of death was higher by 1.9 percentage points (90% confidence interval [CI], −0.6 to 4.4) with the beta-lactam–macrolide strategy than with the beta-lactam strategy and lower by 0.6 percentage points (90% CI, −2.8 to 1.9) with the fluoroquinolone strategy than with the beta-lactam strategy. These results indicated noninferiority of the beta-lactam strategy. The median length of hospital stay was 6 days for all strategies, and the median time to starting oral treatment was 3 days (interquartile range, 0 to 4) with the fluoroquinolone strategy and 4 days (interquartile range, 3 to 5) with the other strategies.

CONCLUSIONS

Among patients with clinically suspected CAP admitted to non-ICU wards, a strategy of preferred empirical treatment with beta-lactam monotherapy was noninferior to strategies with a beta-lactam–macrolide combination or fluoroquinolone monotherapy with regard to 90-day mortality. (Funded by the Netherlands Organization for Health Research and Development; CAP-START ClinicalTrials.gov number, NCT01660204.)

Table 1. Definitions.

Case definitions

Community-acquired pneumonia (CAP) (working diagnosis): The presence of at least two of the diagnostic clinical criteria and in-hospital treatment with antibiotics for clinically suspected CAP as documented by the treating physician. Patients with two or more criteria and an obvious nonrespiratory source of infection were not considered to have a working diagnosis of CAP, nor were patients who had recently been hospitalized (for >48 hours in the previous 2 weeks) or who resided in long-term care facilities.

Radiologically confirmed CAP: A working diagnosis of CAP plus the presence of a new or increased infiltrate on chest radiography or computed tomography (CT) and at least two other clinical criteria.

Diagnostic clinical criteria

Cough

Production of purulent sputum or a change in the character of sputum

Temperature >38°C or <36.1°C

Auscultatory findings consistent with pneumonia, including rales, evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony), or both

Leukocytosis (>10×10^9 white cells per liter or >15% bands)

C-reactive protein level more than 3 times the upper limit of the normal range

Dyspnea, tachypnea, or hypoxemia

New or increased infiltrate on chest radiography or CT scan

Intervention strategies*

Beta-lactam strategy: Preferred empirical treatment with amoxicillin, amoxicillin plus clavulanate, or a third-generation cephalosporin. Penicillin was not allowed as empirical beta-lactam monotherapy.

Beta-lactam–macrolide strategy: Preferred empirical treatment with penicillin, amoxicillin, amoxicillin plus clavulanate, or a third-generation cephalosporin in combination with azithromycin, erythromycin, or clarithromycin

Fluoroquinolone strategy: Preferred empirical treatment with moxifloxacin or levofloxacin

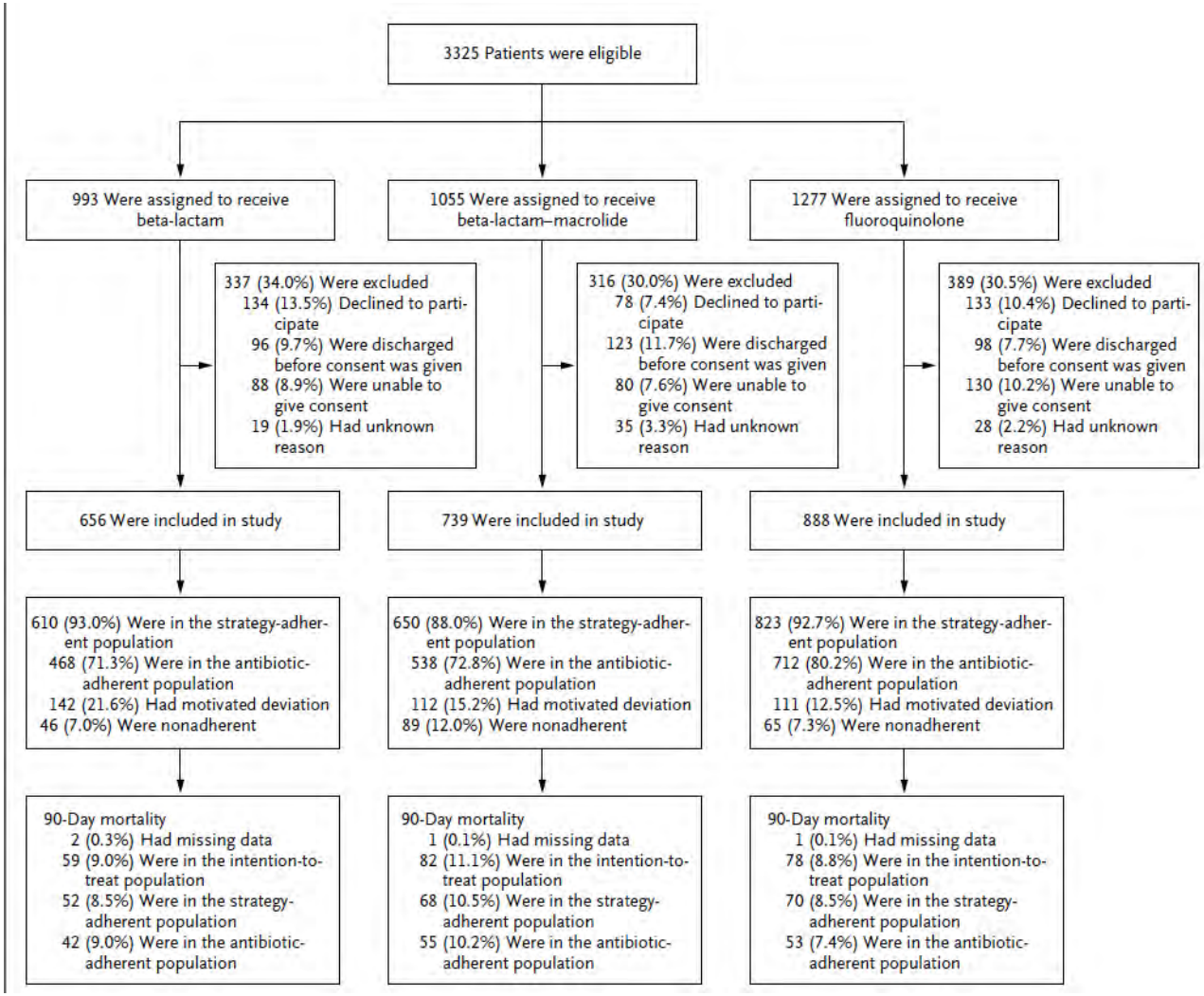

3325 Patients were eligible
993 Were assigned to receive beta-lactam
1055 Were assigned to receive beta-lactam–macrolide
1277 Were assigned to receive fluoroquinolone
337 (34.0%) Were excluded
134 (13.5%) Declined to participate
96 (9.7%) Were discharged before consent was given
88 (8.9%) Were unable to give consent
19 (1.9%) Had unknown reason
316 (30.0%) Were excluded
78 (7.4%) Declined to participate
123 (11.7%) Were discharged before consent was given
80 (7.6%) Were unable to give consent
35 (3.3%) Had unknown reason
389 (30.5%) Were excluded
133 (10.4%) Declined to participate
98 (7.7%) Were discharged before consent was given
130 (10.2%) Were unable to give consent
28 (2.2%) Had unknown reason
656 Were included in study
739 Were included in study
888 Were included in study
610 (93.0%) Were in the strategy-adherent population
468 (71.3%) Were in the antibiotic-adherent population
142 (21.6%) Had motivated deviation
46 (7.0%) Were nonadherent
650 (88.0%) Were in the strategy-adherent population
538 (72.8%) Were in the antibiotic-adherent population
112 (15.2%) Had motivated deviation
89 (12.0%) Were nonadherent
823 (92.7%) Were in the strategy-adherent population
712 (80.2%) Were in the antibiotic-adherent population
111 (12.5%) Had motivated deviation
65 (7.3%) Were nonadherent
90-Day mortality
2 (0.3%) Had missing data
59 (9.0%) Were in the intention-to-treat population
52 (8.5%) Were in the strategy-adherent population
42 (9.0%) Were in the antibiotic-adherent population
90-Day mortality
1 (0.1%) Had missing data
82 (11.1%) Were in the intention-to-treat population
68 (10.5%) Were in the strategy-adherent population
55 (10.2%) Were in the antibiotic-adherent population
90-Day mortality
1 (0.1%) Had missing data
78 (8.8%) Were in the intention-to-treat population
70 (8.5%) Were in the strategy-adherent population
53 (7.4%) Were in the antibiotic-adherent population

Table 2. Baseline Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Antibiotic Treatment Strategy		
	Beta-Lactam (N=656)	Beta-Lactam–Macrolide (N=739)	Fluoroquinolone (N=888)
Median age (interquartile range) — yr	70 (60–79)	70 (59–80)	71 (59–79)
Male sex — no. (%)	381 (58.1)	431 (58.3)	505 (56.9)
Median duration of symptoms (interquartile range) — days	3 (1–7)	3 (1–7)	3 (1–7)
Received antibiotics before admission — no./total no. (%)	219/637 (34.4)	227/721 (31.5)	303/873 (34.7)
Current smoker — no./total no. (%)	109/627 (17.4)	154/723 (21.3)	196/872 (22.5)
Past smoker — no./total no. (%)	379/627 (60.4)	398/723 (55.0)	490/872 (56.2)
Received influenza vaccination — no./total no. (%)	453/624 (72.6)	466/700 (66.6)	572/847 (67.5)
Received pneumococcal vaccination — no./total no. (%)			
PPSV23	16/594 (2.7)	18/671 (2.7)	13/822 (1.6)
PCV13	19/656 (2.9)	7/739 (0.9)	10/888 (1.1)
Dependency in ADL — no./total no. (%)†	199/637 (31.2)	200/714 (28.0)	257/870 (29.5)
Had one or more hospital stays in the previous year — no./total no. (%)	271/653 (41.5)	298/722 (41.3)	351/881 (39.8)
Had coexisting condition — no. (%)			
Cardiovascular disease	153 (23.3)	154 (20.8)	172 (19.4)
COPD or asthma	260 (39.6)	281 (38.0)	377 (42.5)
Other chronic pulmonary disease	64 (9.8)	97 (13.1)	61 (6.9)
Diabetes mellitus	118 (18.0)	101 (13.7)	161 (18.1)
Cancer‡	106 (16.2)	124 (16.8)	151 (17.0)
HIV/AIDS — no. (%)	3 (0.5)	6 (0.8)	6 (0.7)
Chronic renal failure or nephrotic syndrome	10 (1.5)	14 (1.9)	7 (0.8)
Receiving immunosuppressive therapy — no. (%)	59 (9.0)	57 (7.7)	93 (10.5)
Underwent organ or bone marrow transplantation — no. (%)	19 (2.9)	24 (3.2)	29 (3.3)
PSI score§¶	84.6±29.0	84.8±27.8	85.4±28.5
Median CURB-65 score (interquartile range)§‖	1 (1–2)	1 (1–2)	1 (1–2)
Had radiologically confirmed CAP — no. (%)	506 (77.1)	566 (76.6)	665 (74.9)
Blood culture obtained — no. (%)	508 (77.4)	559 (75.6)	670 (75.5)
Sputum culture obtained — no. (%)	306 (46.6)	347 (47.0)	390 (43.9)
PUAT performed — no. (%)	504 (76.8)	582 (78.8)	711 (80.1)
LUAT performed — no. (%)	492 (75.0)	574 (77.7)	668 (75.2)

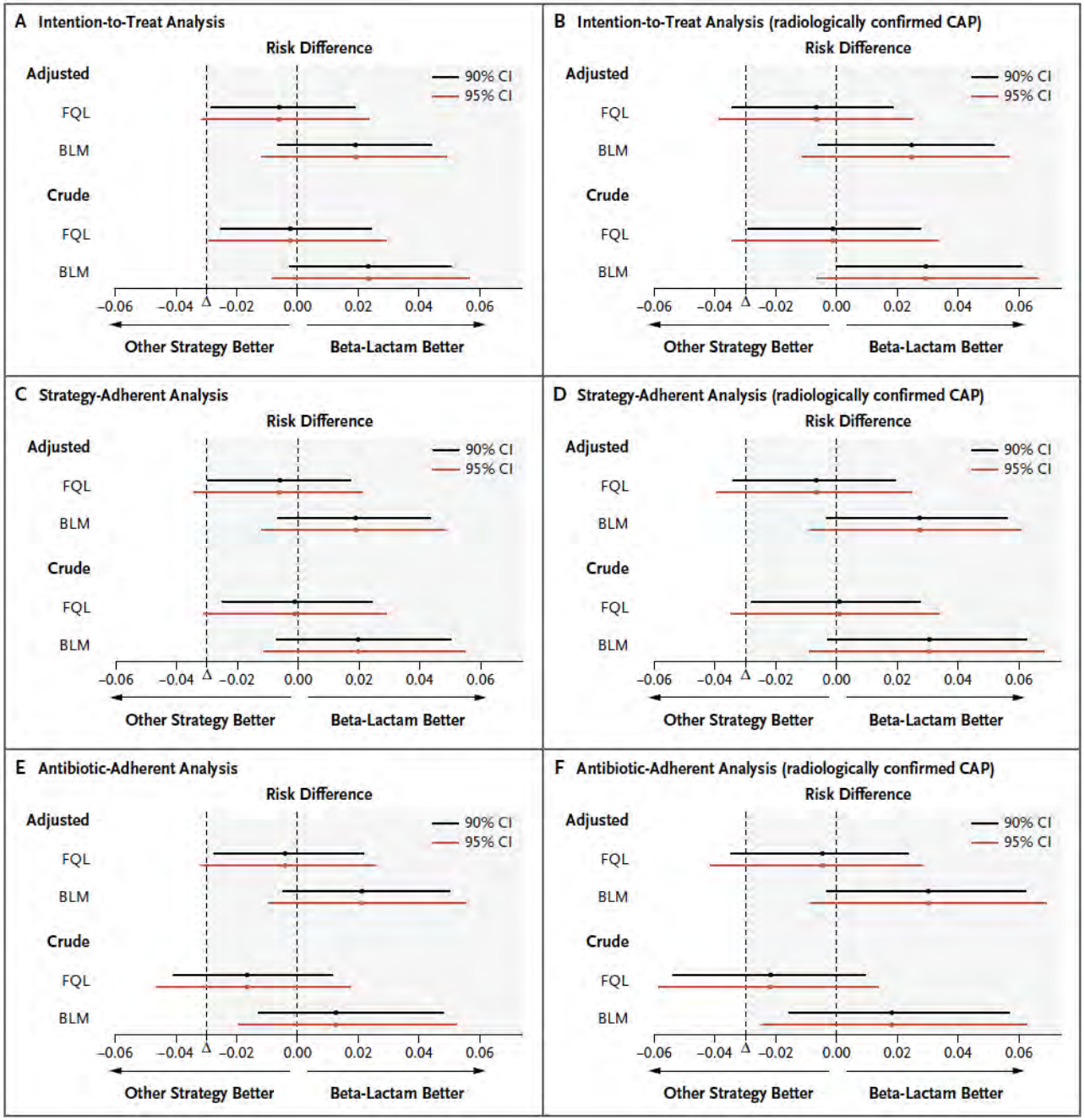

A Intention-to-Treat Analysis
B Intention-to-Treat Analysis (radiologically confirmed CAP)
C Strategy-Adherent Analysis
D Strategy-Adherent Analysis (radiologically confirmed CAP)
E Antibiotic-Adherent Analysis
F Antibiotic-Adherent Analysis (radiologically confirmed CAP)
Risk Difference
Adjusted
FQL
BLM
Crude
FQL
BLM
90% CI
95% CI
−0.06 −0.04 Δ −0.02 0.00 0.02 0.04 0.06
Other Strategy Better
Beta-Lactam Better

Table 3. Effects of Antibiotic Treatment Strategies on Secondary Outcomes.*

Outcome	Antibiotic Treatment Strategy		
	Beta-Lactam (N=656)	Beta-Lactam–Macrolide (N=739)	Fluoroquinolone (N=888)
Median length of stay (IQR) — days†	6 (4–8)	6 (4–10)	6 (4–8)
Rate ratio for discharge alive (95% CI)‡			
Intention-to-treat population			
Crude	Reference	0.86 (0.77–0.96)	1.03 (0.93–1.15)
Adjusted	Reference	0.87 (0.78–0.97)	1.04 (0.94–1.16)
Strategy-adherent population			
Crude	Reference	0.86 (0.77–0.96)	1.03 (0.93–1.15)
Adjusted	Reference	0.86 (0.77–0.97)	1.04 (0.93–1.16)
Antibiotic-adherent population			
Crude	Reference	0.84 (0.74–0.96)	1.04 (0.92–1.17)
Adjusted	Reference	0.84 (0.74–0.95)	1.03 (0.92–1.17)
Time to starting oral treatment§			
Receipt of oral antibiotics as initial in-hospital therapy — no. (%)	87 (13.3)	73 (9.9)	241 (27.1)
Median time receiving IV antibiotic treatment (IQR) — days	4 (3–5)	4 (3–5)	3 (0–4)
Rate ratio for starting oral treatment (95% CI)¶			
Intention-to-treat population			
Crude	Reference	0.95 (0.84–1.08)	1.28 (1.13–1.44)
Adjusted	Reference	0.97 (0.86–1.09)	1.29 (1.15–1.46)
Strategy-adherent population			
Crude	Reference	0.94 (0.82–1.07)	1.30 (1.15–1.48)
Adjusted	Reference	0.94 (0.83–1.08)	1.33 (1.17–1.51)
Antibiotic-adherent population			
Crude	Reference	0.93 (0.78–1.10)	1.47 (1.24–1.73)
Adjusted	Reference	0.93 (0.79–1.11)	1.52 (1.28–1.80)
Complications‖			
None — no. (%)	550 (83.8)	608 (82.3)	725 (81.6)
Minor — no. (%)	72 (11.0)	97 (13.1)	109 (12.3)
Major — no. (%)	32 (4.9)	42 (5.7)	47 (5.3)
Unknown — no. (%)	8 (1.2)	12 (1.6)	26 (2.9)
Odds ratio (95% CI)**			
Intention-to-treat population	Reference	1.06 (0.76–1.48)	1.02 (0.73–1.41)
Strategy-adherent population	Reference	1.06 (0.74–1.52)	1.03 (0.73–1.46)
Antibiotic-adherent population	Reference	1.20 (0.82–1.77)	1.03 (0.71–1.51)

Original Investigation

β-Lactam Monotherapy vs β-Lactam–Macrolide Combination Treatment in Moderately Severe Community-Acquired Pneumonia

A Randomized Noninferiority Trial

Nicolas Garin, MD; Daniel Genné, MD; Sebastian Carballo, MD, DPhil; Christian Chuard, MD; Gerhardt Eich, MD; Olivier Hugli, MD, MPH; Olivier Lamy, MD; Mathieu Nendaz, MD, MHPE; Pierre-Auguste Petignat, MD; Thomas Perneger, MD, PhD; Olivier Rutschmann, MD, MPH; Laurent Seravalli, MD; Stephan Harbarth, MD, MS; Arnaud Perrier, MD

IMPORTANCE The clinical benefit of adding a macrolide to a β-lactam for empirical treatment of moderately severe community-acquired pneumonia remains controversial.

OBJECTIVE To test noninferiority of a β-lactam alone compared with a β-lactam and macrolide combination in moderately severe community-acquired pneumonia.

DESIGN, SETTING, AND PARTICIPANTS Open-label, multicenter, noninferiority, randomized trial conducted from January 13, 2009, through January 31, 2013, in 580 immunocompetent adult patients hospitalized in 6 acute care hospitals in Switzerland for moderately severe community-acquired pneumonia. Follow-up extended to 90 days. Outcome assessors were masked to treatment allocation.

INTERVENTIONS Patients were treated with a β-lactam and a macrolide (combination arm) or with a β-lactam alone (monotherapy arm). *Legionella pneumophila* infection was systematically searched and treated by addition of a macrolide to the monotherapy arm.

MAIN OUTCOMES AND MEASURES Proportion of patients not reaching clinical stability (heart rate <100/min, systolic blood pressure >90 mm Hg, temperature <38.0°C, respiratory rate <24/min, and oxygen saturation >90% on room air) at day 7.

RESULTS After 7 days of treatment, 120 of 291 patients (41.2%) in the monotherapy arm vs 97 of 289 (33.6%) in the combination arm had not reached clinical stability (7.6% difference, $P = .07$). The upper limit of the 1-sided 90% CI was 13.0%, exceeding the predefined noninferiority boundary of 8%. Patients infected with atypical pathogens (hazard ratio [HR], 0.33; 95% CI, 0.13-0.85) or with Pneumonia Severity Index (PSI) category IV pneumonia (HR, 0.81; 95% CI, 0.59-1.10) were less likely to reach clinical stability with monotherapy, whereas patients not infected with atypical pathogens (HR, 0.99; 95% CI, 0.80-1.22) or with PSI category I to III pneumonia (HR, 1.06; 95% CI, 0.82-1.36) had equivalent outcomes in the 2 arms. There were more 30-day readmissions in the monotherapy arm (7.9% vs 3.1%, $P = .01$). Mortality, intensive care unit admission, complications, length of stay, and recurrence of pneumonia within 90 days did not differ between the 2 arms.

CONCLUSIONS AND RELEVANCE We did not find noninferiority of β-lactam monotherapy in patients hospitalized for moderately severe community-acquired pneumonia. Patients infected with atypical pathogens or with PSI category IV pneumonia had delayed clinical stability with monotherapy.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00818610

Figure 1. Randomization of Patients in the Study

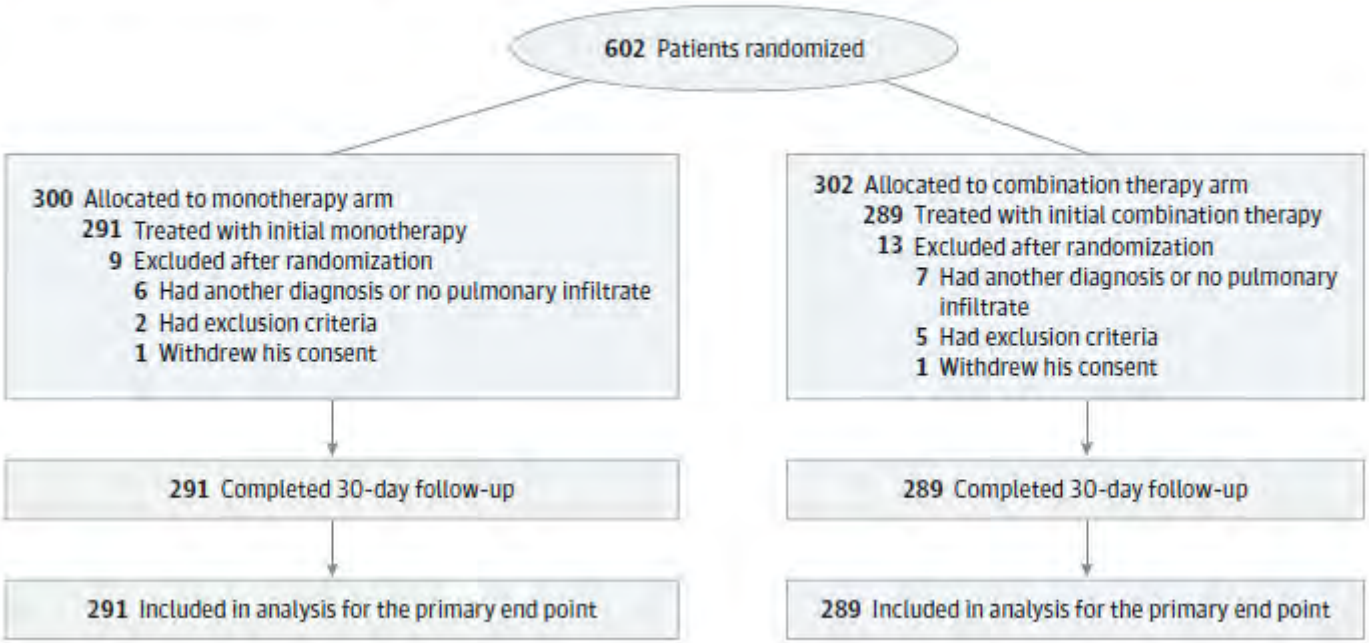


Table 1. Patient Characteristics at Baseline[a]

Characteristic	Monotherapy (n = 291)	Combination Therapy (n = 289)
Age, median (IQR), y	76 (63-84)	76 (64-83)
Male sex	162 (55.7)	171 (59.2)
Comorbidities, median (IQR)	1 (0-2)	1 (0-2)
Chronic heart failure	64 (22.0)	52 (18.0)
Chronic obstructive pulmonary disease	61 (21.0)	61 (21.1)
Diabetes mellitus	44 (15.1)	52 (18.0)
Chronic renal failure	47 (16.2)	41 (14.2)
PSI score, mean (SD)	84.5 (25.8)	84.2 (24.1)
PSI category		
I	31 (10.7)	23 (8.0)
II	50 (17.2)	55 (19.0)
III	83 (28.5)	98 (33.9)
IV	127 (43.6)	113 (39.1)
CURB-65 score ≥2	155 (53.3)	156 (54.0)
Heart rate, mean (SD), /min	100 (21)	97 (18)
Respiratory rate, mean (SD), /min	24.5 (6.2)	23.6 (5.8)
Temperature, mean (SD), °C	37.9 (1.0)	37.9 (1.0)
Hypoxemia[b]	206 (70.8)	219 (75.8)
Pleural effusion	46 (15.8)	51 (17.6)
White blood cells, mean (SD), /μL	13 400 (6300)	13 600 (6500)

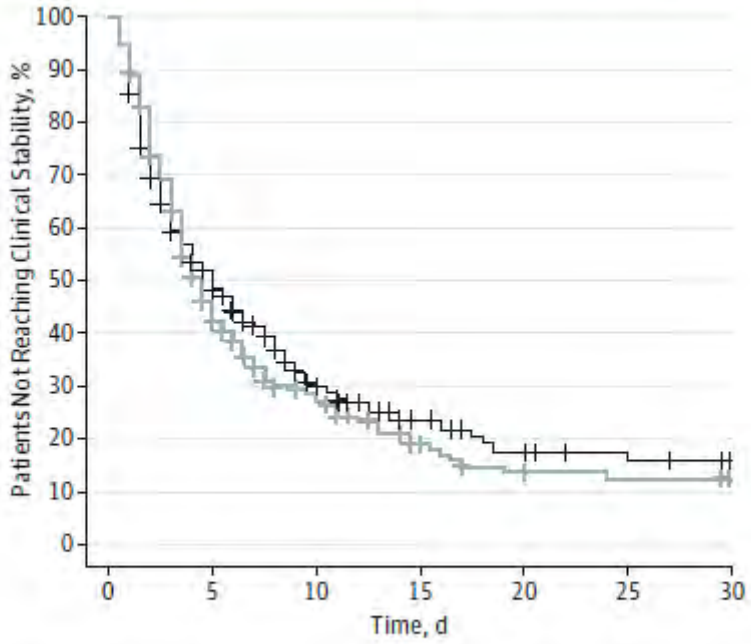
Table 2. Primary and Secondary End Points[a]

End Point	Monotherapy (n = 291)	Combination Therapy (n = 289)	*P* Value
Primary end point			
Patients not reaching clinical stability at day 7[b]	120 (41.2)	97 (33.6)	.07
Secondary end points			
Intensive care unit admission	12 (4.1)	14 (4.8)	.68
Complicated pleural effusion[c]	8 (2.7)	14 (4.8)	.19
Length of stay, median (IQR), d	8 (6-13)	8 (6-12)	.65
Any change in the initial antibiotic treatment	39 (13.4)	46 (15.8)	.39
In-hospital death	8 (2.7)	7 (2.4)	.80
30-Day death	14 (4.8)	10 (3.4)	.42
90-Day death	24 (8.2)	20 (6.9)	.54
30-Day readmission	23 (7.9)	9 (3.1)	.01
90-Day readmission	47 (16.2)	37 (12.7)	.25
New pneumonia within 30 days[d]	10 (3.4)	6 (2.1)	.31

Table 3. Hazard Ratios for Clinical Stability in the Monotherapy Arm vs Combination Arm

Variable	No. of Patients	Hazard Ratio[a] (95% CI)	*P* Value
Unadjusted		0.93 (0.76-1.13)	.46
Adjusted for age and PSI category		0.92 (0.76-1.12)	.41
Stratified			
Atypical	31	0.33 (0.13-0.85)	.02
Nonatypical	549	0.99 (0.80-1.22)	.93
P value for interaction			.03
PSI category IV	240	0.81 (0.59-1.10)	.18
PSI category I-III	340	1.06 (0.82-1.36)	.66
P value for interaction			.18
CURB-65 category 2-5	311	0.80 (0.61-1.06)	.12
CURB-65 category 0-1	269	1.13 (0.85-1.50)	.40
P value for interaction			.09
Age, y			
<65	150	1.09 (0.75-1.59)	.65
≥65	430	0.87 (0.70-1.10)	.25
P value for interaction			.32

Figure 2. Proportions of Patients Not Reaching Clinical Stability



Black line indicates monotherapy arm; blue line, combination arm. $P = .44$ (log-rank test).

Risk factors for 30-day mortality in patients with pneumonia who receive appropriate initial antibiotics: an observational cohort study

Yuichiro Shindo, Ryota Ito, Daisuke Kobayashi, Masahiko Ando, Motoshi Ichikawa, Yasuhiro Goto, Yasutaka Fukui, Mai Iwaki, Junya Okumura, Ikuo Yamaguchi, Tetsuya Yagi, Yoshimasa Tanikawa, Yasuteru Sugino, Joe Shindoh, Tomohiko Ogasawara, Fumio Nomura, Hideo Saka, Masashi Yamamoto, Hiroyuki Taniguchi, Ryujiro Suzuki, Hiroshi Saito, Takashi Kawamura, Yoshinori Hasegawa, on behalf of the Central Japan Lung Study Group

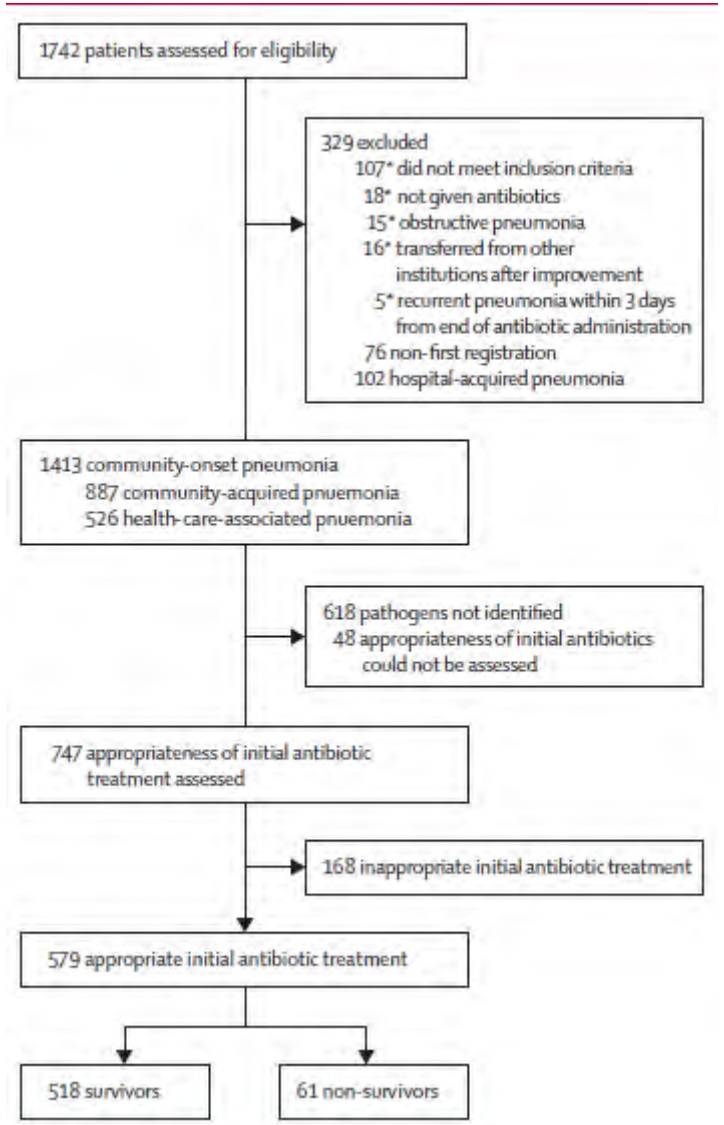
Summary

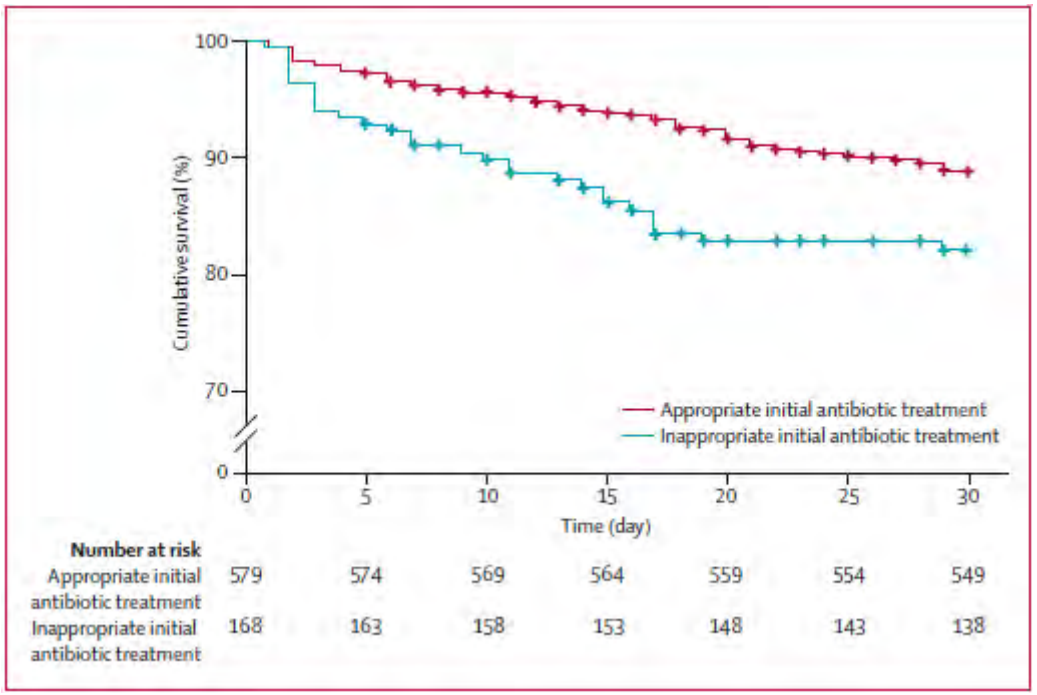
Background Appropriate initial antibiotics are essential for the treatment of infectious diseases. However, some patients with pneumonia might develop adverse outcomes, despite receiving appropriate initial antibiotics. We aimed to clarify the risk factors for 30-day mortality in patients who received appropriate initial antibiotics and to identify potential candidates who would benefit from adjunctive therapy.

Methods From March 15, to Dec 22, 2010, we did a prospective, observational study at ten medical institutions in hospitalised patients (aged ≥20 years) with pneumonia. We did a multivariable logistic regression analysis to calculate odds ratios (ORs) and 95% CI to assess the risk factors for 30-day mortality. This study was registered with the University Medical Information Network in Japan, number UMIN000003306.

Findings The 30-day mortality was 11% (61 of 579 patients) in the appropriate initial antibiotic treatment group and 17% (29 of 168) in the inappropriate initial antibiotic treatment group. Albumin concentration of less than 30 mg/L (adjusted OR 3·39, 95% CI 1·83–6·28), non-ambulatory status (3·34, 1·84–6·05), pH of less than 7·35 (3·13, 1·52–6·42), respiration rate of at least 30 breaths per min (2·33, 1·28–4·24), and blood urea nitrogen of at least 7·14 mmol/L (2·20, 1·13–4·30) were independent risk factors in patients given appropriate initial antibiotic treatment. The 30-day mortality was 1% (one of 126 patients), 1% (two of 168), 17% (23 of 137), 22% (20 of 89), and 44% (14 of 32) for patients with no, one, two, three, and four or five risk factors, respectively.

Interpretation Patients with two or more risk factors were at a higher risk of death during the 30 days assessed than were individuals with no or one risk factor, despite appropriate initial antibiotic treatment. Therefore, adjunctive therapy might be important for improving outcomes in patients with two or more risk factors.


1742 patients assessed for eligibility
329 excluded
107* did not meet inclusion criteria
18* not given antibiotics
15* obstructive pneumonia
16* transferred from other institutions after improvement
5* recurrent pneumonia within 3 days from end of antibiotic administration
76 non-first registration
102 hospital-acquired pneumonia
1413 community-onset pneumonia
887 community-acquired pneumonia
526 health-care-associated pneumonia
618 pathogens not identified
48 appropriateness of initial antibiotics could not be assessed
747 appropriateness of initial antibiotic treatment assessed
168 inappropriate initial antibiotic treatment
579 appropriate initial antibiotic treatment
518 survivors
61 non-survivors



Number at risk							
Appropriate initial antibiotic treatment	579	574	569	564	559	554	549
Inappropriate initial antibiotic treatment	168	163	158	153	148	143	138

	Total (n=579)	Survivors (n=518)	Non-survivors (n=61)
Age ≥ 80 years	244 (42%)	206 (40%)	38 (62%)
Sex, male	372 (64%)	331 (64%)	41 (67%)
Comorbidities			
Neoplastic diseases	83 (14%)	69 (13%)	14 (23%)
Chronic lung diseases	190 (33%)	168 (32%)	22 (36%)
Congestive heart failure	64 (11%)	57 (11%)	7 (11%)
Chronic renal diseases	37 (6%)	32 (6%)	5 (8%)
Chronic dialysis during the preceding 30 days	8 (1%)	5 (1%)	3 (5%)
Chronic liver diseases	22 (4%)	21 (4%)	1 (2%)
CNS disorders	134 (23%)	112 (22%)	22 (36%)
Diabetes	100 (17%)	90 (17%)	10 (16%)
Immunosuppression*	38 (7%)	34 (7%)	4 (6%)
Non-ambulatory status†	155 (27%)	119 (23%)	36 (59%)
Physical findings			
Orientation disturbance, confusion	135 (23%)	106 (20%)	29 (48%)
Systolic blood pressure <90 mm Hg	36 (6%)	31 (6%)	5 (8%)
Pulse rate ≥ 125 beats per min	67 (12%)	55 (11%)	12 (20%)
Respiration rate ≥ 30 breaths per min‡	146 (26%)	117 (23%)	29 (48%)

(Table 1 continues o

	Total (n=579)	Survivors (n=518)	Non-survivors (n=61)	p value
(Continued from previous page)				
Laboratory findings				
White blood cell count ≤ 4 × 10⁹ per L	17 (3%)	13 (3%)	4 (7%)	0·077
Haematocrit <0·3	85 (15%)	71 (14%)	14 (23%)	0·054
Platelet count < 1 × 10¹¹ per L	26 (4%)	21 (4%)	5 (8%)	0·139
Albumin <30 mg/L§	193 (34%)	154 (30%)	39 (64%)	<0·001
Total bilirubin > 20·5 µmol/L¶	100 (17%)	94 (18%)	6 (10%)	0·103
Glucose ≤ 3·3 mmol/L or ≥ 13·9 mmol/L‖	46 (8%)	37 (7%)	9 (15%)	0·039
Blood urea nitrogen ≥ 7·14 mmol/L	312 (54%)	265 (51%)	47 (77%)	<0·001
Creatinine ≥ 106 µmol/L	123 (21%)	107 (21%)	16 (26%)	0·314
Sodium concentration < 130 mmol/L or ≥ 150 mmol/L**	59 (10%)	47 (9%)	12 (20%)	0·010
Potassium concentration < 3 mmol/L or ≥ 6 mmol/L**	21 (4%)	15 (3%)	6 (10%)	0·006
C-reactive protein ≥ 200 mg/L	126 (22%)	113 (22%)	13 (21%)	0·928
pH <7·35††	62 (11%)	45 (9%)	17 (28%)	<0·001
Ratio of arterial oxygen partial pressure to fractional inspired oxygen ≤ 250††	237 (41%)	197 (38%)	40 (66%)	<0·001
Arterial carbon dioxide partial pressure ≤ 30 Torr or ≥ 50 Torr††	143 (25%)	119 (24%)	24 (40%)	0·006
Radiographic findings				
Bilateral lung involvement	269 (46%)	234 (45%)	35 (57%)	0·071
Pleural effusion	130 (22%)	108 (21%)	22 (36%)	0·007
Pneumonia Severity Index class††				<0·001‡‡
I–III	168 (30%)	167 (34%)	1 (2%)	
IV	217 (39%)	197 (40%)	20 (33%)	
V	170 (31%)	131 (26%)	39 (65%)	

	Outcome		Odds ratio (95% CI)	
	Alive	Died	Univariable analysis	Multivariable analysis
Age ≥80 years				
No (n=335)	312	23	1·00	..
Yes (n=244)	206	38	2·50 (1·45–4·32)	..
Sex, male				
No (n=207)	187	20	1·00	..
Yes (n=372)	331	41	1·16 (0·66–2·04)	..
Neoplastic diseases				
No (n=496)	449	47	1·00	..
Yes (n=83)	69	14	1·94 (1·01–3·71)	..
Chronic dialysis during the preceding 30 days				
No (n=571)	513	58	1·00	..
Yes (n=8)	5	3	5·31 (1·24–22·78)	..
CNS disorder				
No (n=445)	406	39	1·00	..
Yes (n=134)	112	22	2·05 (1·17–3·59)	..
Non-ambulatory status				
No (n=424)	399	25	1·00	1·00
Yes (n=155)	119	36	4·83 (2·79–8·37)	3·34 (1·84–6·05)
Orientation disturbance, confusion				
No (n=444)	412	32	1·00	..
Yes (n=135)	106	29	3·52 (2·04–6·08)	..
Bilateral lung involvement				
No (n=310)	284	26	1·00	..
Yes (n=269)	234	35	1·63 (0·96–2·79)	..
Pleural effusion				
No (n=449)	410	39	1·00	..
Yes (n=130)	108	22	2·14 (1·22–3·76)	..
Pulse rate ≥125 beats per min				
No (n=512)	463	49	1·00	..
Yes (n=67)	55	12	2·06 (1·03–4·11)	..
Respiration rate ≥30 breaths per min				
No (n=419)	387	32	1·00	1·00
Yes (n=146)	117	29	3·00 (1·74–5·16)	2·33 (1·28–4·24)
White blood cell count ≤4 × 10^9 per L				
No (n=563)	505	57	1·00	..
(Continued from previous column)				
Platelet count <1 × 10^{11} per L				
No (n=553)	497	56	1·00	..
Yes (n=26)	21	5	2·11 (0·77–5·82)	..
Albumin <30 mg/L				
No (n=382)	360	22	1·00	1·00
Yes (n=193)	154	39	4·14 (2·38–7·22)	3·39 (1·83–6·28)
Total bilirubin >20·5 µmol/L				
No (n=478)	423	55	1·00	..
Yes (n=100)	94	6	0·49 (0·21–1·17)	..
Glucose ≤3·3 mmol/L or ≥13·9 mmol/L				
No (n=530)	478	52	1·00	..
Yes (n=46)	37	9	2·24 (1·02–4·89)	..
Blood urea nitrogen ≥7·14 mmol/L				
No (n=267)	253	14	1·00	1·00
Yes (n=312)	265	47	3·21 (1·72–5·97)	2·20 (1·13–4·30)
Sodium concentration <130 mmol/L or ≥150 mmol/L				
No (n=519)	470	49	1·00	..
Yes (n=59)	47	12	2·45 (1·22–4·93)	..
Potassium concentration <3 mmol/L or ≥6 mmol/L				
No (n=557)	502	55	1·00	..
Yes (n=21)	15	6	3·65 (1·36–9·79)	..
pH <7·35				
No (n=502)	459	43	1·00	1·00
Yes (n=62)	45	17	4·03 (2·13–7·64)	3·13 (1·52–6·42)
Ratio of arterial oxygen partial pressure to fractional inspired oxygen ≤250				
No (n=342)	321	21	1·00	..
Yes (n=237)	197	40	3·10 (1·78–5·42)	..
Arterial carbon dioxide partial pressure ≤30 Torr or ≥50 Torr				
No (n=421)	385	36	1·00	..
Yes (n=143)	119	24	2·16 (1·24–3·76)	..

Table 3: **Risk factors for 30-day mortality in patients who were given appropriate initial antibiotic treatment**

	Risk factor 0	Risk factor 1	Risk factor 2	Risk factor 3	Risk factor 4 or 5
Patients given appropriate initial antibiotic treatment	126	168	137	89	32
30-day mortality	1 (1%)	2 (1%)	23 (17%)	20 (22%)	14 (44%)
Ambulatory patients	126	149	95	28	4
30-day mortality	1 (1%)	2 (1%)	13 (14%)	7 (25%)	1 (25%)
Non-ambulatory patients	–	19	42	61	28
30-day mortality	–	0	10 (24%)	13 (21%)	13 (46%)
Patients given appropriate initial antibiotic treatment in whom community-acquired pneumonia non-drug-resistant pathogens were identified	125	164	132	79	30
30-day mortality	1 (1%)	2 (1%)	21 (16%)	19 (24%)	12 (40%)
Patients given usual therapy for community-acquired pneumonia‡	72	62	18	9	1
30-day mortality	0 (0%)	1 (2%)	0 (0%)	1 (11%)	1 (100%)
Patients given non-anti-pseudomonal β-lactam monotherapy§	34	61	56	42	15
30-day mortality	1 (3%)	1 (2%)	9 (16%)	11 (26%)	5 (33%)
Patients given anti-pseudomonal antibiotics¶	16	31	52	21	14
30-day mortality	0 (0%)	0 (0%)	12 (23%)	7 (33%)	6 (43%)
Patients given appropriate initial antibiotic treatment, in whom community-acquired pneumonia drug-resistant pathogens were identified	1	4	5	10	2
30-day mortality	0 (0%)	0 (0%)	2 (40%)	1 (10%)	2 (100%)

Data are number or number (%). * Risk factors for 30-day mortality were non-ambulatory status, respiratory rate of at least 30 breaths per min, albumin concentration of less than 30 mg/L, blood urea nitrogen of at least 7·14 mmol/L, and a pH of less than 7·35. †27 patients, including one patient who died, were not included because of missing values for the risk factors. ‡Combination therapy with β lactams (ceftriaxone or ampicillin–sulbactam) plus macrolides (azithromycin, clarithromycin, or erythromycin); during the study, erythromycin was the only available intravenous macrolide in Japan. §Ampicillin, ampicillin–sulbactam, ceftriaxone, and cefotaxime. ¶Piperacillin–tazobactam, piperacillin, ceftazidime, cefepime, cefozopran, cefoperazone–sulbactam, aztreonam, imipenem–cilastatin, meropenem, doripenem, biapenem, ciprofloxacin, pazufloxacin, tobramycin, isepamycin, amikacin, and arbekacin.

Table 4: **30-day mortality in patients with different numbers of risk factors**

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Corticosteroids on Treatment Failure Among Hospitalized Patients With Severe Community-Acquired Pneumonia and High Inflammatory Response

A Randomized Clinical Trial

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IMPORTANCE In patients with severe community-acquired pneumonia, treatment failure is associated with excessive inflammatory response and worse outcomes. Corticosteroids may modulate cytokine release in these patients, but the benefit of this adjunctive therapy remains controversial.

OBJECTIVE To assess the effect of corticosteroids in patients with severe community-acquired pneumonia and high associated inflammatory response.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, double-blind, placebo-controlled trial conducted in 3 Spanish teaching hospitals involving patients with both severe community-acquired pneumonia and a high inflammatory response, which was defined as a level of C-reactive protein greater than 150 mg/L at admission. Patients were recruited and followed up from June 2004 through February 2012.

INTERVENTIONS Patients were randomized to receive either an intravenous bolus of 0.5 mg/kg per 12 hours of methylprednisolone (n = 61) or placebo (n = 59) for 5 days started within 36 hours of hospital admission.

MAIN OUTCOMES AND MEASURES The primary outcome was treatment failure (composite outcome of early treatment failure defined as [1] clinical deterioration indicated by development of shock, [2] need for invasive mechanical ventilation not present at baseline, or [3] death within 72 hours of treatment; or composite outcome of late treatment failure defined as [1] radiographic progression, [2] persistence of severe respiratory failure, [3] development of shock, [4] need for invasive mechanical ventilation not present at baseline, or [5] death between 72 hours and 120 hours after treatment initiation; or both early and late treatment failure). In-hospital mortality was a secondary outcome and adverse events were assessed.

RESULTS There was less treatment failure among patients from the methylprednisolone group (8 patients [13%]) compared with the placebo group (18 patients [31%]) (P = .02), with a difference between groups of 18% (95% CI, 3% to 32%). Corticosteroid treatment reduced the risk of treatment failure (odds ratio, 0.34 [95% CI, 0.14 to 0.87]; P = .02). In-hospital mortality did not differ between the 2 groups (6 patients [10%] in the methylprednisolone group vs 9 patients [15%] in the placebo group; P = .37); the difference between groups was 5% (95% CI, −6% to 17%). Hyperglycemia occurred in 11 patients (18%) in the methylprednisolone group and in 7 patients (12%) in the placebo group (P = .34).

CONCLUSIONS AND RELEVANCE Among patients with severe community-acquired pneumonia and high initial inflammatory response, the acute use of methylprednisolone compared with placebo decreased treatment failure. If replicated, these findings would support the use of corticosteroids as adjunctive treatment in this clinical population.

Figure 1. Flow Diagram of the Study With Detailed Information on Allocation and the Excluded Patients

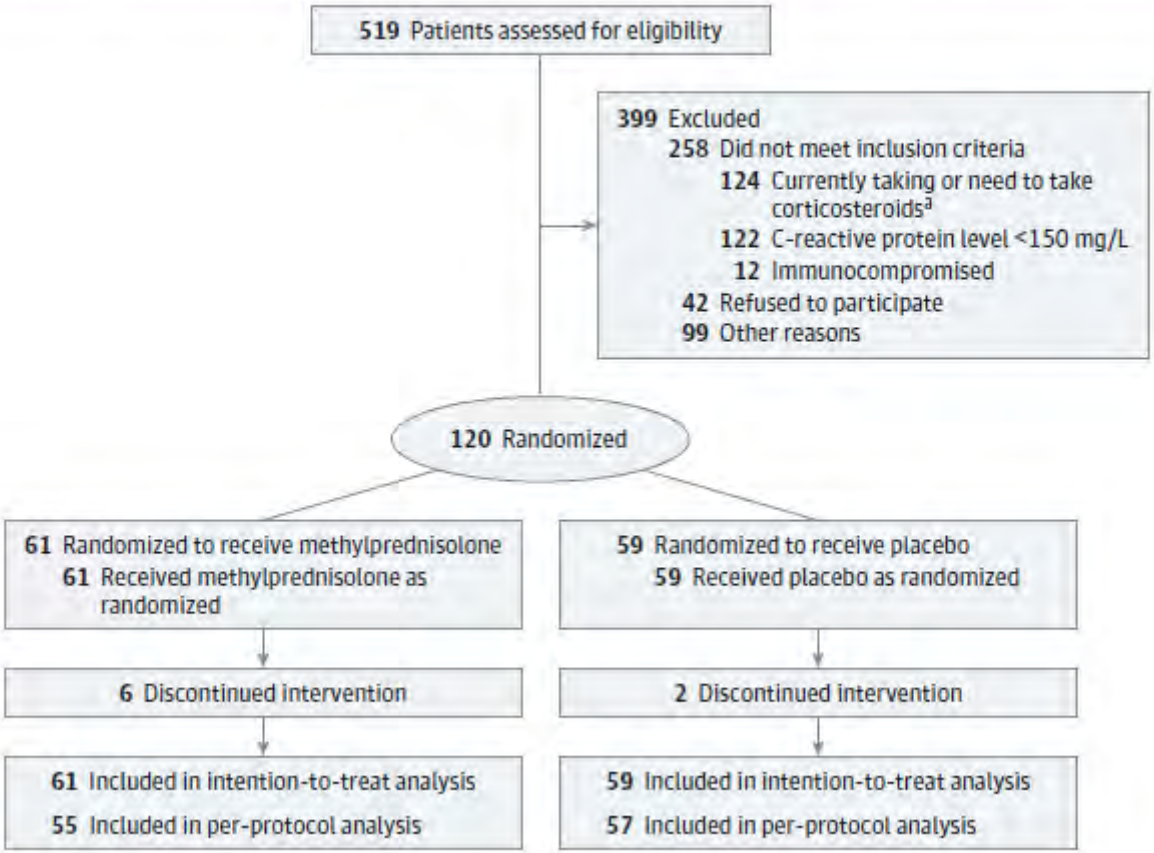


Table 1. Baseline Characteristics of the Intention-to-Treat Population

	Methylprednisolone (n = 61)	Placebo (n = 59)
Age, mean (SD), y	64.5 (19.1)	66.1 (20.1)
Male sex, No. (%)	35 (57)	39 (66)
Current smoker, No. (%)	15 (25)	17 (29)
Preexisting comorbid conditions, No. (%)[a]		
Diabetes mellitus	10 (16)	13 (22)
Chronic pulmonary disease	7 (11)	12 (20)
Congestive heart failure	22 (36)	24 (41)
History of malignancy	3 (5)	8 (14)
Ischemic heart disease	12 (20)	9 (15)
Symptoms, No. (%)		
Fever	48 (79)	41 (69)
Altered mental status	13 (21)	14 (24)
Breathlessness	35 (57)	36 (61)
Cough	46 (75)	40 (68)
Chills	23 (38)	20 (34)
Chest pain	21 (34)	26 (44)
Clinical signs, mean (SD)		
Temperature, °C	37.6 (1.1)	37.6 (1.0)
Respiratory rate, breaths/min	30.0 (8.0)	29.7 (8.9)
Heart rate, beats/min	105.5 (20.6)	113.5 (23.7)
Serum levels, median (IQR)		
Glucose, mg/dL	131 (106-159)	129 (107-180)
Creatinine, mg/dL	1.3 (0.9-1.8)	1.3 (1.0-1.8)
Platelets, $\times 10^9$/L	214 (176-282)	217 (175-283)
White blood cell count, $\times 10^9$/L	12.7 (9.0-17.2)	14.4 (9.2-23.0)
C-reactive protein, mg/L[b]	273 (202-292)	244 (172-289)
Procalcitonin, ng/dL[b]	1.3 (0.4-4.4)	3.1 (0.8-9.5)
IL-6, pg/dL[b]	256 (133-674)	316 (182-834)
IL-8, pg/dL[b]	74 (34-107)	88 (55-182)
IL-10, pg/dL[b]	4.7 (2.8-9.2)	8.1 (4.0-13.5)

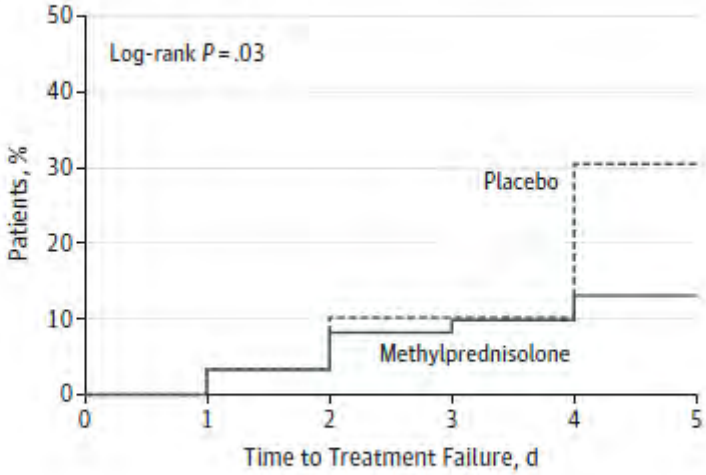
Table 2. Clinical Outcomes Using Descriptive Statistics for the Intention-to-Treat and Per-Protocol Populations

	Intention-to-Treat Population				Per-Protocol Population			
	Methylprednisolone Group (n = 61)	Placebo Group, (n = 59)	*P* Value	Difference Between Groups, % (95% CI)	Methylprednisolone Group (n = 55)	Placebo Group (n = 57)	*P* Value	Difference Between Groups, % (95% CI)
Primary Clinical Outcome								
Treatment failure, No. (%)[a]	8 (13)	18 (31)	.02	18 (3 to 32)	5 (9)	16 (28)	.01	19 (5 to 33)
Early treatment failure (0-72 h), No. (%)[b]	6 (10)	6 (10)	.95	0 (−10 to 11)	3 (5)	4 (7)	>.99	2 (−7 to 11)
Early mechanical ventilation	4 (7)	5 (8)	.74	2 (−8 to 11)	2 (4)	3 (5)	>.99	2 (−6 to 9)
Early septic shock	2 (3)	3 (5)	.68	2 (−5 to 9)	1 (2)	2 (4)	>.99	2 (−4 to 8)
Death	2 (3)	2 (3)	>.99	0 (−6 to 7)	0	0		
Late treatment failure (72-120 h), No. (%)[b]	2 (3)	15 (25)	.001	22 (10 to 34)	2 (4)	14 (25)	.002	21 (9 to 33)
Radiographic progression	1 (2)	9 (15)	.007	14 (4 to 23)	1 (2)	8 (14)	.03	12 (3 to 22)
Respiratory failure	1 (2)	5 (8)	.11	7 (−1 to 15)	1 (2)	5 (9)	.21	7 (−1 to 15)
Late mechanical ventilation	1 (2)	4 (7)	.20	5 (−2 to 12)	1 (2)	4 (7)	.36	5 (−2 to 13)
Late septic shock	0	4 (7)	.06	7 (0 to 13)	0	4 (7)	.12	7 (0 to 14)
Death	0	0			0	0		
Secondary Clinical Outcomes								
Time to clinical stability, median (IQR), d[c]	4 (3 to 6)	5 (3 to 7)	.28	1 (−0.4 to 2.4)	4 (3 to 6)	5 (3 to 7)	.13	1 (0 to 2)
Length of stay, median (IQR), d								
Hospital	11 (7.5 to 14)	10.5 (8 to 15)	.83	−0.5 (−4.6 to 3.6)	11 (8 to 14)	11.5 (8 to 15)	.70	0.5 (−3.3 to 4.3)
ICU[d]	5 (3 to 8)	6 (4 to 8)	.63	1 (−0.4 to 2.4)	5 (3 to 8)	6 (4 to 8)	.38	1 (0 to 2)
In-hospital mortality, No. (%)	6 (10)	9 (15)	.37	5 (−6 to 17)	3 (5)	7 (12)	.21	7 (−4 to 17)

Table 3. Clinical Outcomes for the Methylprednisolone Group vs Placebo Group Using Logistic Regression or Cox Proportional Hazards Models for the Intention-to-Treat and Per-Protocol Populations

	Intention-to-Treat Population				Per-Protocol Population			
	Unadjusted OR or HR (95% CI)	*P* Value	Adjusted OR or HR (95% CI)[a]	*P* Value	Unadjusted OR or HR (95% CI)	*P* Value	Adjusted OR or HR (95% CI)[a]	*P* Value
Primary Clinical Outcome								
Treatment failure[b]	0.34 (0.14-0.87)	.02	0.33 (0.12-0.90)	.03	0.26 (0.09-0.76)	.01	0.26 (0.08-0.79)	.02
Early treatment failure (0-72 h)[c]	0.96 (0.29-3.18)	.95	1.14 (0.28-4.67)	.86	0.76 (0.16-3.58)	.73	0.93 (0.17-5.06)	.94
Early mechanical ventilation	0.76 (0.19-2.97)	.69	1.02 (0.18-5.83)	.98	0.68 (0.11-4.23)	.68	0.77 (0.09-6.46)	.81
Early septic shock	0.63 (0.10-3.93)	.62	0.38 (0.03-4.42)	.44	0.51 (0.05-5.78)	.59	0.42 (0.04-4.90)	.49
Death	0.97 (0.13-7.09)	.97	1.35 (0.04-40.84)	.86				
Late treatment failure (72-120 h)[c]	0.10 (0.02-0.46)	.003	0.09 (0.02-0.47)	.004	0.12 (0.03-0.54)	.006	0.11 (0.02-0.52)	.006
Radiographic progression	0.09 (0.01-0.76)	.03	0.09 (0.01-0.78)	.03	0.11 (0.01-0.94)	.04	0.10 (0.01-0.84)	.03
Respiratory failure	0.18 (0.02-1.59)	.12	0.14 (0.01-1.35)	.09	0.19 (0.02-1.71)	.14	0.15 (0.02-1.50)	.11
Late mechanical ventilation	0.23 (0.03-2.11)	.19	0.20 (0.02-1.91)	.16	0.25 (0.03-2.27)	.22	0.22 (0.02-2.10)	.19
Late septic shock	0 (0-∞)[d]	>.99	0 (0-∞)[d]	>.99	0 (0-∞)[d]	>.99	0 (0-∞)[d]	>.99
Death	0		0		0		0	
Secondary Clinical Outcomes								
Time to clinical stability, d[e]	1.16 (0.78-1.73)	.46	1.11 (0.72-1.71)	.64	1.24 (0.83-1.87)	.29	1.20 (0.77-1.85)	.42
Length of stay, d								
Hospital	0.66 (0.23-1.85)	.43	0.61 (0.19-1.93)	.40	0.47 (0.12-1.81)	.27	0.40 (0.10-1.63)	.20
ICU[f]	0.18 (0.02-1.46)	.11	0.13 (0.01-1.44)	.10	0.02 (0-60.31)	.33	0 (0-∞)[d]	.29
In-hospital mortality	0.61 (0.20-1.82)	.37	0.57 (0.16-2.00)	.38	0.41 (0.10-1.68)	.22	0.38 (0.08-1.70)	.21

Figure 2. Kaplan-Meier Analysis of the Effect of Methylprednisolone on Time to Treatment Failure



No. at risk						
Placebo	59	57	53	53	41	41
Methylprednisolone	61	59	56	55	53	53

Hôpitaux Universitaires
Paris Ile-de-France Ouest
RAYMOND POINCARÉ • BERCK
AMBROISE PARÉ • SAINTE PÉRINE

Service de pneumologie le 15 novembre 2013

Durée de traitement des pneumonies : intérêt et faisabilité des traitements de durée courte

Aurélien DINH,
Référent antibiotique
Hôpitaux Paris Ile de France Ouest

Antibiotic-Resistant Bugs in the 21st Century
A Clinical Super-Challenge

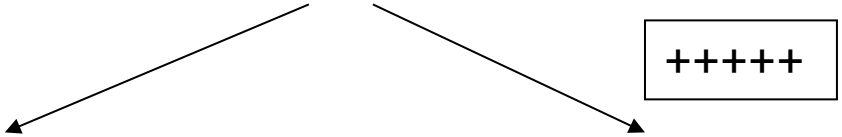
N ENGL J MED 360;5 NEJM.ORG JANUARY 29, 2009

Cesar A. Arias, M.D., Ph.D., and Barbara E. Murray, M.D.

Multidrug-Resistant Bacterial Organisms Causing Major Clinical Problems.*

Organism and Antibiotic Resistance	Common Mechanism of Resistance	Recent, Resurrected, and Future Antimicrobial Agents with Potential Clinical Use
Hospital-associated MRSA†		
Vancomycin (both VISA and VRSA)	Thickening of cell wall (not fully elucidated); change in the last amino acid of peptidoglycan precursors	Linezolid, quinupristin–dalfopristin, daptomycin, tigecycline, ceftobiprole, ceftaroline, dalbavancin, telavancin, oritavancin, iclaprim
Daptomycin	Associated with changes in cell wall and cell membrane (not fully elucidated)	Linezolid, quinupristin–dalfopristin, tigecycline, ceftobiprole, ceftaroline, dalbavancin, telavancin, oritavancin, iclaprim
Linezolid	Mutations in the 23S ribosomal RNA genes; rarely, acquisition of a methyltransferase gene (*cfr*)	Daptomycin, quinupristin–dalfopristin, tigecycline, ceftobiprole, ceftaroline, dalbavancin, telavancin, oritavancin, iclaprim
Vancomycin-resistant *Enterococcus faecium*‡		
Ampicillin (common)	Mutation and overexpression of *pbp5*	Linezolid, quinupristin–dalfopristin, daptomycin, tigecycline
High-level resistance to aminoglycosides	Acquisition of aminoglycoside-modifying enzymes; ribosomal mutations (streptomycin)	No alternative for a reliable bactericidal effect alone or in combination
Linezolid	Mutations in the 23S ribosomal RNA genes	Quinupristin–dalfopristin, daptomycin, tigecycline
Daptomycin	Unknown	Linezolid, quinupristin–dalfopristin, tigecycline
Quinupristin–dalfopristin	Enzymes that inactivate quinupristin–dalfopristin, target modification	Daptomycin, linezolid, tigecycline
Escherichia coli, klebsiella species, and enterobacter species§		
Oxyimino-cephalosporins (ceftriaxone, cefotaxime, ceftazidime, and cefepime)	Extended-spectrum β-lactamases (includes hyperproduction of the AmpC enzymes by Enterobacteriaceae family)	Carbapenems, tigecycline
Carbapenems	Production of carbapenemases, decreased permeability	Polymyxins, tigecycline
Acinetobacter species¶		
Carbapenems	Decreased permeability, increased efflux, and production of carbapenemases	Polymyxins
Pseudomonas aeruginosa¶		
Carbapenems	Decreased permeability, increased efflux, and production of carbapenemases	Polymyxins

Mécanisme d'émergences de résistances



- **Direct :** Émergence de résistance au site infectieux
  - **Une seule espèce**
  - **Faible nombre de bactéries**
  - **Ne touche que les patients réellement infectés**
  - **Un seul mécanisme de résistance**

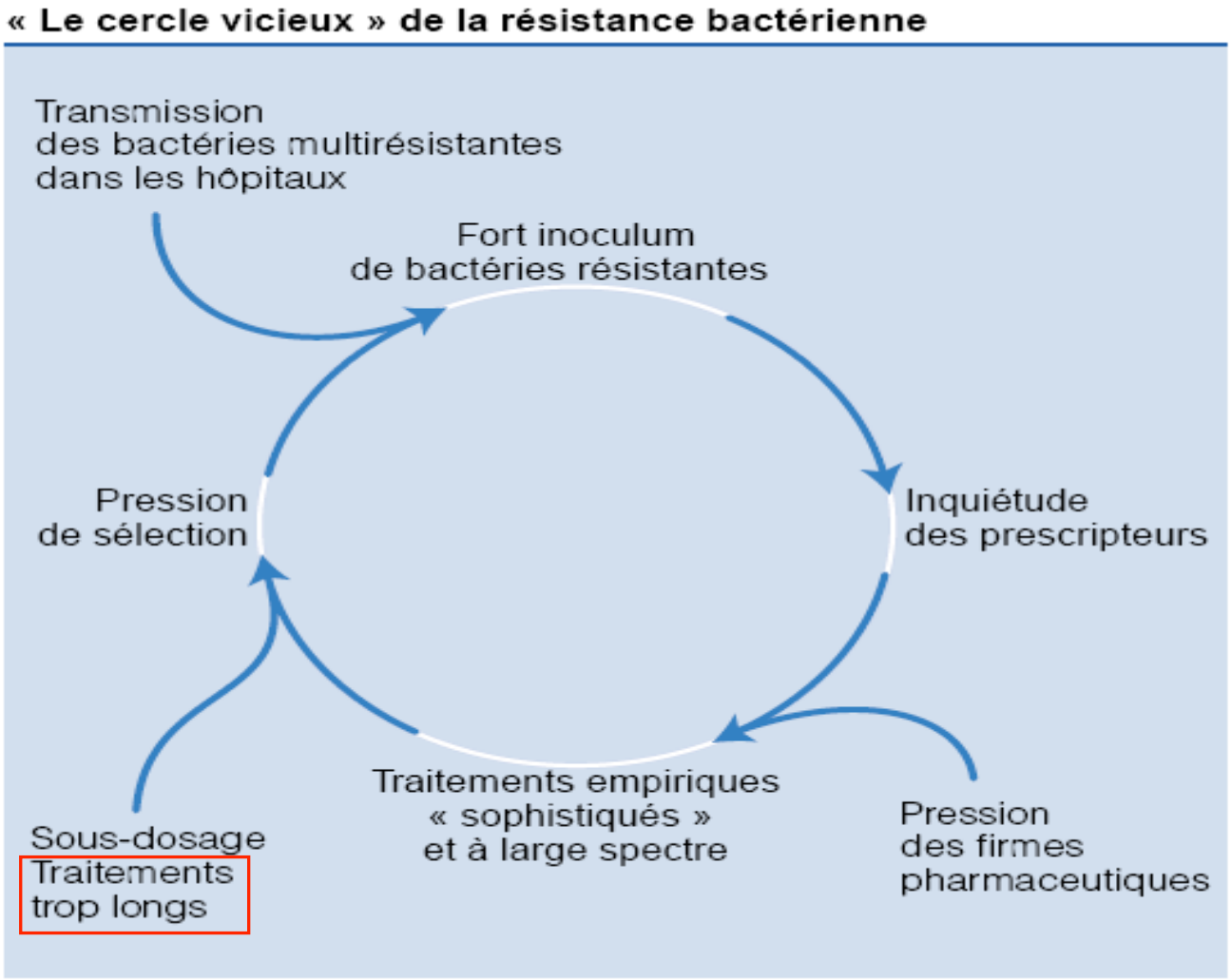
- **Indirecte :** émergence de résistance au niveau de la flore commensale (cutanée, digestive)
  - **Plusieurs espèces**
  - **Grand nombre de bactéries**
  - **Mécanismes de résistance multiple**
  - **Touche tous les patients mêmes non traités**

Rationnel

- 48h d'ATB >> modification des flores digestives et cutanées avec augmentation de la proportion de la résistance bactérienne (Korinek, Ann fr anesth rea 2000).
- Flore commensale contribue à la dissémination des gènes de résistance aux antibiotiques (AC Crémieux, AAC 2003)
- La quantité d'ATB prescrite est liée au taux de résistance bactérienne (Goossens H. Lancet 2005, Schrag SJ JAMA 2001)

Impact sur les flores commensales

Cercle vicieux de la résistance

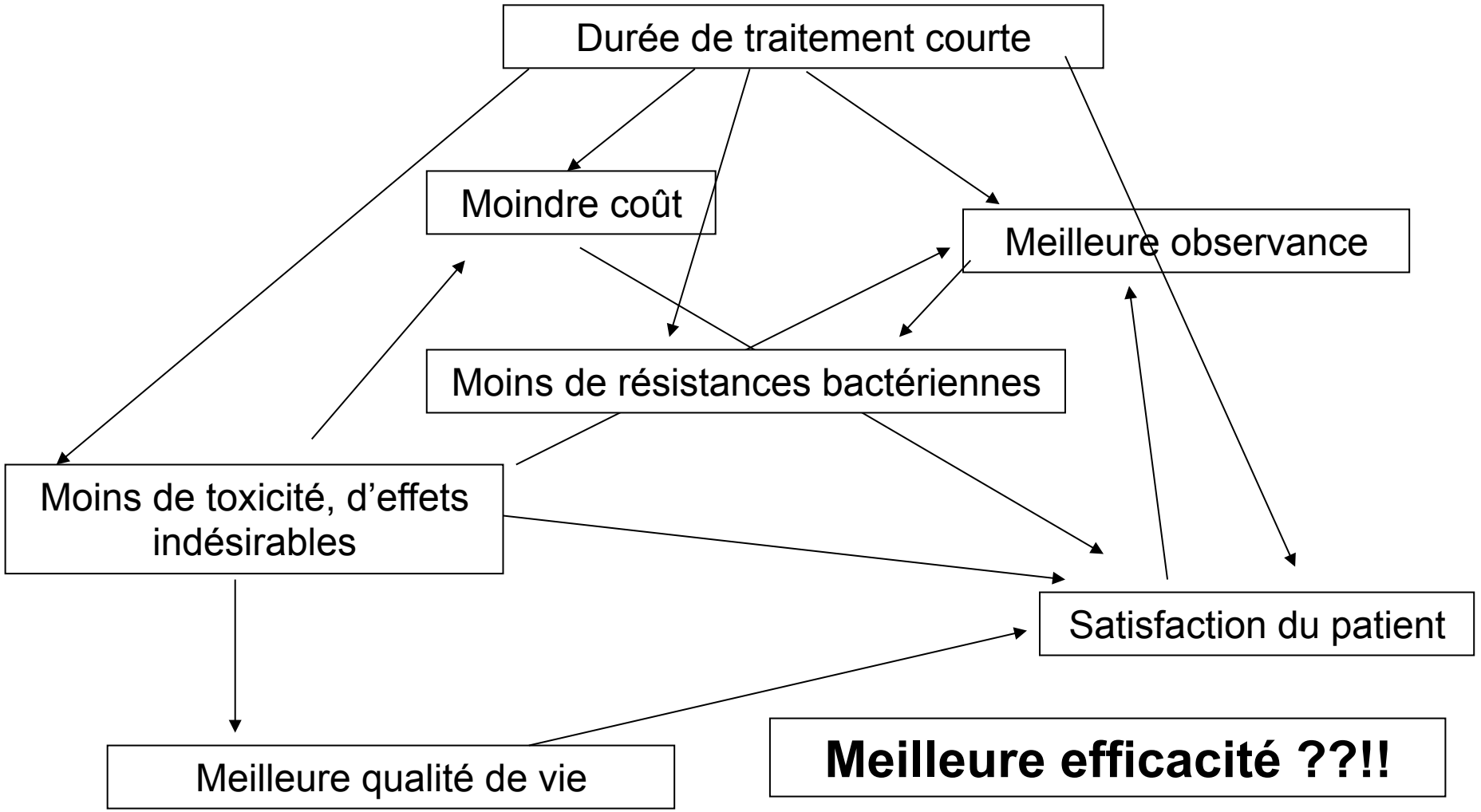


D'après Jean Carlet

Traitements courts ou prolongés

- Traitement **prolongé** bien établi pour
  - Infections à Staphylocoque doré,
  - Endocardite,
  - IOA
- Traitement **court** bien établi pour
  - Prophylaxie chirurgicale,
  - IST (Gonococcie),
  - IU basse
- Surprenant manque de preuve en faveur de TTT courts pour des **infections fréquentes** (PNA, PNP, DHD…)

Intérêt d'une durée courte pour une même efficacité !!



D'après Li JZ. Am Med J 2007

Effets indésirables de l'antibiothérapie

Flore digestive

- C2G et C3G >> modifications rapides mais transitoires de la flore digestive
- traitement 5 à 10 jours : diarrhée
  - chez 17,5 % des adultes, (<2j dans 2/3 des cas)
  - chez 11 % des enfants

Khan R. J Hosp Infect 2003;54:104-8

CDAD et usage des céphalosporines

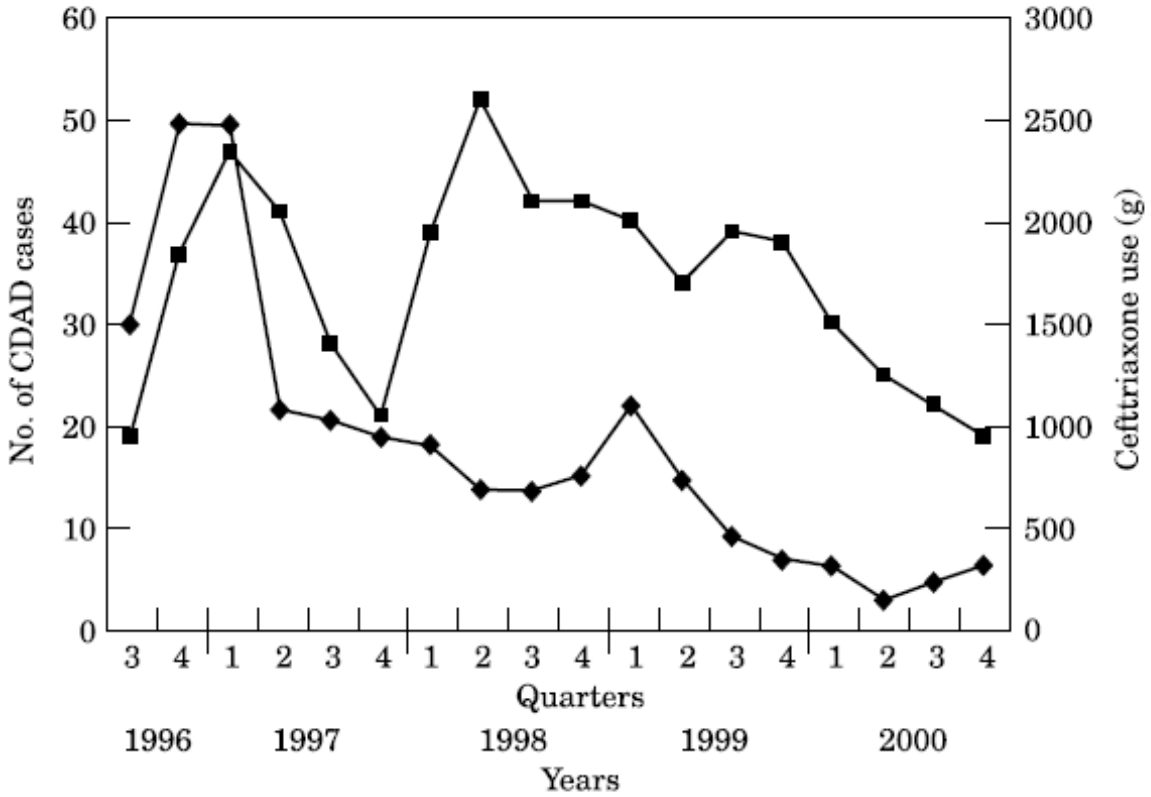


Figure 2 Relationship of CDAD cases to ceftriaxone use by quarter (medical unit only). —■— CDAD; —◆— ceftriaxone.

Khan R. J Hosp Infect 2003;54:104-8

Volontaires traités par céphalosporines orales

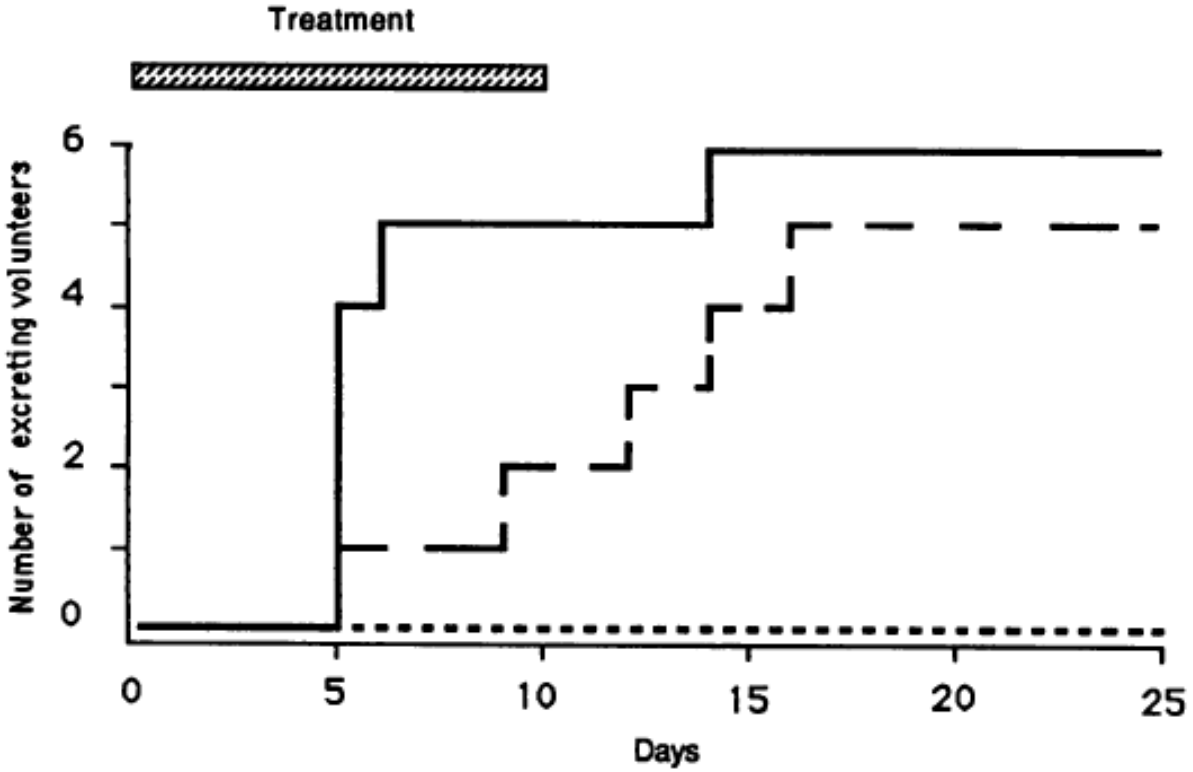


FIG. 1. Excretion of *C. difficile* by healthy volunteers treated for 10 days with placebo (- - - -), cefixime (— —), or cefpodoxime proxetil (——).

Cachaty et al. AAC 1992

Short- versus Long-Course Antibacterial Therapy for Community-Acquired Pneumonia

A Meta-Analysis

George Dimopoulos,[1,2] *Dimitrios K. Matthaiou,*[1] *Drosos E. Karageorgopoulos,*[1] *Alexandros P. Grammatikos,*[3] *Zoe Athanassa*[1] and *Matthew E. Falagas*[1,4,5]

Table II. Data from the included randomized controlled trials regarding the primary and secondary outcomes of the meta-analysis

Study (year)	Clinical success [n/N (%)] at EOT and *late FU*		Microbiological success [n/N (%)] at EOT and *late FU*		Relapses [n/N (%)]		Mortality [n/N (%)]		Pts with adverse events [n/N (%)]		Pt withdrawals due to adverse events [n/N (%)]	
	SC	LC	SC	LC	SC	LC	SC	LC	SC	LC	SC	LC
File et al.[20] (2007)	236/247 (95.5) *230/242 (95)*	226/236 (95.8) *209/227 (92.1)*	101/108 (93.5) *96/105 (91.4)*	121/126 (96) *110/121 (90.9)*	NR	NR	0/256 (0)	1/254 (0.4)	54/256 (21)	53/254 (21)	3/256 (1.2)	5/254 (2)
El Moussaoui et al.[21] (2006)	50/54 (92.6) *47/52 (90.4)*	56/60 (93.3) *49/56 (87.5)*	22/25 (88) *20/25 (80)*	19/20 (95) *15/20* (75)	NR	NR	0/56 (0)	0/63 (0)	6/56 (10.7)	13/63 (20.6)	0/56 (0)	0/63 (0)
Agarwal et al.[22] (2004)	980/1033 (94.9) *NR*	983/1026 (95.8) *NR*	NR	NR	58/1095 (5.3)	48/1093 (4.4)	0/1095 (0)	0/1093 (0)	NR	NR	NR	NR
Tellier et al.[23] (2004)	142/159 (89.3) *NR*	143/161 (88.8) *NR*	57/65 (87.7) *NR*	52/65 (80) *NR*	NR	NR	1/193 (0.5)	2/195 (1.0)	47/193 (24.4)	41/195 (21)	9/193 (4.7)	6/195 (3.1)
Leophonte et al.[24] (2002)	82/91 (90.1) *69/94 (73.4)*	81/87 (93.1) *67/92 (72.8)*	NR	NR	NR	NR	4/125 (3.2)	7/119 (5.9)	100/125 (80)	98/119 (82.4)	4/125 (3.2)[a]	5/119 (4.2)[a]
MASCOT[25] (2002)	803/980 (81.9) *791/980 (80.7)*	811/973 (83.4) *798/973 (82)*	NR	NR	12/980 (1.2)	13/973 (1.3)	0/980 (0)	1/973 (0.1)	43/980 (4.4)	57/973 (5.9)	0/980 (0)	0/973 (0)
Siegel et al.[26] (1999)	NR *21/24 (87.5)*	NR *20/22 (90.9)*	NR	NR	0/24 (0)	0/22 (0)	1/24 (4.2)	0/22 (0)	NR	NR	0/24 (0)	0/22 (0)

a Withdrawals due to adverse events or another disease.

EOT = end of therapy; **FU** = follow-up; **LC** = long course; **NR** = not reported; **pt** = patient; **SC** = short course.

Coût de l’antibiothérapie

The Cost of Treating Community-Acquired Pneumonia

Michael S. Niederman, MD,[1] Jeffrey S. McCombs, PhD,[2] Alan N. Unger, PhD,[3] Amit Kumar, MD,[3] and Robert Popovian, MS, PharmD[4]

Table V. Drug costs as fraction of total hospital costs for Medicare patients (≥65 years) with community-acquired pneumonia.

Department	Average Charge	Average Cost	% of Cost
Drugs	$2424	$873*	12.2
All others	$10,148	$6293†	87.8
Total	$12,572	$7166	100.0

Data from Medicare Standard Analytical File Part A total charges and drug charges.
*Deflated by drug department cost-to-charge ratio.
†Deflated by overall hospital average cost-to-charge ratio.

Table X. Antibiotic drug costs as percentage of total outpatient costs.

Visit Site	Outpatient Costs (in millions of dollars) Excluding Drug Costs	Antibiotic Drug Costs	Total Costs	Antibiotic Drug Costs as Percentage of Total
Office	223.260	29.814	253.074	11.8
Emergency department	96.143	26.338	122.481	21.5
Outpatient clinic	32.563	3.577	36.140	9.9
Other (skilled nursing facility, nursing home, etc)	32.502	4.340*	36.842	11.8
Total	384.468	64.069	448.537	14.3

Data from National Ambulatory Medical Care Survey[12] and National Hospital Ambulatory Medical Care Survey[13]; drug visits times average drug costs.

*Since direct estimates of drug usage and costs were not available for this category, drug costs were assumed to constitute the same share of total costs as for office visits.

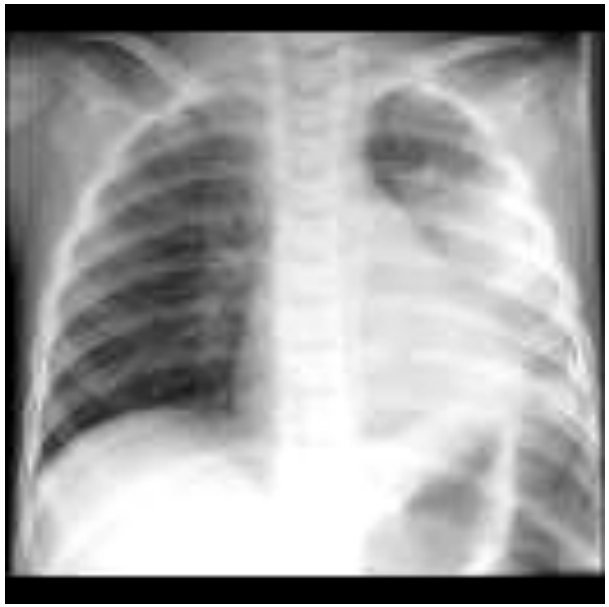
Comment définir la durée d'un traitement antibiotique ?

- **Largement fondée sur des données empiriques**
- **Guérison difficile à affirmer ,**
  - **possibilité de rechute tardive de certaines infections,**
  - **Intérêt des scores clinico biologiques ?**
- **Exprimée le plus souvent sous la forme d'une fourchette**
- **Rarement mentionnée dans l'AMM des antibiotiques**
- **Sources : ouvrages médicaux (PILLY , POPI , GENetPi …) ,**
- **Conférences de Consensus , Recommandations AFSSAPS , Conférences d'Experts**
- **Essais cliniques (peu nombreux)**

Histoire de traitement ex de la PNA

	1ère apparition	Résistance	R aujourd'hui	Durée de traitement
Sulfamides	1950	1958	30%	42 j
Acide Nalidixique	1965	1974	20%	
Cotrimoxazole	1974	1979	15-30%	
Amoxicilline	1974	1977	35-45%	42 j
A-AC	1978	1983	20-25%	
Ceftriaxone	1981	1986	<2%	10-14 j
Fluoroquinolones	1986	1992	2-7%	5-7 j

Revue des données concernant des Pneumopathies



Conclusion

- Il y a une place pour les traitements courts dans les PAC !
- Reste à définir la population concernée
- Jusqu'où « descendre » ?
- Bien évaluer ces traitements afin d'éviter un recours « sauvage »
- Donc nécessité de nouvelles études (difficultés méthodologiques)

Comment y arriver ?

- Conseil/intervention pharmacien, informatique…/cours, formation
- Essai randomisé de durée de traitement
- Biomarqueurs : PCT ?

Table 3. Clinical Success Rates at Days 10 and 30 Among Different Severity Groups Defined by PSI Class[a]

PSI Class	No. (%) of Participants		*P* Value
	Control Group	Intervention Group	
Clinical Success at Day 10			
PSI classes I-III			
Intent to treat	41/86 (47.7)	58/101 (57.4)	.18
Per protocol	39/80 (48.8)	58/94 (61.7)	.09
PSI classes IV-V			
Intent to treat	30/60 (50)	32/59 (54.2)	.64
Per protocol	28/53 (52.8)	28/50 (56)	.75
Clinical Success at Day 30			
PSI classes I-III			
Intent to treat	83/88 (94.3)	93/102 (91.2)	.41
Per protocol	80/82 (97.6)	89/95 (93.7)	.29
PSI classes IV-V			
Intent to treat	49/61 (80.3)	54/58 (93.1)	.04
Per protocol	46/54 (85.2)	47/49 (95.9)	.10

Questions (2)

- Back office ?
- Données centralisées transmises directement et surveillance (TEC)>> données manquantes
- Alertes :
  - Prise médicamenteuse >> compliance
  - Arrêt traitement >> durée adaptée
  - Aggravation >> avis médical (réglementaire)

Contexte

- **Résistance bactérienne** : incidence croissante = enjeu de santé publique mondial
- PAC : **infections bactériennes** les plus **fréquentes** et 1ère cause de prescriptions d'antibiotiques
- **Durée de traitement** antibiotique des PAC :
  - Non standardisée
  - Recommandations variables
  - Pas de preuves univoques
- **Diminution de la durée de traitement** → diminution de la durée d'hospitalisation, de l'incidence des effets indésirables, des coûts.

Conclusions

CLINICAL SIGNIFICANCE

- Adults with mild-moderate community-acquired pneumonia can be effectively treated with an antibiotic regimen of 7 days or less.
- This result is consistent among the 4 antibiotic classes studied (macrolide, fluoroquinolone, beta-lactam, and ketolide).
- There is a trend toward decreased adverse events with antibiotic regimens of 7 days or less.