

# Revision SWAB guideline CAP (2005)



STICHTING WERKGROEP ANTIBIOTICABELEID

## Optimaliseren van het antibioticabeleid in Nederland VIII

### Herziene SWAB-richtlijnen voor antimicrobiële therapie bij thuis-opgelopen pneumonie

Stichting Werkgroep Antibioticabeleid (SWAB), April 2005

Vorbereidingscommissie: Prof Dr B.J. Kullberg (voorzitter), Drs J.A. Schouten (coördinator), Dr J.M. Prins (VIZ), Prof Dr M.J. Bonten (VIZ), Prof Dr J.E. Degener (NVMM), Dr R. Janknegt (NVZA), Drs J.M.R. Hollander (NVZA), Dr R. E. Jonkers (NVALT), Dr W.J. Wijnands (NVALT), Prof Dr T.J. Verheij (NHG), Dr A.P.E. Sachs (NHG).

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# Key questions

|     |   |
|-----|---|
| 1.  | Which are the causative microorganisms of CAP (in the Netherlands) and what is their susceptibility to commonly used antibiotics? |
| 2.  | Is it possible to predict the causative agent of CAP on the basis of simple clinical data at first presentation?                  |
| 3.  | Which prognostic factors (e.g. co-morbidity, age, medical history) are important for the choice of initial treatment?             |
| 4.  | Is the severity of disease upon presentation of importance for the choice of initial treatment?                                   |
| 5.  | What is the role of radiological investigations in the diagnostic work-up of patients with a clinical suspicion on CAP?           |
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| 13. | What is the recommended policy in patients with parapneumonic effusion?   |
| 14. | What are reasonable quality indicators for antibiotic therapy in patients with CAP?   |

**Table 4. Most common aetiologies of community-acquired pneumonia in the United States and Europe (excluding the Netherlands)**

|                               | Patient type               |  |  |
|-------------------------------|----------------------------|--|--|
|                               | Outpatients                | Hospital   | Intensive Care unit  |
|                               | 8 studies <sup>19-26</sup> | Based on collective data from recent studies <sup>5, 9, 27</sup> | Based on collective data from recent studies <sup>5, 9, 27</sup> |
| <i>S. pneumoniae</i>          | 6 – 42 %                   | 12 – 39 %  | 16 – 28 %  |
| <i>H. influenzae</i>          | 0 – 14 %                   | 5 – 10 %   | 2 – 8 %  |
| <i>Legionella spp</i>         | 0 – 4 %                    | 1 – 8 %  | 4 – 24 %   |
| <i>S. aureus</i>              | 0 – 3 %                    | 1 – 2 %  | 5 – 14 %   |
| <i>M. catharalis</i>          | 0 – 1 %                    | 0 – 2 %  | 0 – 6 %  |
| <i>Enterobacteriaceae</i>     | 0 – 4 %                    | 1 – 2 %  | 1 – 10 %   |
| <i>M. pneumoniae</i>          | 0 – 16 %                   | 7 – 32 %   | 1 – 6 %  |
| <i>Chlamydia spp</i>          | 0 – 13 %                   | 2 – 9 %  | 0 – 5 %  |
| <i>C. burnetii</i>            | 0 – 2 %                    | 0 – 1 %  | 0 – 2 %  |
| <i>Viral (e.g. Influenza)</i> | 15 – 29 %                  | 1 – 23 %   | 1 – 15 %   |
| <i>Other</i>                  | 1 – 4 %                    | 1 – 2 %  | 2 – 10 %   |
| <i>No pathogen identified</i> | 39 – 58 %                  | 30 – 46 %  | 25 – 46 %  |

Data derived from most recent studies and categorized per patient type.

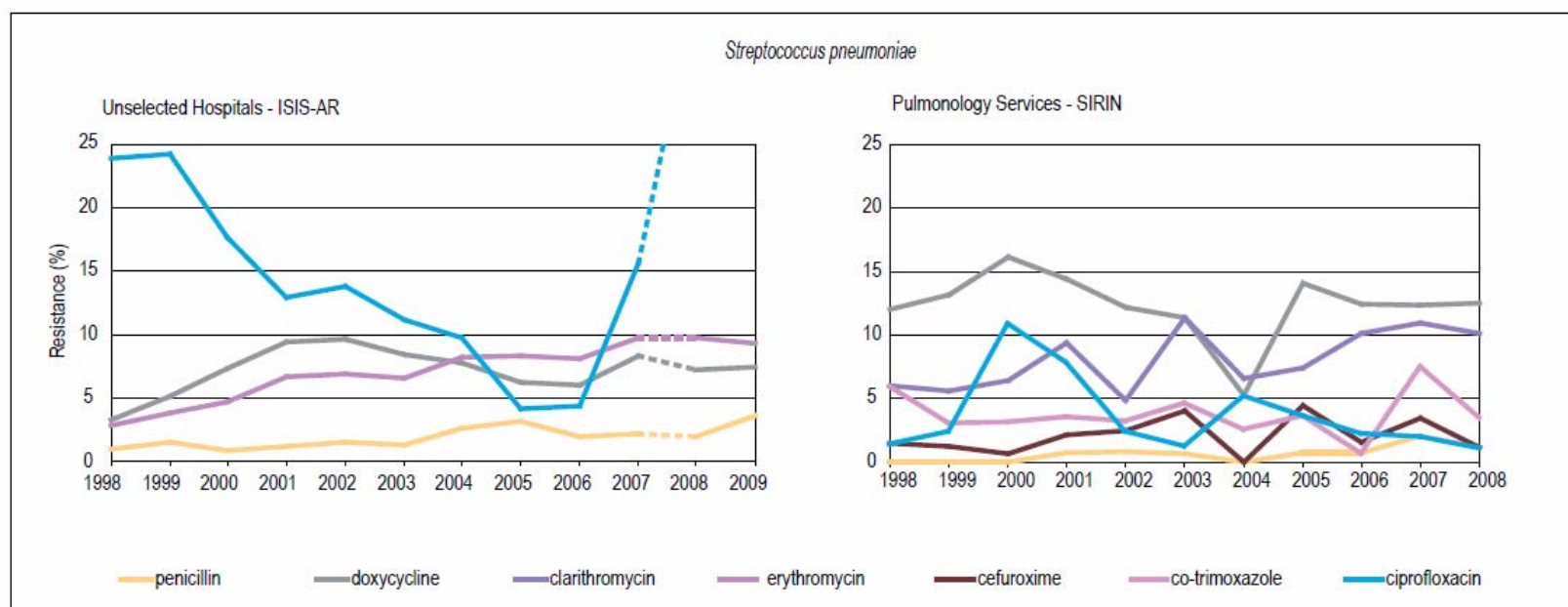


Figure 48. Resistance among clinical strains of *Streptococcus pneumoniae* (N=5.000-21.000) from Unselected Hospital Departments, calculated from the values for intermediate susceptibility and resistance (I+R) reported to ISIS-AR and trends in antibiotic resistance among clinical strains of *S. pneumoniae* from Pulmonology Services (N=1.858), calculated according to the breakpoints for resistance of EUCAST†.

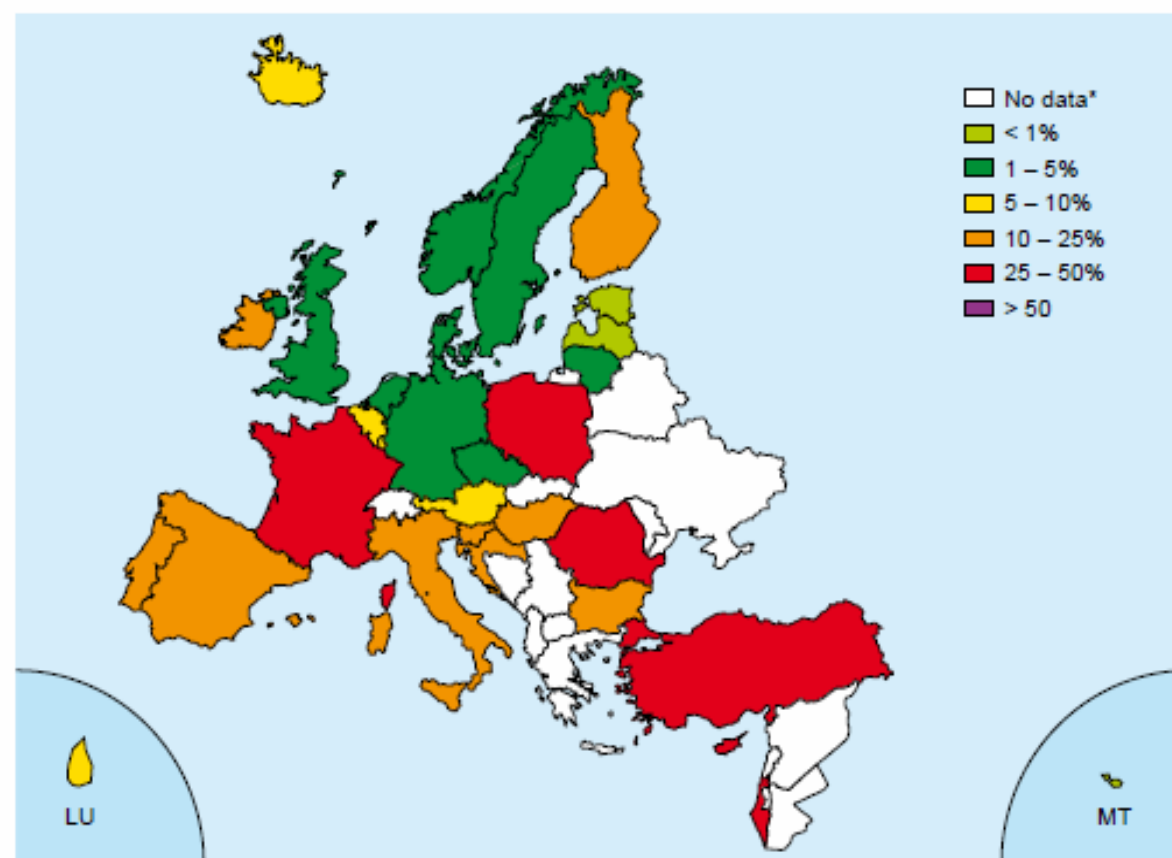


Figure 4.1. *Streptococcus pneumoniae*: proportion of invasive isolates non-susceptible to penicillin (PNSP) in 2007.

\* These countries did not report any data or reported less than 10 isolates.

**Tabel 6. Antibiotic resistance among common causative bacteria of CAP in the Netherlands in 2009**

| %                     | Penicillin | Amoxicillin | Co-amoxiclav | Co-trimoxazole | Azithromycine | Clarithromycin | Erythromycin | Ciprofloxacin | Levofloxacin | Moxifloxacin | Doxycycline | Cefotaxim/ceftazidim | Cefuroxim |
|-----------------------|------------|-------------|--------------|----------------|---------------|----------------|--------------|---------------|--------------|--------------|-------------|----------------------|-----------|
| <i>S. pneumoniae</i>  | 1          | 1           | -            | 6              | -             | 10             | 10           | 37*           | 0-1          | 0-1          | 10          | 0-1                  | 0-1       |
| <i>H. influenzae</i>  | -          | 15-30       | 3-17         | 17             | -             | 12             | 98           | 0-1           | -            | -            | 2-8         | 1                    | 1         |
| <i>Legionella spp</i> | 100        | 100         | 100          | -              | 0             | 0              | 0            | 0             | 0            | 0            | 0           | 100                  | 100       |
| <i>S. aureus</i>      | -          | 82          | -            | 3              | -             | 10             | 11           | 11            | -            | 7            | 7           | -                    | -         |
| <i>M. catharalis</i>  | -          | 88          | 0-1          | -              | -             | 2              | 8            | 0-1           | -            | 0            | 2           | 0-1                  | 0-1       |
| <i>M. pneumoniae</i>  | 100        | 100         | 100          | 100            | 0             | 0              | 0            | 0             | 0            | 0            | 0           | 1                    | 1         |
| <i>Chlamydophila</i>  | 100        | 100         | 100          | 100            | 0             | 0              | 0            | 0             | 0            | 0            | 0           | 100                  | 100       |

Values given are percentage (%) of observed resistance to the antibiotic. Data are derived from clinical strains from Unselected Hospital Departments and Pulmonology Services<sup>18, 49</sup>.

\* There are considerable differences in reported levels of resistance to ciprofloxacin and levofloxacin as a result of different breakpoint for susceptibility as recommended by European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI)<sup>49</sup>.

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# Prediction of causative agent?

**TABLE 6. Comparison of clinical symptoms by major etiologies**

|                     | Pneumococcus<br>(%) | <i>H. influenzae</i><br>(%) | <i>Legionella</i> spp.<br>(%) | <i>C. pneumoniae</i><br>(%) | Gram Negative<br>(%) |
|---------------------|---------------------|-----------------------------|-------------------------------|-----------------------------|----------------------|
| Shortness of breath | 67                  | 66                          | 50                            | 60                          | 83                   |
| Cough               | 94                  | 100                         | 79                            | 76                          | 90                   |
| Chest pain          | 46                  | 33                          | 14                            | 32                          | 18                   |
| Sputum production   | 74                  | 87                          | 75                            | 62                          | 80                   |
| Hemoptysis          | 17                  | 8                           | 13                            | 20                          | 11                   |
| Chills              | 58                  | 35                          | 42                            | 53                          | 50                   |
| Diarrhea            | 4                   | 5                           | 21                            | 20                          | 5                    |
| Abdominal pain      | 4                   | 16                          | 17                            | 0                           | 11                   |
| Vomiting            | 15                  | 11                          | 9                             | 5                           | 20                   |
| Headache            | 12                  | 6                           | 17                            | 17                          | 11                   |
| Viral prodrome      | 27                  | 39                          | 29                            | 37                          | 35                   |

**TABLE 7. Comparison of physical signs by major etiologies**

|                                       | Pneumococcus<br>(%) | <i>H. influenzae</i><br>(%) | <i>Legionella</i> spp.<br>(%) | <i>C. pneumoniae</i><br>(%) | Gram Negative<br>(%) |
|---------------------------------------|---------------------|-----------------------------|-------------------------------|-----------------------------|----------------------|
| Temperature $\geq 40^{\circ}\text{C}$ | 6                   | 5                           | 21                            | 5                           | 0                    |
| Mental changes                        | 15                  | 13                          | 22                            | 38                          | 23.8                 |
| Hypotension                           | 11                  | 18                          | 17                            | 18                          | 14.3                 |
| Consolidation                         | 35                  | 21                          | 33                            | 32                          | 15.0                 |



**Table 2. Methodological quality of individual studies**

| Evidence level | Definition  |
|----------------|---|
| A1             | Systematic review of at least two independent A2-level studies  |
| A2             | Randomised Controlled Trial (RCT) of sufficient methodological quality and power<br>or<br>Prospective cohort study with sufficient power and with adequate confounding corrections  |
| B              | Comparative Study lacking the same quality as mentioned at A2 (including patient-control and cohort studies)<br>or<br>Prospective cohort study lacking the same quality as mentioned at A2, retrospective cohort study or patient-control study |
| C              | Non-comparative study   |
| D              | Evidence based on the opinion of members of the guideline committee   |

**Table 3. Levels of evidence<sup>13</sup>**

| Evidence level | Definition   |
|----------------|--|
| Level 1        | Study of level A1 or at least two independent studies of level A2    |
| Level 2        | One study of level A2 or at least two independent studies of level B |
| Level 3        | One study of level B or C  |
| Level 4        | Expert opinion   |

### Update since 2005 guideline

No significant new studies have been published on this subject since the last guideline was published.

### Conclusions

|                     |  |
|---------------------|--|
| <b>Conclusion 7</b> | Clinical presentation on admission is not sufficient for the prediction of the causative agent of CAP.                 |
| <b>Level 2</b>      | B-C: Farr <sup>57</sup> , Moine <sup>58</sup> , Sopena <sup>59</sup> , Riquelme <sup>64</sup> , Metlay <sup>65</sup> . |

### Other considerations

None

### Recommendations

|  |   |
|--|---|
| Is it possible to predict the causative agent of CAP on the basis of simple clinical data at first presentation? |   |
| <b>Recommendation</b>  | Clinical presentation on admission is not sufficient for prediction of the causative agent of CAP. Concepts such as “typical” and “atypical” pneumonia should not longer be used. |

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## Conclusions

|  |  |
|--|--|
| <b>Conclusion 8</b><br><br><b>Level 3</b>  | Prognostic factors such as co-morbidity, age and medical history are only of modest importance for the choice of initial antibiotic treatment. In the case of aspiration, anaerobes and <u>enterobacteriaceae</u> are more often identified.<br><br>B-C: Logroscino <sup>69</sup> , Ruiz <sup>70</sup> , Leroy <sup>75</sup> |
| <b>Conclusion 9</b><br><br><b>Level 3</b>  | There is no convincing evidence that <i>H. influenzae</i> and <i>M. catarrhalis</i> are more common causes of CAP among patients with COPD.<br><br>B: Torres <sup>72</sup>   |
| <b>Conclusion 10</b><br><br><b>Level 3</b> | CAP caused by <i>S. aureus</i> is often preceded by an influenza virus infection; however the incidence of a <i>S. aureus</i> pneumonia is low.<br><br>C: MacFarlane <sup>81</sup> , McNabb <sup>82</sup> , White <sup>83</sup> , Alkhayer <sup>79</sup> , Woodhead <sup>84</sup>  |
| <b>Conclusion 11</b><br><br><b>Level X</b> | For patients with CAP who recently visited a country with a high prevalence of penicillin-resistant <u>pneumococci</u> (PRSP), this must be taken into account when initial therapy is chosen.<br><br>* EARSS Annual Report 2008 ( <a href="http://www.rivm.nl/earss">http://www.rivm.nl/earss</a> )                         |
| <b>Conclusion 12</b><br><br><b>Level 3</b> | Risk factors for <u>Legionellosis</u> are travelling abroad, staying in a hotel, male sex and current smoking.<br><br>B: Den Boer <sup>86</sup>  |

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**Step 1. Is the patient low risk (class I) based on history and physical examination and not a resident of a nursing home?**

- Age 50 years or younger, and
- None of the coexisting conditions or physical examination findings listed in step 2

NO      ☐ →      Go to step 2

YES      ☐ →      Outpatient treatment is recommended

**Step 2. Calculate risk score for classes II–V**

| Patient Characteristics                                       | Points Assigned | Patient's Points     |
|---|-----------------|----------------------|
| <b>Demographic factors</b>                                    |                 |                      |
| Age (in years)  |                 |                      |
| Males   | Age             | <input type="text"/> |
| Females   | Age – 10        | <input type="text"/> |
| Nursing home resident   | + 10            | <input type="text"/> |
| <b>Coexisting conditions</b>                                  |                 |                      |
| Neoplastic disease  | + 30            | <input type="text"/> |
| Liver disease   | + 20            | <input type="text"/> |
| Congestive heart failure                                      | + 10            | <input type="text"/> |
| Cerebrovascular disease                                       | + 10            | <input type="text"/> |
| Renal disease   | + 10            | <input type="text"/> |
| <b>Initial physical examination findings</b>                  |                 |                      |
| Altered mental status   | + 20            | <input type="text"/> |
| Respiratory rate $\geq 30/\text{min}$                         | + 20            | <input type="text"/> |
| Systolic BP $< 90$ mmHg                                       | + 20            | <input type="text"/> |
| Temperature $< 35^\circ$ or $\geq 40^\circ$ C                 | + 15            | <input type="text"/> |
| Pulse $\geq 125/\text{min}$                                   | + 10            | <input type="text"/> |
| <b>Initial laboratory findings (score zero if not tested)</b> |                 |                      |
| pH $< 7.35$   | + 30            | <input type="text"/> |
| BUN $> 30$ mg/dl  | + 20            | <input type="text"/> |
| Sodium $< 130$ mEq/L  | + 20            | <input type="text"/> |
| Glucose $\geq 250$ mg/dl                                      | + 10            | <input type="text"/> |
| Hematocrit $< 30\%$   | + 10            | <input type="text"/> |
| Po <sub>2</sub> $< 60$ mmHg or O <sub>2</sub> sat $< 90\%$    | + 10            | <input type="text"/> |
| Pleural effusion  | + 10            | <input type="text"/> |
| <b>Total score (sum of patient's points):</b>                 |                 | <input type="text"/> |

# PSI score

## 30-Day Mortality Data by Risk Class

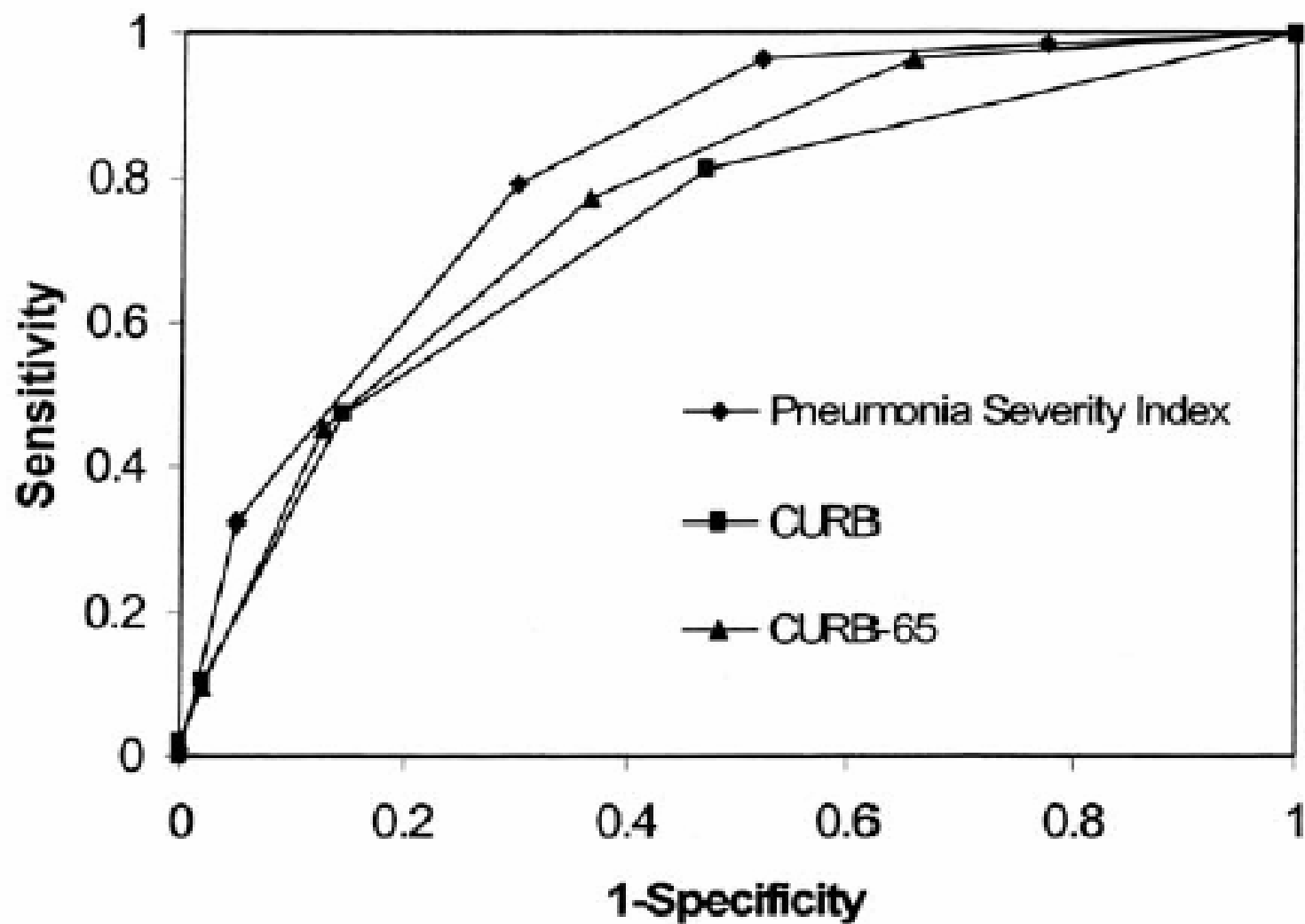
| Total Score       | Risk Class | Recommended Site of Treatment | Mortality Range Observed in Validation Cohorts, % |
|-------------------|------------|-------------------------------|---|
| None (see step 1) | I          | Outpatient                    | 0.1   |
| ≤ 70              | II         | Outpatient                    | 0.6   |
| 71–90             | III        | Outpatient                    | 0.9–2.8   |
| 91–130            | IV         | Inpatient                     | 8.2–9.3   |
| > 130             | V          | Inpatient                     | 27.0–29.2   |

Fine, N Engl J Med 1997;336:243



**Table 7. CURB-65 score<sup>105</sup>**

| CURB-65 criteria   |               |                  |
|--|---------------|------------------|
| <ul style="list-style-type: none"> <li>• Confusion: defined as a new disorientation in person, place or time</li> </ul>  |               |                  |
| <ul style="list-style-type: none"> <li>• Urea &gt; 7 mmol/l</li> </ul>   |               |                  |
| <ul style="list-style-type: none"> <li>• Respiratory Rate <math>\geq 30</math> / min</li> </ul>  |               |                  |
| <ul style="list-style-type: none"> <li>• Blood pressure: Systolic Blood Pressure &lt; 90 mmHg or Diastolic Blood Pressure <math>\leq 60</math> mmHg</li> </ul> |               |                  |
| <ul style="list-style-type: none"> <li>• Age <math>\geq 65</math></li> </ul>   |               |                  |
| Core criteria  | Score CURB-65 | 30-day mortality |
| No core criteria   | 0             | 0,7%             |
| One core criterion   | 1             | 3,2%             |
| Two core criteria  | 2             | 13%              |
| Three core criteria  | 3             | 17%              |
| Four core criteria   | 4             | 41,5%            |
| Five core criteria   | 5             | 57%              |



Aujesky, Am J Med 2005;118:384-92

# A prospective comparison of severity scores for identifying patients with severe community acquired pneumonia: reconsidering what is meant by severe pneumonia

K L Buising, K A Thursky, J F Black, L MacGregor, A C Street, M P Kennedy and G V Brown

**Table 2** Predictive value of scores for mortality

| Severity score       | Sensitivity<br>(95% CI) | Specificity<br>(95% CI) | PPV<br>(95% CI)     | NPV<br>(95% CI) (%) | Area under<br>ROC   |
|----------------------|-------------------------|-------------------------|---------------------|---------------------|---------------------|
| PSI class V          | 67.5 (50.2 to 81.9)     | 82.1 (77.6 to 85.9)     | 28.4 (19.3 to 39.0) | 96.0 (93.1 to 97.9) | 0.82 (0.76 to 0.87) |
| PSI class IV+V       | 97.3 (85.8 to 99.9)     | 47.9 (42.5 to 53.2)     | 16.4 (11.7 to 22.0) | 99.4 (96.7 to 99.9) | 0.82 (0.76 to 0.87) |
| CURB ( $\geq 2$ )    | 89.2 (74.5 to 96.9)     | 58.1 (52.7 to 63.3)     | 18.3 (12.9 to 24.7) | 98.1 (95.1 to 99.4) | 0.82 (0.75 to 0.88) |
| CURB-65 ( $\geq 3$ ) | 81.0 (64.8 to 92.0)     | 67.9 (62.7 to 72.7)     | 20.8 (14.5 to 28.4) | 97.2 (94.2 to 98.8) | 0.82 (0.76 to 0.88) |
| Modified BTS         | 91.9 (78.1 to 98.3)     | 49.8 (44.5 to 55.2)     | 16.2 (11.4 to 21.8) | 98.3 (95.1 to 99.6) | 0.71 (0.65 to 0.75) |
| rATS                 | 40.5 (24.7 to 57.9)     | 84.6 (80.4 to 88.2)     | 21.7 (12.7 to 33.3) | 93.1 (89.7 to 95.6) | 0.63 (0.54 to 0.71) |

ROC, receiver operator characteristics curve.

# Severity scores

- Predict mortality: broad empiric coverage
- More *Legionella*, *S. aureus* and gram-negatives

→ broader spectrum

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# Rapid diagnostic tests

- PCR
  - Mycoplasma ++
  - Q-koorts ++ (week 1-2)
  - Legionella t.b.d.
- Multiplex PCR “Respiratory pathogens”



# Molecular techniques

MAJOR ARTICLE

## Improved Diagnosis of the Etiology of Community-Acquired Pneumonia with Real-Time Polymerase Chain Reaction

**Kate E. Templeton, Sitha A. Scheltinga, Willian C. J. F. M. van den Eeden,<sup>2</sup> A. Willy Graffelman,<sup>3</sup>  
Peterhans J. van den Broek,<sup>2</sup> and Eric C. J. Claas<sup>1</sup>**

Departments of <sup>1</sup>Medical Microbiology and <sup>2</sup>Infectious Diseases, and <sup>3</sup>Center of Infectious Diseases and Department of General Practice  
and Nursing Home Medicine, Leiden University Medical Center, Leiden, The Netherlands

Microbiological diagnosis: **76%** vs. **50%** of patients

Clin Infect Dis 2005;41:345

# Helpful?

## Impact of Rapid Detection of Viral and Atypical Bacterial Pathogens by Real-Time Polymerase Chain Reaction for Patients with Lower Respiratory Tract Infection

**Jan Jelrik Oosterheert,<sup>1</sup> Anton M. van Loon,<sup>2,3</sup> Rob Schuurman,<sup>2,3</sup> Andy I. M. Hoepelman,<sup>1,3</sup> Eelko Hak,<sup>4</sup> Steven Thijsen,<sup>6</sup> George Nossent,<sup>5</sup> Margriet M. E. Schneider,<sup>1</sup> Willem M. N. Hustinx,<sup>7</sup> and Marc J. M. Bonten<sup>1,3,4</sup>**

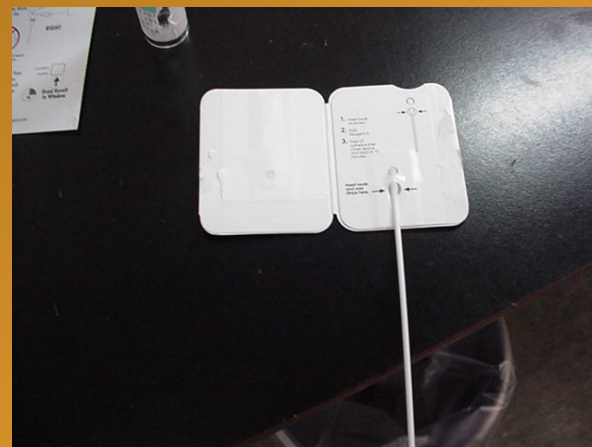
interval, 2–19), but overall antibiotic use was comparable in the intervention group and the control group (median duration of treatment, 10.0 vs. 9.0 days;  $P =$  not significant). Use of real-time PCR increased treatment and diagnostic costs with €318.17 per patient.

Clin Infect Dis 2005;41:1438

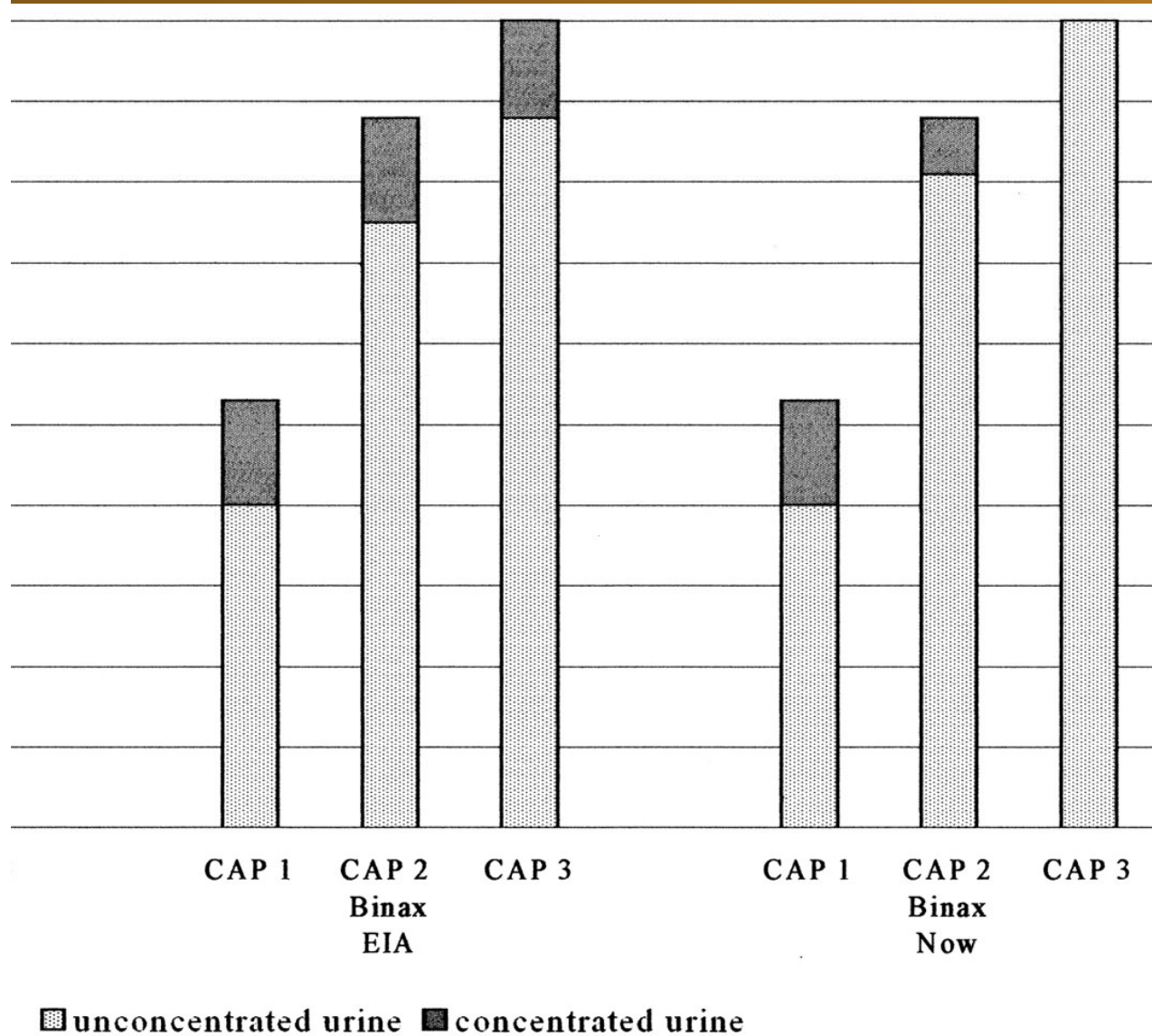
# Pneumococcal-antigen test urine

- Sensitivity 65-92% (definite), 27-74% (probable)
- Specificity 80-100%
- Useful after starting antibiotics
- Role in mild/moderate CAP?
- Role in severe CAP: streamlining in case of positive urine test (and negative *Legionella* urine test)?

# *Legionella* urine test



# Sensitivity *Legionella* Urine test



Yzerman et al, J Clin  
Microbiol 2002

### Recommendations

What is the role of rapid diagnostic tests in the initial treatment decision for patients with CAP?

|                       |   |
|-----------------------|---|
| <b>Recommendation</b> | The rapid Gram stain on sputum can give an early indication of the cause of the CAP. The test is however not sufficiently validated to be used as a decisive diagnostic tool. |
|-----------------------|---|

|                       |   |
|-----------------------|---|
| <b>Recommendation</b> | A urinary antigen test for <i>Legionella spp</i> should be performed for all patients with severe CAP. However one should be aware that in the early phase of the disease the urinary antigen test for <i>Legionella spp</i> can be false negative. Sensitivity is not optimal (70-80 %), especially in mild pneumonia. |
|-----------------------|---|

|                       |   |
|-----------------------|---|
| <b>Recommendation</b> | If amoxicillin is not the initial choice of therapy, a urinary antigen test for <i>S.pneumoniae</i> should be performed in all patients hospitalized with severe CAP. In patients with a positive test result and without another pathogen detected, antibiotic treatment can be streamlined to penicillin or amoxicillin once clinical stability (often within 48 hours) has been reached. |
|-----------------------|---|

# Key questions

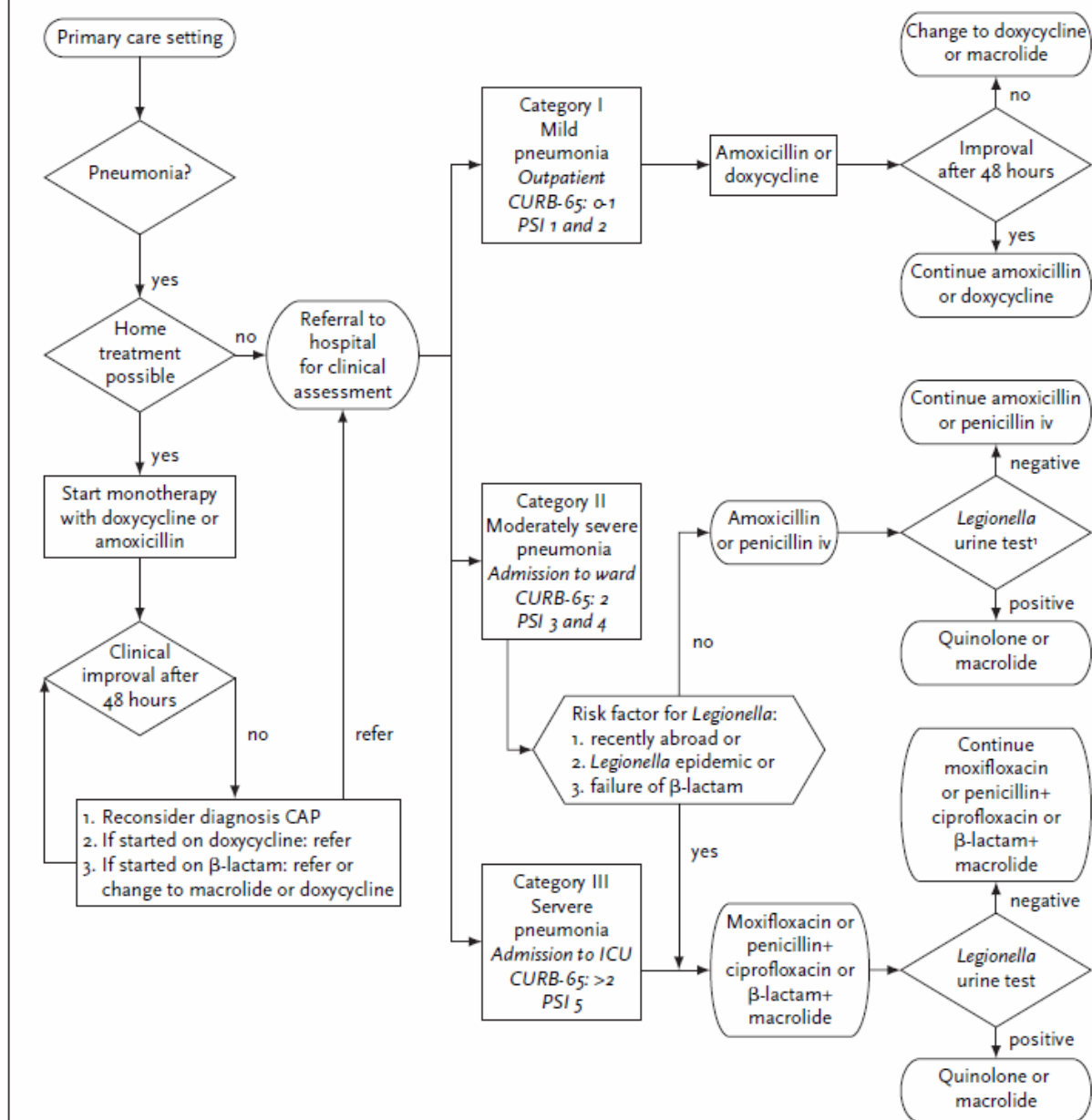
|     |   |
|-----|---|
| 1.  | Which are the causative microorganisms of CAP in the Netherlands and what is their susceptibility to commonly used antibiotics? |
| 2.  | Is it possible to predict the causative agent of CAP on the basis of simple clinical data at first presentation?                |
| 3.  | Which prognostic factors (e.g. co-morbidity, age, medical history) are important for the choice of initial treatment?           |
| 4.  | Is the severity of disease upon presentation of importance for the choice of initial treatment?                                 |
| 5.  | What is the role of radiological investigations in the diagnostic work-up of patients with a clinical suspicion on CAP?         |
| 6.  | What is the role of rapid diagnostic tests in the initial treatment decision for patients with CAP?                             |
| 7.  | What is the optimum initial treatment for patients with CAP?  |
| 8.  | When should the first dose of antibiotics be given to patients admitted to the hospital?  |
| 9.  | What is the optimal duration of antibiotic treatment for CAP?   |
| 10. | When can antibiotic therapy be switched from the intravenous to the oral route?   |
| 11. | What is the optimal antibiotic choice when specific pathogens have been identified?   |
| 12. | What is the role of adjunctive immunotherapy for patients with CAP?   |
| 13. | What is the recommended policy in patients with parapneumonic effusion?   |
| 14. | What are reasonable quality indicators for antibiotic therapy in patients with CAP?   |



# Optimal treatment

- Severity
- *Legionella* antigen test
- Specific circumstances

Figure 2 Flowchart of guideline recommendations on antibiotic treatment of CAP



¹Always perform a *Legionella* urine antigen test in patients with a PSI score 4 or presence of ≥ 2 CURB-65 criteria.

**Figure 1. Flow chart of guideline recommendations on antibiotic treatment of CAP**

- Macrolides should not be used as initial therapy. They can be used in the event of penicillin allergy and when doxycycline cannot be used due to pregnancy or lactation. If doxycycline is given, start with a loading dose of 200 mg.
- In the event of penicillin allergy, give a 2<sup>nd</sup> or 3<sup>rd</sup> generation cephalosporin or moxifloxacin.
- In the event of aspiration, the possibility of anaerobes or enterobacteriaceae should be taken into account: penicillin is replaced by amoxicillin-clavulanate.
- In the case of fulminant pneumonia after an episode of influenza, penicillin is replaced by a beta-lactam antibiotic with activity against *S. aureus*.
- Patients with demonstrated colonization of the respiratory tract with *Pseudomonas spp* receive penicillin & ceftazidime or ciprofloxacin for category II and penicillin & ciprofloxacin for category III.
- For patients with CAP who recently visited a country with a high prevalence of penicillin-resistant *S. pneumoniae* (PRPS) the dose of penicillin is increased to 2 IU 6 dd (or continuous infusion) or 2000 mg ceftriaxone 1 dd is given.
- If amoxicillin is not the initial choice of therapy, a urinary antigen test for *S. pneumoniae* should be performed in all patients hospitalized with severe CAP. In patients with a positive test result and without another pathogen detected, antibiotic treatment can be streamlined to penicillin or amoxicillin once clinical stability (often within 48 hours) has been reached.

**Table 5** Guideline for the choice of initial therapy for community-acquired pneumonia

|                        | Antibiotic                 | IV/oral | Dose                       | Frequency | SWAB comments  |
|------------------------|----------------------------|---------|----------------------------|-----------|--|
| <b>Category I</b>      |                            |         |                            |           |  |
| 1 <sup>st</sup> choice | Amoxicillin                | oral    | 500-750 mg                 | Q6-8h     | Macrolides should not be used as initial therapy. They can be used in the event of penicillin allergy and when doxycycline cannot be used due to pregnancy or lactation. If doxycycline is given, start with a loading dose of 200 mg  |
| 2 <sup>nd</sup> choice | Doxycycline                | oral    | 100 mg                     | QD        |  |
|                        | Feneticillin               | oral    | 500 mg                     | Q6h       |  |
| <b>Category II</b>     |                            |         |                            |           |  |
| 1 <sup>st</sup> choice | Penicillin                 | IV      | 1 million IU               | Q6h       | In the event of penicillin allergy, give a 2 <sup>nd</sup> or 3 <sup>rd</sup> generation cephalosporin or moxifloxacin   |
| 2 <sup>nd</sup> choice | Amoxicillin                | IV      | 1000 mg                    | Q6h       |  |
| <b>Category III</b>    |                            |         |                            |           |  |
| Monotherapy            | Moxifloxacin               | IV/oral | 400 mg                     | QD        | In the event of aspiration, the possibility of anaerobes or enterobacteriaceae should be taken into account: penicillin is replaced by amoxicillin-clavulanate   |
| Combination therapy    | Penicillin + Ciprofloxacin | IV      | 1 million IU               | Q4h       |  |
|                        |                            | IV/oral | 400 mg (IV)/ 500 mg (oral) | Q12h      | In the case of fulminant pneumonia after an episode of influenza, penicillin is replaced by a $\beta$ -lactam antibiotic with activity against <i>S. aureus</i>  |
| Combination therapy    | Penicillin + erytromycin   | IV      | 1 million IU               | Q4h       |  |
| Combination therapy    |                            | IV      | 500 mg                     | Q6h       | Patients with demonstrated colonisation of the respiratory tract with <i>Pseudomonas</i> spp. receive penicillin + ceftazidime or penecillin + ciprofloxacin for category II and penicillin + ciprofloxacin for category III<br>For patients with CAP who have recently visited a country with a high prevalence of penicillin-resistant <i>S. pneumoniae</i> (PRPS) the dose of penicillin is increased to 2 million IU Q4h (or continuous infusion) or 2000 mg ceftriaxone QD is given |
|                        | Ceftriaxone or             | IV      | 2000 mg                    | QD        |  |
|                        | cefotaxime                 | IV      | 1000 mg                    | Q6h       |  |
|                        | + erytromycin              | IV      | 500-1000 mg                | Q6h       |  |



Table 6 *Pathogen-directed therapy in CAP*

| Pathogen   | Oral   | Intravenous   |
|--|--|---|
| <i>S. pneumoniae</i>   | 1. Amoxicillin<br>2. Feneticillin<br>3. Macrolide or doxycycline*                              | 1. Penicillin G<br>2. Amoxicillin<br>3. 2 <sup>nd</sup> or 3 <sup>rd</sup> generation cephalosporin or 4 <sup>th</sup> generation quinolone*    |
| <i>H. influenzae</i><br>β-lactamase negative   | 1. Amoxicillin<br>2. Macrolide or doxycycline*   | 1. Amoxicillin<br>2. 2 <sup>nd</sup> or 3 <sup>rd</sup> generation cephalosporin*   |
| β-lactamase positive   | 1. Amoxicillin-clavulanate<br>2. Doxycycline or macrolide*                                     | 1. Amoxicillin-clavulanate<br>2. 2 <sup>nd</sup> or 3 <sup>rd</sup> generation cephalosporin  |
| <i>Legionella</i> spp.   | 1. Quinolone<br>2. Azitromycin or claritromycin<br>3. Doxycycline                              | 1. Quinolone<br>2. Erytromycin  |
| <i>M. pneumoniae</i> , <i>C. psittaci</i> , or<br><i>C. pneumoniae</i>   | 1. Doxycycline<br>2. Macrolide   | 1. Doxycycline<br>2. Macrolide  |
| <i>S. aureus</i> (non-MRSA)  | 1. Flucloxacillin<br>2. Amoxicillin-clavulanate<br>3. 1 <sup>st</sup> generation cephalosporin | 1. Flucloxacillin<br>2. Amoxicillin-clavulanate<br>3. 1 <sup>st</sup> generation cephalosporin<br>4. Vancomycin* + aminoglycoside or rifampicin |
| <i>P. aeruginosa</i>   | 1. Ciprofloxacin   | 1. Cefazidim<br>2. Ciprofloxacin  |
| <i>K. pneumoniae</i>   | 1. Amoxicillin-clavulanate<br>2. Trimethoprim/sulfamethoxazole                                 | 1. Amoxicillin-clavulanate<br>2. 2 <sup>nd</sup> or 3 <sup>rd</sup> generation cephalosporin<br>3. Trimethoprim/sulfamethoxazole                |
| Anaerobe bacteria**  | 1. Amoxicillin-clavulanate<br>2. Clindamycin<br>3. Metronidazole                               | 1. Amoxicillin-clavulanate<br>2. Clindamycin<br>3. Metronidazole  |
| *In the event of penicillin allergy; **usually polymicrobial.<br>Table based on literature and NVALT, BTS and IDSA guidelines. <sup>3,10,83,84</sup> |  |   |

# Key questions

|     |   |
|-----|---|
| 1.  | Which are the causative microorganisms of CAP in the Netherlands and what is their susceptibility to commonly used antibiotics? |
| 2.  | Is it possible to predict the causative agent of CAP on the basis of simple clinical data at first presentation?                |
| 3.  | Which prognostic factors (e.g. co-morbidity, age, medical history) are important for the choice of initial treatment?           |
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| 5.  | What is the role of radiological investigations in the diagnostic work-up of patients with a clinical suspicion on CAP?         |
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# Rapid administration of antibiotics

Mortality risk with first dose < 8 hour  
OR 0.85 (0.75-0.96)

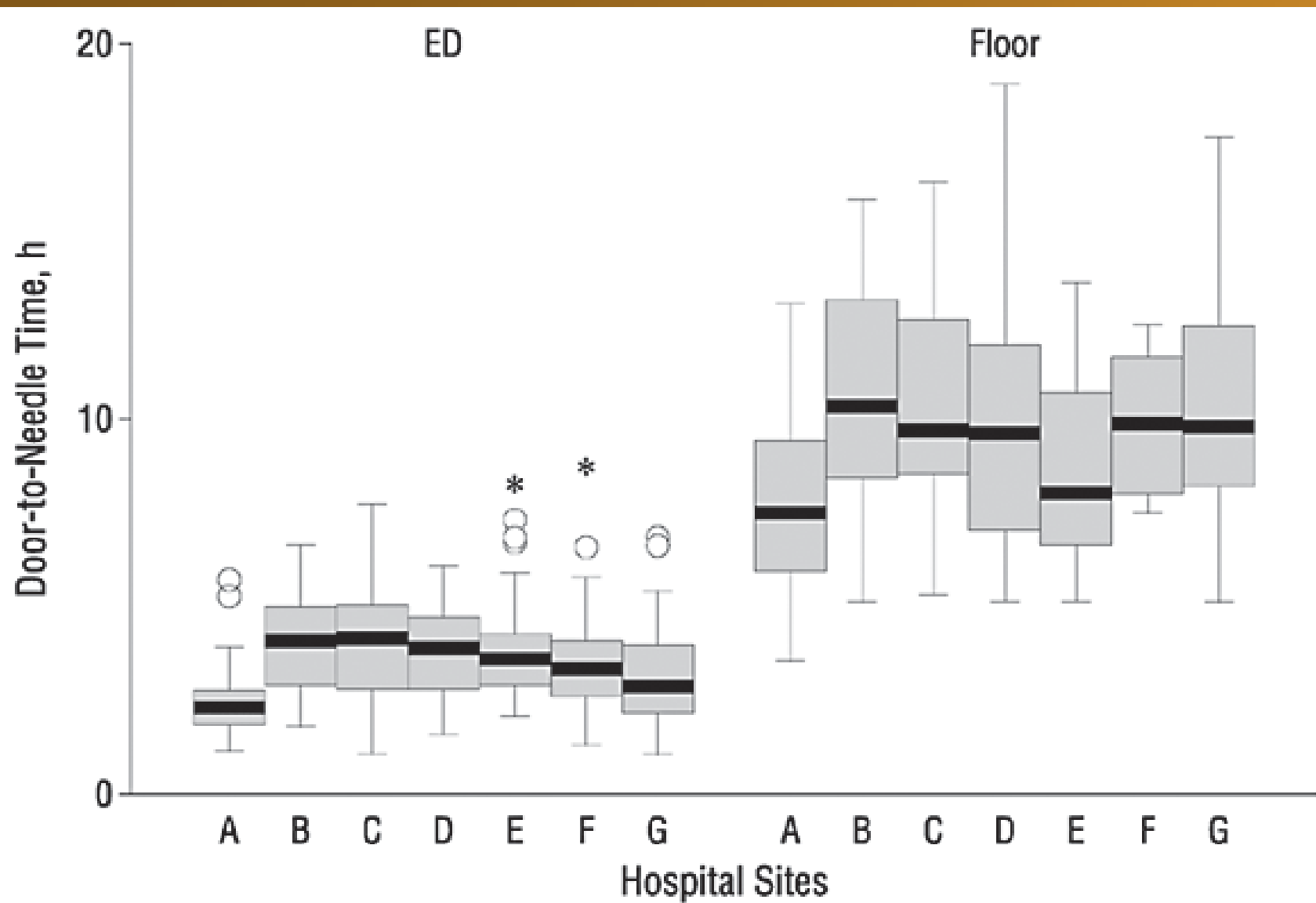
Meehan et al, JAMA 1997;278:2080-4



**Table 2. Associations of Demographic, Clinical, and Process Variables With Prolonged Length of Stay (pLOS)\***

| Variable   | Patients With pLOS<br>(n = 136) | Patients Without pLOS<br>(n = 473) | Odds Ratio (95% Confidence Interval) |                                 |
|--|---------------------------------|------------------------------------|--------------------------------------|---------------------------------|
|  |                                 |                                    | Univariate                           | Multivariate                    |
| Demographic  |                                 |                                    |                                      |                                 |
| Age, mean $\pm$ SD, y                                      | 74 $\pm$ 16.9                   | 65 $\pm$ 19.4                      | 1.28 (1.15-1.44) <sup>†‡</sup>       | 1.28 (1.12-1.46) <sup>†‡</sup>  |
| Sex, % male  | 46                              | 45                                 | 1.01 (0.69-1.48)                     | ...                             |
| Ethnicity, % white   | 62                              | 38                                 | 1.49 (1.02-2.19) <sup>§</sup>        | 1.39 (0.91-2.12)                |
| Admit site, % SNF  | 21                              | 15                                 | 1.51 (0.93-2.44)                     | ...                             |
| Payer, % Medicaid/self-pay                                 | 52                              | 49                                 | 1.19 (0.81-1.74)                     | 0.75 (0.48-1.16)                |
| Clinical   |                                 |                                    |                                      |                                 |
| COPD, %  | 31                              | 25                                 | 1.38 (0.91-2.08)                     | 0.69 (0.42-1.15)                |
| Other comorbid illness, %                                  | 74                              | 53                                 | 2.39 (1.57-3.65) <sup>†</sup>        | 2.64 (1.55-4.49) <sup>†</sup>   |
| WBC at admission, mean $\pm$ SD, $\times 10^3/\mu\text{L}$ | 13 $\pm$ 6.5                    | 12 $\pm$ 5.8                       | 1.08 (0.93-1.26) <sup>  </sup>       | 1.16 (0.98-1.38) <sup>  </sup>  |
| RR at admission, mean $\pm$ SD, beats/min                  | 23 $\pm$ 5.7                    | 26 $\pm$ 7.5                       | 1.28 (1.11-1.48) <sup>  ¶</sup>      | 1.23 (1.04-1.45) <sup>  ¶</sup> |
| Positive CXR, %  | 93                              | 91                                 | 1.29 (0.64-2.65)                     | ...                             |
| Process  |                                 |                                    |                                      |                                 |
| Initial antibiotics, % ED                                  | 51                              | 71                                 | 0.42 (0.28-0.61) <sup>†</sup>        | 0.31 (0.19-0.48) <sup>†</sup>   |
| Appropriate antibiotic, %                                  | 55                              | 57                                 | 0.94 (0.64-1.38)                     | 0.55 (0.35-0.88) <sup>§</sup>   |

Battleman, Arch Intern Med 2002;162:682



Battleman, Arch Intern Med 2002;162:682

# Antibiotics within 4 hours

**Table 5. Antibiotic Administration\***

| Outcome Measures            | Adjusted†        |         |
|-----------------------------|------------------|---------|
|                             | AOR (95% CI)     | P Value |
| All patients                |                  |         |
| 30-d mortality              | 0.85 (0.76-0.95) | .005    |
| In-hospital mortality       | 0.85 (0.74-0.98) | .03     |
| Length of stay >5 d         | 0.90 (0.83-0.96) | .003    |
| 30-d readmission            | 0.95 (0.85-1.06) | .34     |
| PSI risk classes II and III |                  |         |
| 30-d mortality              | 0.62 (0.42-0.93) | .02     |
| In-hospital mortality       | 0.77 (0.42-1.44) | .42     |
| Length of stay >5 d         | 0.86 (0.75-0.99) | .03     |
| 30-d readmission            | 0.87 (0.70-1.07) | .19     |
| PSI risk classes IV and V   |                  |         |
| 30-d mortality              | 0.87 (0.78-0.98) | .03     |
| In-hospital mortality       | 0.86 (0.74-1.00) | .04     |
| Length of stay >5 d         | 0.92 (0.84-1.00) | .04     |
| 30-d readmission            | 0.99 (0.88-1.12) | .89     |

Houck et al, Arch Intern Med 2004;164:637

*Time to first antibiotic dose.*

29. For patients admitted through the emergency department (ED), the first antibiotic dose should be administered while still in the ED. (Moderate recommendation; level III evidence.)

Rather than designating a specific window in which to initiate treatment, the committee felt that hospitalized patients with CAP should receive the first antibiotic dose in the ED.

ARTICLE

## Time for first antibiotic dose is not predictive for the early clinical failure of moderate–severe community-acquired pneumonia

A. H. W. Bruns • J. J. Oosterheert • W. N. M. Hustinx •  
C. A. J. M. Gaillard • E. Hak • A. I. M. Hoepelman

**Table 2** The effect of the TFAD within four hours on early clinical outcome

|                        | <4h, <i>n</i> (%) | >4h, <i>n</i> (%) | OR (95% CI)        | <i>P</i> -value |
|------------------------|-------------------|-------------------|--------------------|-----------------|
| Clinical instability   | 24 (26.4)         | 22 (36.1)         | 0.65 (0.32–1.31)   | 0.22            |
| ICU admission          | 3 (3.3)           | 0 (0.0)           | 2.04 (0.21–20.05)* | 0.16            |
| Mortality              | 1 (1.1)           | 1 (1.6)           | 0.65 (0.04–10.68)  | 0.77            |
| Early clinical failure | 27 (29.7)         | 23 (37.7)         | 0.69 (0.35–1.35)   | 0.28            |

\*To estimate the odds ratio mortality in the group, >4 h is set as 1



# CHEST

Original Research

COMMUNITY-ACQUIRED PNEUMONIA

## **Misdiagnosis of Community-Acquired Pneumonia and Inappropriate Utilization of Antibiotics\***

### **Side Effects of the 4-h Antibiotic Administration Rule**

*Manreet Kanwar, MD; Navkiranjot Brar, MD; Riad Khatib, MD; and  
Mohamad G. Fakih, MD, MPH*

Chest 2007;131:1865

Arch Intern Med 2008;168:351



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0736-4679/09 \$—see front matter

doi:10.1016/j.jemermed.2009.06.127



## **American Academy of Emergency Medicine**

### **THE MEASUREMENT OF TIME TO FIRST ANTIBIOTIC DOSE FOR PNEUMONIA IN THE EMERGENCY DEPARTMENT: A WHITE PAPER AND POSITION STATEMENT PREPARED FOR THE AMERICAN ACADEMY OF EMERGENCY MEDICINE**

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Reprint Address: Jesse M. Pines, MD, MBA, MSCE, Department of Emergency Medicine, University of Pennsylvania School of Medicine, 3400 Spruce Street, Ground Ravdin, Philadelphia, PA 19104

□ **Abstract—Background:** Measurement of time to first antibiotic dose (TFAD) in the emergency department (ED) in community-acquired pneumonia (CAP) has been controversial. **Objective:** To evaluate original articles reporting

ment. The American Academy of Emergency Medicine recommends that measurement of TFAD in CAP be discontinued. © 2009 Elsevier Inc.

# 4-hour rule

- Sepsis: per hour delay ↑ mortality
- CAP: less clear
- 1<sup>e</sup> dose Emergency dpt?



# Key questions

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

**G. H. Rée\* and M. Davlet†**

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

### **Summary**

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

# Duration: procalcitonin-guided?

## **Procalcitonin Guidance of Antibiotic Therapy in Community-acquired Pneumonia**

### **A Randomized Trial**

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

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

Am J Resp Crit Care Med 2006;174:84

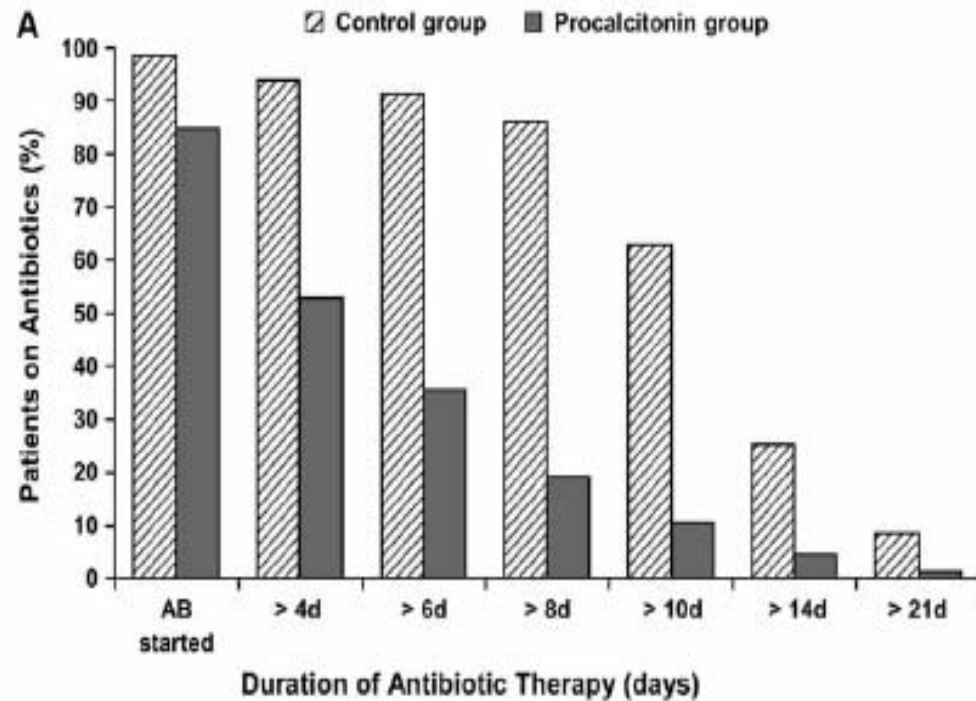
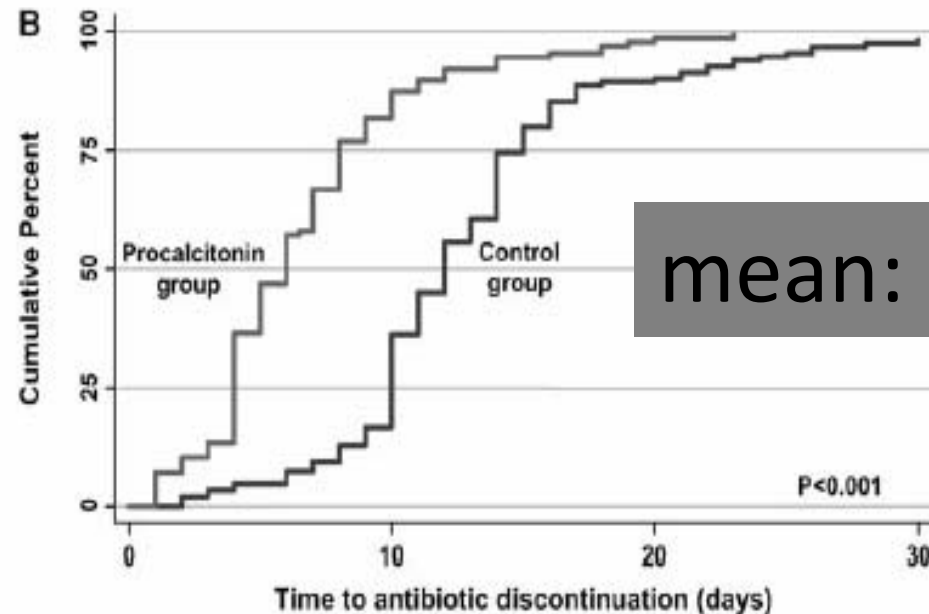


Figure 2. (A) Percentage of patients receiving antibiotic therapy in the control group and the procalcitonin group on admission and during the course of the disease. AB = antibiotics. (B) Cumulative frequency distribution curve for the time to discontinuation in patients for whom antibiotic therapy was prescribed. Patients in the procalcitonin group were compared with those in the control group.



mean: 5 vs 12 dg

# Effect of Procalcitonin-Based Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections

## The ProHOSP Randomized Controlled Trial

Philipp Schuetz, MD

Mirjam Christ-Crain, MD

Robert Thomann, MD

Claudine Falconnier, MD

**Context** In previous smaller trials, a procalcitonin (PCT) algorithm reduced antibiotic use in patients with lower respiratory tract infections (LRTIs).

**Objective** To examine whether a PCT algorithm can reduce antibiotic exposure without increasing the risk for serious adverse outcomes.

| Community-acquired pneumonia                | (n = 460)      | (n = 465)        |
|---|----------------|------------------|
| Antibiotic exposure, mean (median [IQR]), d | 7.2 (7 [4-10]) | 10.7 (10 [8-12]) |

JAMA 2009;302:1059

## 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

### Abstract

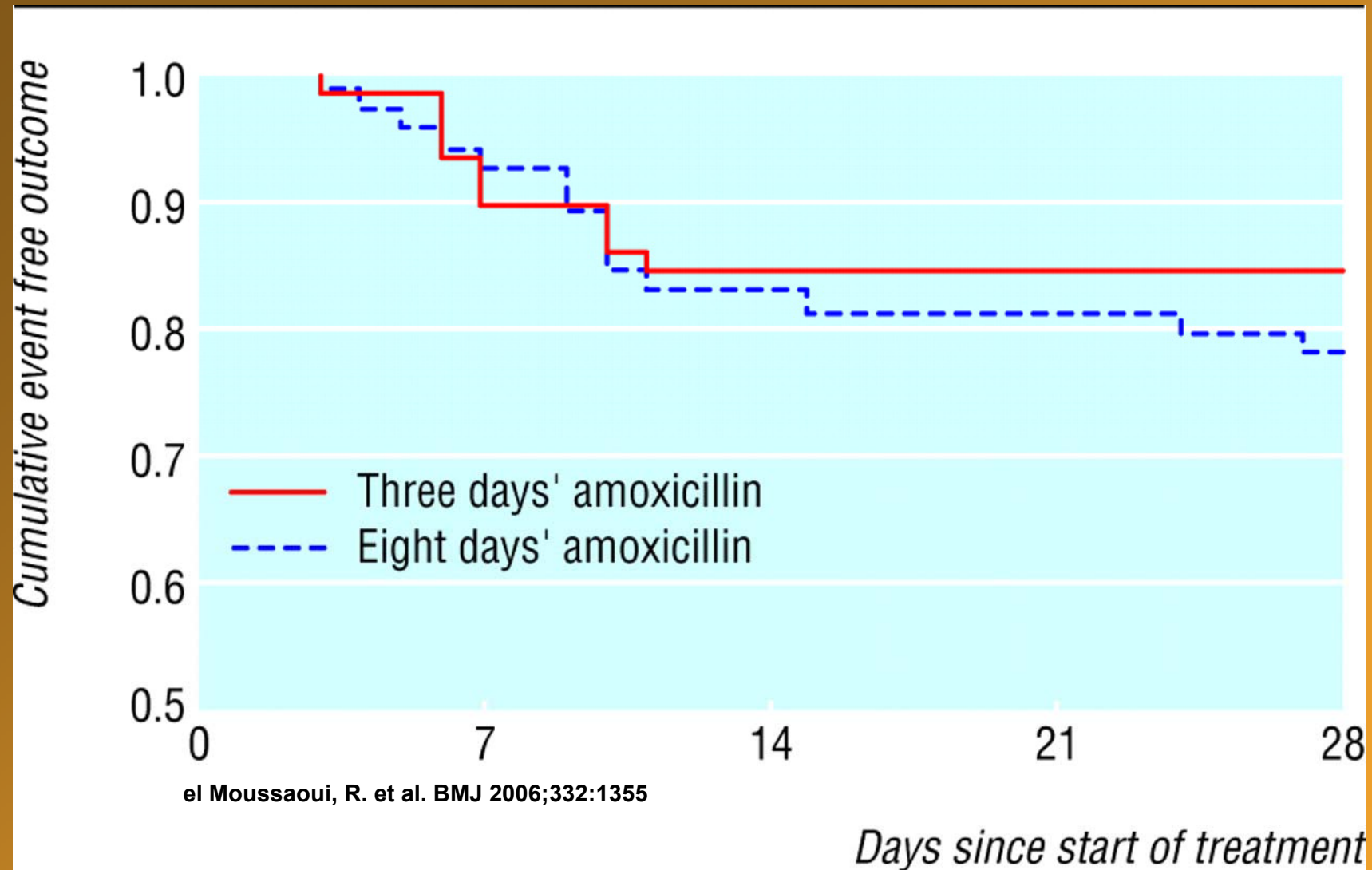
**Objective** To compare the effectiveness of discontinuing treatment with amoxicillin after three days or eight days in adults admitted to hospital with mild to moderate-severe community acquired pneumonia who substantially improved after an initial three days' treatment.

**Design** Randomised, double blind, placebo controlled

7-10 days for uncomplicated pneumonia is not based on scientific evidence but has nevertheless gained acceptance over the years. Two older studies in adults have suggested that a significantly shorter duration than 7-10 days might be justified.<sup>4 5</sup> These studies do not, however, meet the required standards of clinical trials.

If a shorter duration of therapy is equally effective, this can be of major importance in decreasing antibiotic consumption. On a

Proportion of patients considered clinical successes in intention to treat population.





*Journal of Antimicrobial Chemotherapy* (2004) **54**, 515–523

DOI: 10.1093/jac/dkh356

Advance Access publication 21 July 2004

JAC

**Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate community-acquired pneumonia**

**Guy Tellier<sup>1\*</sup>, Michael S. Niederman<sup>2,3</sup>, Roomi Nusrat<sup>4</sup>, Manish Patel<sup>4</sup> and Bruce Lavin<sup>4</sup>**

*Journal of Antimicrobial Chemotherapy* (2007) **60**, 112–120

doi:10.1093/jac/dkm119

Advance Access publication 30 May 2007

JAC

**Gemifloxacin once daily for 5 days versus 7 days for the treatment of community-acquired pneumonia: a randomized, multicentre, double-blind study**

**Thomas M. File, Jr<sup>1\*</sup>, Lionel A. Mandell<sup>2</sup>, Glenn Tillotson<sup>3†</sup>, Kosta Kostov<sup>4</sup>  
and Ognian Georgiev<sup>5</sup>**



## @ Clinical efficacy of 3 days versus 5 days of oral amoxicillin for treatment of childhood pneumonia: a multicentre double-blind trial

*Pakistan Multicentre Amoxicillin Short Course Therapy (MASCOT) pneumonia study group\**

### Summary

**Background** For most infections, especially acute respiratory infections (ARIs), the recommended duration of therapy is not based on strong scientific or clinical criteria. Shorter courses of antibiotics for non-severe pneumonia would result in lower costs, enhance patient compliance, and might help to contain antimicrobial resistance. We aimed to compare the clinical efficacy of 3-day and 5-day courses of amoxicillin in children with non-severe pneumonia.

**Methods** We recruited 2000 children, aged 2–59 months, with non-severe pneumonia (WHO criteria) diagnosed in the outpatient departments of seven hospitals. Patients were randomly assigned to 3 days or 5 days of treatment with oral amoxicillin. The primary outcome was treatment failure. Analyses were by intention to treat.

### Introduction

Pneumonia is one of the major causes of death in children aged younger than 5 years in less-developed countries.<sup>1</sup> To reduce the number of people dying from pneumonia, WHO developed standard guidelines<sup>2</sup> for management of patients with this disease. These guidelines have been used widely in several less-developed countries for many years and recommend 5 days of oral co-trimoxazole or amoxicillin for treatment of non-severe pneumonia. This recommendation is based on data from less-developed countries, which show that *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common causes of bacterial pneumonia.<sup>3</sup> These guidelines have effectively reduced death from pneumonia in less-developed countries.<sup>4</sup>

Conventionally, antibiotics are continued until the patient no longer has a fever or laboratory measurements of infection are normal. Clinicians recognise that patients tend to be over-treated with antibiotics, but this is not reflected in the guidelines.

### Recommendations

What is the optimal duration of antibiotic treatment for CAP?

|                       |   |
|-----------------------|---|
| <b>Recommendation</b> | If adult patients with mild to moderate-severe CAP are treated with a <u><math>\beta</math>-lactam</u> antibiotic or <u>fluoroquinolones</u> , the length of antibiotic treatment can be shortened to 5 days in those patients who have substantially improved after 3 days of treatment. There have been no studies on the optimal duration of treatment for CAP with <u>doxycycline</u> . We suggest continuing 7 days of treatment in these cases. |
| <b>Recommendation</b> | Pneumonia caused by <i>S. aureus</i> should be treated for at least 14 days, pneumonia caused by <i>M. pneumoniae</i> or <i>Chlamydophila spp.</i> 14 to 21 days.   |
| <b>Recommendation</b> | For <i>Legionella</i> pneumonia a treatment duration of 7-10 days is sufficient in patients with a good clinical response.  |

# Key questions

|     |   |
|-----|---|
| 1.  | Which are the causative microorganisms of CAP in the Netherlands and what is their susceptibility to commonly used antibiotics? |
| 2.  | Is it possible to predict the causative agent of CAP on the basis of simple clinical data at first presentation?                |
| 3.  | Which prognostic factors (e.g. co-morbidity, age, medical history) are important for the choice of initial treatment?           |
| 4.  | Is the severity of disease upon presentation of importance for the choice of initial treatment?                                 |
| 5.  | What is the role of radiological investigations in the diagnostic work-up of patients with a clinical suspicion on CAP?         |
| 6.  | What is the role of rapid diagnostic tests in the initial treatment decision for patients with CAP?                             |
| 7.  | What is the optimum initial treatment for patients with CAP?  |
| 8.  | When should the first dose of antibiotics be given to patients admitted to the hospital?  |
| 9.  | What is the optimal duration of antibiotic treatment for CAP?   |
| 10. | When can antibiotic therapy be switched from the intravenous to the oral route?   |
| 11. | What is the optimal antibiotic choice when specific pathogens have been identified?   |
| 12. | What is the role of adjunctive immunotherapy for patients with CAP?   |
| 13. | What is the recommended policy in patients with parapneumonic effusion?   |
| 14. | What are reasonable quality indicators for antibiotic therapy in patients with CAP?   |

# Switch-studies

**Table 4. Features of Prospective Interventional Controlled Trials**

| Source, y                                  | Intervention Group |                    | Control Group   |                     | $\delta$ Length of Stay, d*   |
|--|--------------------|--------------------|-----------------|---------------------|---|
|  | No. of Subjects    | Length of Stay, d* | No. of Subjects | Length of Stay, d*  |   |
| Marrie et al, <sup>8</sup> 2000            | 9†                 | 8.2 (8.1 to 8.3)   | 10†             | 9.6 (9.5 to 9.7)    | -1.4 (-3.35 to 0.55)  |
| Rhew et al, <sup>11</sup> 1998             | 67                 | 3.6 (3.5 to 3.7)   | 85              | 3.5 (3.4 to 3.6)    | 0.1 (-0.87 to 1.07)   |
| Omidvari et al, <sup>10</sup> 1998         | 58                 | 7.3 (7.1 to 7.5)   | 37              | 9.7 (9.4 to 10)     | -2.4 (-4.85 to 0.05)  |
| Siegel et al, <sup>16</sup> 1996‡          | 16                 | 6.0 (4.4 to 7.6)   | 15              | 11.0 (10.5 to 11.6) | -5.0 (-6.67 to -3.33)   |
|  | 15                 | 8.0 (6.9 to 9.1)   | ...             | ...                 | ...   |
| Weingarten et al, <sup>13</sup> 1996       | 68                 | 4.0 (3.6 to 4.4)   | 78              | 4.2 (3.9 to 4.5)    | -0.2 (-0.67 to 0.27)  |
| Hendrickson and North, <sup>15</sup> 1995§ | 16                 | 4.8                | 15              | 6.0                 | -1.2  |
| Pooled                                     | <b>249</b>         | 6.0 (4.4 to 7.7)   | <b>240</b>      | 7.6 (4.9 to 10.3)   | -1.64 (-3.30 to 0.02)   |
|  |                    |                    |                 |                     | Without the studies<br>by Rhew <sup>11</sup> and Weingarten<br>and colleagues <sup>13</sup> :<br>-3.04 (-4.90 to -1.19) |

Rhew et al, Arch Intern Med 2001;161:722-7

## Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial

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### Abstract

**Objectives** To compare the effectiveness of an early switch to oral antibiotics with the standard 7 day course of intravenous antibiotics in severe community acquired pneumonia.

**Design** Multicentre randomised controlled trial.

**Setting** Five teaching hospitals and 2 university medical centres in the Netherlands.

The concept of early transition from intravenous to oral antibiotics in the treatment of community acquired pneumonia has been evaluated before, but only in mild to moderately severe disease and rarely in randomised trials.<sup>4-14</sup> For patients with more severe forms of the disease, effects on outcome and length of hospital stay have not been determined in randomised trials. Therefore, we conducted a multicentre randomised trial to evaluate the effectiveness of an early switch from intravenous to

**Table 3** Outcomes in multicentre randomised trial of early switch from intravenous to oral antibiotics in severe community acquired pneumonia. Intention to treat analysis. Values are number of patients (percentage) unless stated otherwise

| Clinical outcome                                   | Treatment group         |                    | Mean difference (95% CI) |
|--|-------------------------|--------------------|--------------------------|
|  | Intervention<br>(n=132) | Control<br>(n=133) |                          |
| Death after day 3                                  | 5 (4)                   | 8 (6)              | 2% (–3% to 8%)           |
| Clinical cure                                      | 110 (83)                | 113 (85)           | 2% (–7% to 10%)          |
| Clinical failure:                                  | 22 (17)                 | 20 (15)            | –2% (–10% to 7%)         |
| Clinical cure but still in hospital                | 9 (7)                   | 6 (5)              | –2% (–4% to 8%)          |
| Clinical deterioration                             | 8 (6)                   | 6 (5)              | –1% (–4% to 7%)          |
| Death  | 5 (4)                   | 8 (6)              | 2% (–3% to 8%)           |
| Clinical deterioration and death                   | 13 (10)                 | 14 (11)            | 1% (–1% to 8%)           |
| Mean (SD) length of hospital stay (days)           | 9.6 (5.0)               | 11.5 (4.9)         | 1.9 (0.6 to 3.2)         |
| Mean (SD) duration of intravenous treatment (days) | 3.6 (1.5)               | 7.0 (2.0)          | 3.4 (2.8 to 3.9)         |

|                       |   |
|-----------------------|---|
| <b>Recommendation</b> | It is advised always to start with intravenous antimicrobial therapy for CAP in the following conditions: severe pneumonia, functional or anatomical reasons for <u>malabsorption</u> or in the case of vomiting. |
|-----------------------|---|



|                       |   |
|-----------------------|---|
| <b>Recommendation</b> | Patients should be switched from intravenous to oral therapy when they have substantially improved clinically and are <u>hemodynamically stable</u> *. In this case patients can be discharged from hospital. |
|-----------------------|---|

\* Useful criteria for clinical stability include: temperature < 37.8 °C; heart rate < 100 beats/min; respiratory rate < 24 breaths/min; systolic blood pressure > 90 mmHg; arterial oxygen saturation > 90% or pO<sub>2</sub> > 60 mmHg on room air; ability to maintain oral intake; normal mental status<sup>9</sup>.



# Key questions

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# C. Everett Koop

“Medicines only work in patients who take them”

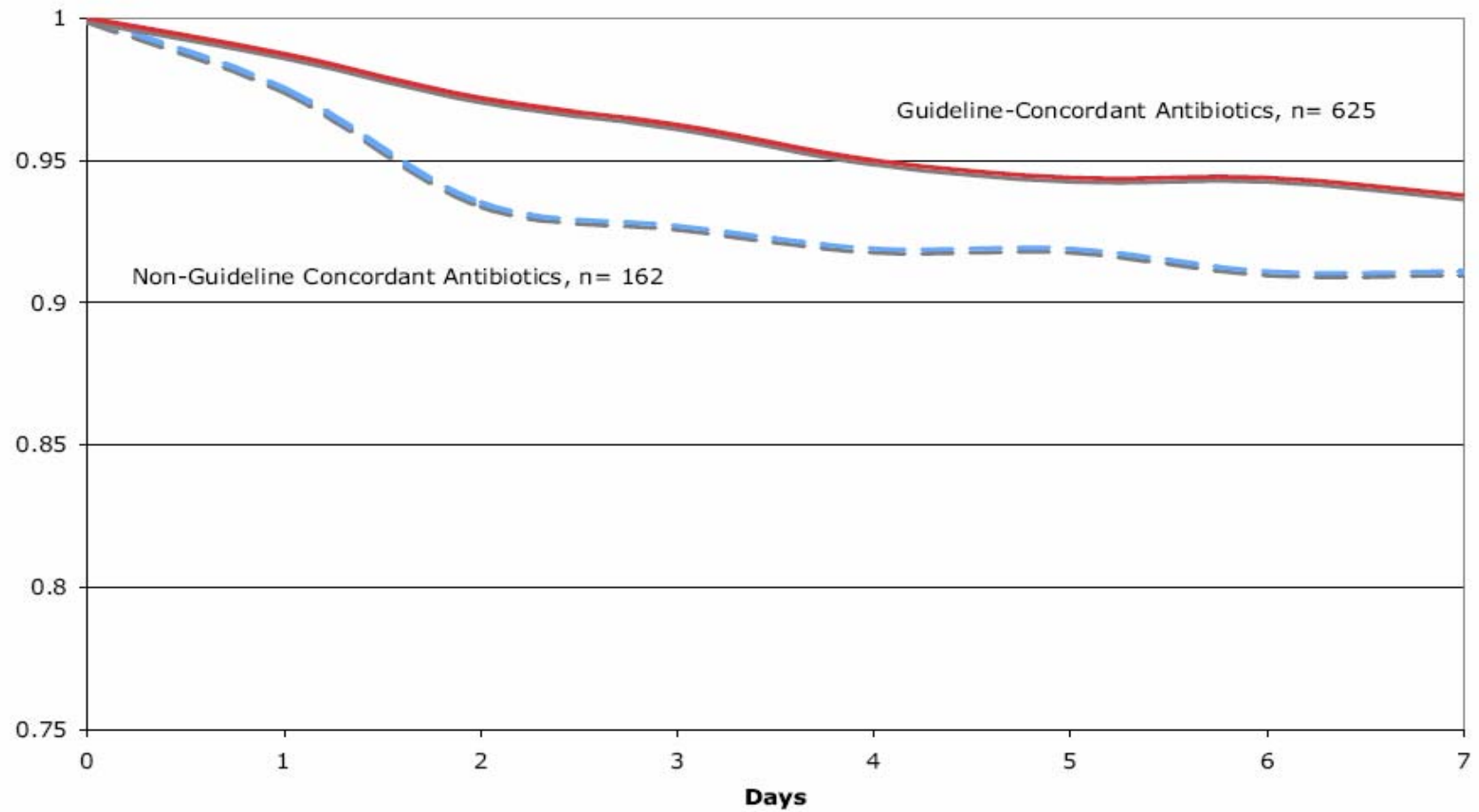
The same holds true for guidelines

TABLE 5. Predictors of treatment failure and mortality: results of regression logistic analyses

| Independent Variables                  | Treatment Failure |        | Mortality       |         |
|--|-------------------|--------|-----------------|---------|
|  | OR (95% CI)       | p      | OR (95% CI)     | P       |
| Adherence                              | 0.65 (0.5–0.9)    | < 0.05 | 0.55 (0.3–0.9)  | < 0.03  |
| Residents and pneumologists vs. others | 0.6 (0.4–0.9)     | < 0.05 |                 |         |
| Fine IV–V vs. I–III                    |                   |        | 10.8 (5.3–21.8) | < 0.001 |

*Definition of abbreviations:* CI = confidence interval; OR = odds ratio.

Area under receiver operating characteristic curve for treatment failure and death: 0.6 and 0.77, respectively.



**Table 3** Health Care Endpoints for Community-Acquired Pneumonia Patients Initially Treated with Guideline-Concordant and Guideline-Discordant Antibiotic Therapy\*

| Health care endpoint            | Guideline-Concordant Antibiotics |                  | Per Protocol<br><i>P</i> Value‡ | Intention to Treat<br><i>P</i> Value§ |
|---------------------------------|----------------------------------|------------------|---------------------------------|---------------------------------------|
|                                 | Yes<br>(n = 357)‡                | No<br>(n = 274)‡ |                                 |                                       |
| Time to clinical stability (d)† | 2.1 ± 1.5                        | 2.3 ± 1.8        | .25                             | .03                                   |
| Time to switch therapy (d)†     | 4.5 ± 3.0                        | 5.9 ± 3.6        | <.01                            | <.01                                  |
| Length of hospital stay (d)†    | 5.0 ± 3.8                        | 6.2 ± 4.2        | <.01                            | <.01                                  |
| In-hospital mortality           | 3%                               | 7%               | .04                             | .04                                   |

**Table 3. Subgroup Analysis: Relationship Between Appropriate Antibiotic Selection and Prolonged Length of Stay**

| Group        | No. of Patients | Odds Ratio<br>(95% Confidence Interval) |                   |
|--------------|-----------------|---|-------------------|
|              |                 | Univariate                              | Multivariate      |
| All patients | 609             | 0.94 (0.64-1.38)                        | 0.55 (0.35-0.88)† |

Battleman, Arch Intern Med 2002;162:682

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## Implementation of Guideline Recommendations

1. Locally adapted guidelines should be implemented to improve process of care variables and relevant clinical outcomes. (Strong recommendation; level I evidence.)

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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.