*ERJ Express*. Published on May 31, 2012 as doi: 10.1183/09031936.00029412

# Barriers to an early switch from intravenous to oral antibiotic therapy in hospitalized patients with community-acquired pneumonia

M.F. Engel [1], D.F. Postma [1], M.E.J.L. Hulscher [2] F. Teding van Berkhout [3], M.H. Emmelot-Vonk [4], S. Sankatsing [5], C.A.J.M. Gaillard [6,7], A.H.W. Bruns [1,6], A.I.M. Hoepelman [1], J.J. Oosterheert [1]

1. Department of Internal Medicine and Infectious Diseases, Utrecht University Medical Centre, the Netherlands.
2. Scientific Institute for Quality of Healthcare, Radboud University Medical Centre, the Netherlands.
3. Department of Pulmonary Diseases, Utrecht University Medical Centre, the Netherlands.
4. Department of Geriatric Diseases, Utrecht University Medical Centre, the Netherlands.
5. Department of Internal Medicine, Diakonessen Hospital, Utrecht, the Netherlands.
6. Department of Internal Medicine, Meander Medical Centre, Amersfoort, the Netherlands.
7. Department of Nephrology, VU University Medical Centre, Amsterdam, the Netherlands.

| | |
|---|---|
| Corresponding author: | Drs. M.F. Engel |
| Mailing address: | University Medical Centre Utrecht |
| | Department of internal medicine and infectious disease |
| | Intern mail: F02.126 |
| | Po Box 85500 Utrecht |
| | The Netherlands |
| Telephone: | 0031-(0)88-7556228 |
| Fax number: | 0031-(0)30-2523741 |
| E-mail: | Drs. M.F. Engel: m.f.engel-2@umcutrecht.nl |
| | Drs. D.F. Postma: d.f.postma@umcutrecht.nl |
| | Prof. Dr. M.E.J.L. Hulscher: m.hulscher@iq.umcn.nl |
| | Drs. F. Teding van Berkhout; f.teding@umcutrecht.nl |
| | Dr. M.H. Emmelot-Vonk: m.h.emmelotVonk@umcutrecht.nl |
| | Dr. S. Sankatsing: ssankatsing@diakhuis.nl |
| | Dr. C.A.J.M. Gaillard: cajm.gaillard@meandermc.nl |
| | Dr. A.H.W. Bruns: a.h.w.bruns@umcutrecht.nl |
| | Prof. Dr. A.I.M. Hoepelman: i.m.hoepelman@umcutrecht.nl |
| | Dr. J.J. Oosterheert: j.j.oosterheert@umcutrecht.nl (alternate corresponding author) |

The e-mail address of the corresponding author may be published.

Reprints are not available from the authors.

Funding: Sources: Netherlands Organisation for Health Research and Development (ZonMw) Grant no. 171103003

Word count full text 3437, abstract 250. Number of figures and tables 4, appendices 5.

Running head: Barriers to an early switch in pneumonia.

## INTRODUCTION

Community-acquired pneumonia (CAP) is the leading cause of death from infectious diseases and a substantial burden on healthcare resources in western countries.[1] Hospital admission is usually required because of intravenous antibiotic treatment, which ensures optimal tissue penetration. Intravenous therapy is often continued until patients have definitely overcome the infection.[2] A recent meta-analysis showed that an early switch to oral therapy in clinically stable patients on day 2-4 of hospital admission, as opposed to prolonged intravenous treatment, resulted in an estimated decrease of length of hospital stay of 3.4 days and less medication side effects.[2] The treatment effect, the number of recurrent infections and mortality were comparable. Even in severe forms of CAP an early switch strategy is usually possible on day 3 of admission.[3] Large scale implementation of early switch strategies would lead to a substantial reduction in health care costs.[3,4] Therefore, (inter-)national guidelines advocate an early switch to oral treatment for hospitalized CAP patients.[1,5,6]

Despite its obvious and proven benefits, an early switch to oral therapy has not been implemented in routine clinical practice for all admitted CAP patients to date. It has been shown that health care staff experience barriers towards implementation of an early switch strategy in lower respiratory tract infections due to several factors including a perceived lack of clear guideline recommendations and a lack of outcome expectancy.[7,8] The level of adherence to an early switch strategy (i.e. patients being switched to oral agents as soon as clinical stability is reached) in CAP is 58% on average, but varies greatly between different hospitals (22-94%).[9] This suggests considerable room for improvement of the adherence to an early switch strategy.

Merely publishing results of randomized controlled trials and issuing of guidelines seems to be insufficient for implementation of an early switch strategy in daily practice.[10] Generally,

implementation strategies are ideally preceded by a proper analysis of barriers to implementation on different levels.[11-13] Therefore, we aimed to evaluate whether physicians base the conversion to oral treatment on guideline advice, what patient and physician characteristics influence the timing of the switch to oral treatment and whether physicians perceive barriers to an early switch strategy. Identification of these barriers may form the basis of a targeted implementation strategy.

## METHODS

### Design and setting

In a prospective, observational, multi-centre study, we evaluated the timing of the switch (e.g. cessation of intravenous antibiotics with or without conversion to oral antibiotics) and possible perceived barriers to an early switch strategy in CAP patients admitted to internal and pulmonary medicine wards. Two teaching hospitals in the Netherlands (Diakonessen hospital in Utrecht, 627 beds and Meander Medical Centre in Amersfoort, 982 beds) and 1 university hospital (Utrecht University Medical Centre, 1042 beds) participated in the study. The study protocol was approved by the local medical ethics committees. As the objective of this study was to describe physician behaviour and the main measurements were performed through physician interviews, obtaining patient informed consent was not required.

### Patients and procedures

All consecutive adult patients admitted to one of the participating hospitals for intravenous CAP treatment were eligible for analysis (appendix I). Patients were excluded if they were admitted to the intensive care unit before the switch to oral antibiotics was made or had a history of cystic fibrosis or lung transplantation, because prolonged intravenous treatment is often necessary in these patients. Patients with co-infections that needed immediate intravenous antibiotic treatment were excluded because of presumed interference with the duration of intravenous therapy.

In each participating centre an investigator identified cases eligible for inclusion by screening the admission lists twice weekly and by attending the daily reports where new admissions are discussed. Generally, in the Netherlands, CAP patients needing hospitalisation are admitted to one of the wards immediately after initial evaluation on the emergency department; within 8 hours of after presentation. After inclusion, severity scores (the confusion-urea-respiratory rate-blood pressure-age score (CURB-65)[14] and the Pneumonia Severity Index (PSI/Fine score)[15]) and the antibiotics administered were recorded on the day of admission (day 0). As in routine practice, calculation of the CURB-65 and Fine score was based on the available data only.

At five time points during follow up (day 3, 6, 14, 21 and 28 after admission) clinical patient data and the route of antibiotic administration (intravenous/orally) were recorded. Clinical stability was assessed, defined as: temperature <37.8°C, oxygen saturation >92% without additional administration of oxygen, stable blood pressure without the need for saline infusion or vasopressive medication, heart rate <100/min, respiratory rate <25/min and absence of mental confusion that arose after the onset of infection.[16-18] If patients were able to swallow and were free of nausea or vomiting they were marked as 'able to take oral medication'. Parameters not recorded in the medical chart were assumed to be normal. Recording of clinical data ceased after a patient was switched to oral antibiotics, was discharged or died. Visits to the outpatient clinic, readmissions and mortality were noted retrospectively 28 days after admission.

*Physician interviews*

Residents or senior students functioning as such, treating included patients on the third day of admission were labelled as 'the treating physician' and were asked to fill out a case specific questionnaire or were interviewed using this questionnaire (appendix II). Generally, the resident treating a patient admitted to a ward on a specific time point is responsible for

that patient during the entire admission. We did not record if a change in treating residents occurred during the treatment of one of the including patients because in practice this seldom occurs (e.g. when residents rotate after 6 months on a specific ward). Treating physicians were informed about the study purpose in general terms, stating that the aim was to record the physicians motivation to choose for oral or intravenous antibiotic administration. Physicians were asked if they considered the patient to be clinically stable and if they could identify factors that were of influence on their choice for oral or intravenous administration of antibiotics. During the interview the researcher pointed out that factors can play a role on different levels, such as organisation or patient level, in order to stimulate the physicians to provide complete answers. Open ended questions were used, in order to provide the opportunity to identify various barriers. Because the residents receive daily supervision by medical specialists, their answers were considered a reflection of the specialist's opinion.

After the inclusion period, senior medical students, residents and supervising medical specialists, involved in the treatment of included patients, were invited to participate in a semi-structured in depth interview using a physician specific questionnaire (appendix III). This interview addressed the physicians' general knowledge, clinical experience and opinion on the optimal timing of the switch to oral antibiotics in CAP patients. If the provided answers seemed incomplete, the physicians were encouraged to elucidate their answers. All interviews were executed by the same investigator (ME) in a standardized manner.

**Sample size calculation, outcome measurement and data analysis**

The primary outcome was the number of patients adequately switched to oral therapy on day 3 of treatment. Based on previous studies, a baseline adherence to an early switch therapy in about 58% of cases can be expected.[8,9] According to the Wilson's score interval, a sample size of 140 patients would produce a two-sided 95 confidence interval with a width equal to 0.16 when the sample proportion is 0.58. The size of the study population was not suitable

for a multilevel analysis; instead physician and hospital characteristics were evaluated on the patient level using logistic regression analysis.

Secondary outcomes included the patient and physician factors associated with an early switch strategy. Factors possibly associated with continuous intravenous treatment on day three were assessed in univariate analysis. Ratio variables were evaluated as such, and not per category (e.g. Fine score risk classes) to minimize the loss of information. Variables with a p-value <0.05 and with less than 15% missing values were used for multivariate analysis using the forward likelihood ratio model. The goodness of fit of the model was tested with the Hosmer-Lemeshow test. All statistical analyses were performed using SPSS version 15.0.

Remaining secondary outcomes were barriers to an early switch strategy and the optimal time to switch in CAP patients in general as perceived by the treating physicians. For these qualitative data, the frequency of specific answers provided during the interviews was calculated by counting the number of times a specific answer was provided per case or per physician.

## RESULTS

### Patient and physician characteristics

Between October 2010 and May 2011, 162 patients admitted to one of the 3 participating hospitals were enrolled. 13 (8%) Patients were excluded because they were transferred to another hospital (1), had missing data (6) or other reasons (6). Of the 149 included patients, one patient died before day 3; this left 148 cases for analysis (figure 1). Overall, the mean age was 67 years (SD 17) and 71 (48%) were female. Ninety five patients (64%) had ≥1 co-morbidities; the most frequent co-morbidities were lung disease (n=49; 33%) and malignancy (n=18; 12%). The mean PSI score on admission was 88 (SD 32) (table 1). All included patients were treated on the ward they were initially admitted on for at least three days.

107 Physicians were involved in the treatment of the 149 included cases and invited for a physician specific interview, 97 (91%) were interviewed (figure 1). Ten (9%) physicians were excluded because they refused to participate (4), were no longer working in the hospital (2) or were on long term leave (4). Reasons to refuse participation were insufficient time in 3 cases and unclear in one case. The interviewed physicians consisted of 35 (36%) specialists with 417.5 cumulative years of experience as a medical specialist, 53 (55%) residents with 142.5 cumulative years of clinical experience and 9 (9%) senior students. The physicians gained their experience in over 30 Dutch centres and 2 foreign hospitals.

**Timing of the switch**

Overall, intravenous antibiotics were continued for 4.7 days (SD 2.8) and the length of hospital stay was 8.2 days (SD 5.5) (table 2). In 68/148 (46%) cases, a switch to oral agents was possible based on the predefined clinical criteria (figure 1-2). However, in 27/68 (40%) cases, intravenous antibiotics were still administered on/beyond day 3 (figure 1). The case mix on lung and non-lung wards was comparable, aside from the higher number of co-morbid lung diseases on the lung-wards (41/80 (51%) vs. 8/68 (12%) p<0.00). The percentage of patients switched timely was comparable as well (11/31 (36%) vs. 16/37 (43%) p=0.52). Furthermore, the timing of the switch in the first and second half of the study (4.9 (SD 3.2) vs. 4.5 (SD 2.5) p=0.38), was comparable, which makes a learning effect unlikely.

**Adherence to guideline recommendations**

Strikingly, 91 (94%) of the 97 treating physicians were not aware of the existence of any clear guidelines on the adequate timing of the switch. Indeed, participating hospitals did not provide these guidelines through antibiotic booklets or the intranet, but there are clear (inter-) national guidelines on this subject accessible online.[1] In the physician specific interviews, some reported switch criteria matched the criteria used in this study, like the absence of fever for 36 (37%) physicians, declining/no need for oxygen for 24 (25%) and hemodynamic stability for 21 (22%) (table 3). Additional factors, not matching our criteria were a decrease

in C-reactive protein for 47 (48%) physicians and signs of clinical improvement (e.g. clinical judgement or not specified) for 36 (37%). Notably, 16 (16%) physicians mentioned 'the patient feeling better' as a criterion to switch to oral antibiotics.

Of the 116 patients marked as clinically stable by the resident (but not yet discharged) on day three, 59 (51%) did not meet the objective criteria derived from research findings. For example, some patients with high heart rate (up to 182 beats per minute), fever (up to 39,2° C) or still needing oxygen were marked as clinically stable. In contrast, some physicians noted that they did not apply an early switch strategy in specific patients because of 'fever' (36.7°C) or 'tachycardia' (72 beats per minute).

**Barriers to an early switch strategy**

To evaluate factors that influence the decision to convert to oral antibiotics, characteristics of the 84 (56%) patients still on intravenous antibiotics on day 3, were compared to the 65 (44%) patients on oral antibiotics (table 1-2). Variables univariately associated with a prolonged duration of intravenous administration of antibiotics ($p<0.05$) were abnormalities on auscultation suggesting pneumonia ($p=0.02$) and a high CURB-65 ( $p=0.046$, 95% CI -0.76- -0.017) score on admission; admission to a secondary care hospital, as opposed to a university medical centre ($p=0.03$); a high respiratory rate ($p=0.04$, 95% CI -5.38- -0.08), high temperature ($p=0.00$, 95% CI -0.70- -0.21), oxygen administration ($p=0.01$) and clinical instability according to the resident ($p=0.00$) on day three. The respiratory rate was not recorded in 103 (69%) patients, therefore this variable was excluded, the remaining variables were used in multivariate analysis. In this analysis 9 (6%) out of 148 patients were excluded because they were discharged before measurements on day three could be taken, an additional 10 (7%) had missing values because of incomplete recording. Variables that tested significant in multivariate analysis were high temperature (odds ratio (OR) 2.9, 95% confidence interval (CI) 1.5-5.4) and oxygen administration (OR 2.5, 95% CI 1.8-5.5) on day three.

As shown, patients still on intravenous antibiotics on day 3 had a higher temperature, respiratory rate and oxygen was administered more often as compared to the remaining patients. The observed mortality (due to pulmonary disease and all cause) was significantly higher in the group still receiving intravenous therapy on day 3 (8% vs. 0% p=0.02 and 10.7% vs. 0% p=0.01). These data suggest that patients still on intravenous antibiotics on day three were more severely ill. Therefore, we performed an additional analysis and compared the characteristics of the 27 patients who were not switched while this was possible to the characteristics to the 41 patients who were adequately switched (appendix IV). The aforementioned 27 patients appeared to be comparable to the patients adequately switched, for example clinical parameters on day 3 and mortality rate were not significantly different.

By means of the case-specific interviews, we evaluated the barriers to a conversion to oral antibiotics. We evaluated the barriers reported by physicians treating the 27 (18%) patients in whom a switch to oral antibiotics was possible but not performed (table 4). The most frequently mentioned barriers were “supervisor’s opinion”, “day 3 of admission was a Saturday or a Sunday” and “a switch to oral agents was possible, but forgotten”, each mentioned in 5 (19%) cases. Overall, the reported barriers can be grouped into three main categories: practical considerations mentioned in 28% (13/47), organisational factors mentioned in 17% (8/47) and misconceptions mentioned in 55% (28/47).

Through the physician specific interviews, additional theoretical barriers to an early switch strategy were identified (table 6). Prominent discrepancies between the barriers mentioned in practice (patient specific questionnaire) and in theory (physician specific questionnaire) were forgetting to switch to oral agents (19% in practice vs. 2% in theory), absence of an oral variant for the administered intravenous antibiotic (18% in theory vs. 4% practice) and co-morbidities delaying the switch (22% theory vs. 4% practice).

## DISCUSSION

In this study, a conversion from intravenous to oral antibiotics before/on day 3 of treatment was possible in but not performed in 40% (27/68) of patients hospitalised with community-acquired pneumonia (CAP). Ninety-four percent of physicians were not aware of current guideline recommendations on the conversion to oral antibiotics. Perceived barriers to an early switch strategy included mainly misconceptions, practical considerations and organisational factors. It is therefore likely that the majority of the barriers identified in this study, can be reduced by means of an educational intervention and structural organisational changes.[7,19] This may reduce the duration intravenous antibiotics treatment and consequently the length of hospital stay (LOS) in CAP patients.

There are several strengths of this study. Through intensive screening we included all patients consecutively hospitalized with CAP in both teaching and university hospital settings. The age and sex distribution, incidence of comorbidities, severity of presentation and duration of intravenous therapy are comparable to other cohorts of CAP patients, which enhances the generalizability of our results.[7,19,20] The percentage of patients in which an appropriate switch strategy was applied in this study was comparable to the percentage found in a similar study (60 vs. 58%).[9] Furthermore, physicians with working experience in over 32 different hospitals were included and reasons for non-participation were unlikely to have influenced study results. Reasonably, the professional experience and expertise of the participating physicians represents those of all physicians working in the same setting in the Netherlands and possibly other countries with a similar health care system as well.[10]

There are three main drawbacks of the chosen study design. Firstly, measuring clinical parameters on several selected days of follow up as opposed to each day of admission may have led to a underestimation of the amount of patients that were not switched timely, since

several of these patients might had reached clinical stability before day three and a switch to oral agents would have been appropriate at that time. Secondly, the type of observation might have influenced study results. By asking physicians about their motivation to administer the antibiotic intravenously or orally, in specific cases on set times during the admission, their attention is drawn to the chosen treatment and they are likely to re-evaluate their choices. This phenomenon might be reflected by the notable high percentage of patients that are switched on day 3; the first day of follow up (figure 2). On the other hand, this effect could also be caused by the general awareness of the importance of an early switch strategy as shown through the physician specific questionnaires, in which a majority of physicians state that the ideal timing of the switch is before/on day 3. However, the potential influence of the latter drawback would lead to an underestimation of the amount of patients that are not timely switched and does not lessen the room for improvement in this field. Lastly, our study results may have been different if carried out in more than three hospitals. However, the number of participating physicians is quite large as compared to other studies[7,21] and physicians working in a teaching hospital as well as in a university hospital setting were included. Therefore, we feel our results may adequately reflect current practice in the Netherlands.

Optimization of antibiotic therapy in CAP by implementation of guideline advice has been the focus of attention for several years. Hagaman et al. evaluated the effect of the implementation of American Thoracic Society (ATS) guidelines on the switch to oral antibiotics.[8] Unfortunately, besides assessing the guideline knowledge of physicians, practical barriers to an early switch strategy were not studied. The implementation effect could have been greater if aimed at specific identified barriers.[11-13] Schouten and colleagues and Halm et al. assessed barriers to an early switch strategy in CAP patients as perceived by physicians through semi-structured interviews and written surveys respectively.[7,22] Perceived barriers to a timely switch strategy identified in these studies are mainly reflected by our study results as well and include unfamiliarity with guideline recommendations, lack of

outcome expectancy and misconceptions. In contrast to the latter studies, we are the first to compare the barriers mentioned in theory to the ones experienced in practice, completing the analysis of barriers to a timely switch strategy as a whole. In addition, currently, little is known about the quality and quantity of the influence of patients' knowledge, behaviour and assertiveness on the antibiotic treatment regimen in hospital care.[10] Our study shows a modest role for these patient related factors; the switch to oral antibiotics was delayed because the patient felt ill in only 1 (4%) out of 27 cases.

The results of this study stress the need for a tailored intervention aimed at the identified barriers in order to stimulate an early switch in CAP patients. The effectiveness of such an intervention needs to be evaluated in a study setting. If effective, the implementation strategy can be applied in other centres and possibly for other types of infection as well. Ideally, maximal results are obtained and all patients are switched to oral antibiotics timely after implementation. Based on our study results, theoretical implementation of an early switch strategy in all CAP patients in the Netherlands would lead to reduction of LOS of 3.4 days[2] in an additional 18% of patients and consequently to a reduction of health care costs of nearly 9.6 million euro (based on 31.000 admissions annually and €505,- per admission day)).[23,24]

In conclusion, the switch from intravenous to oral antibiotics is often unnecessarily delayed in patients hospitalised with CAP, this is mostly based on misconceptions and practical and organisational issues. A tailored intervention aimed at these factors is most likely to reduce the duration of treatment with intravenous antibiotics and consequently LOS.

**ACKNOWLEDGEMENT**

We thank all participating physicians and patients.

**REFERENCES**

1. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; Mar 1;44 Suppl 2:S27-72.

2. Athanassa Z, Makris G, Dimopoulos G, Falagas ME. Early switch to oral treatment in patients with moderate to severe community-acquired pneumonia: a meta-analysis. *Drugs* 2008;68(17):2469-81.

3. Oosterheert JJ, Bonten MJ, Schneider MM, Buskens E, Lammers JW, Hustinx WM, et al. Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. *BMJ* 2006; Dec 9;333(7580):1193.

4. Arnold FW, LaJoie AS, Brock GN, Peyrani P, Rello J, Menendez R, et al. Improving outcomes in elderly patients with community-acquired pneumonia by adhering to national guidelines: Community-Acquired Pneumonia Organization International cohort study results. *Arch Intern Med* 2009; Sep 14;169(16):1515-24.

5. Schouten JA, Prins JM, Bonten MJ, Degener J, Janknegt RE, Hollander JM, et al. Revised SWAB guidelines for antimicrobial therapy of community-acquired pneumonia. *Neth J Med* 2005; Sep;63(8):323-35.

6. Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009; Oct;64 Suppl 3:iii1-55.

7. Schouten JA, Hulscher ME, Natsch S, Kullberg BJ, van der Meer JW, Grol RP. Barriers to optimal antibiotic use for community-acquired pneumonia at hospitals: a qualitative study. *Qual Saf Health Care* 2007; Apr;16(2):143-9.

8. Hagaman JT, Yurkowski P, Trott A, Rouan GW. Getting physicians to make "the switch": the role of clinical guidelines in the management of community-acquired pneumonia. *Am J Med Qual* 2005; Jan-Feb;20(1):15-21.

9. Schouten JA, Hulscher ME, Trap-Liefers J, Akkermans RP, Kullberg BJ, Grol RP, et al. Tailored interventions to improve antibiotic use for lower respiratory tract infections in hospitals: a cluster-randomized, controlled trial. *Clin Infect Dis* 2007; Apr 1;44(7):931-41.

10. Hulscher ME, Grol RP, van der Meer JW. Antibiotic prescribing in hospitals: a social and behavioural scientific approach. *Lancet Infect Dis* 2010; Mar;10(3):167-75.

11. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. *Lancet* 2003; Oct 11;362(9391):1225-30.

12. Baker R, Camosso-Stefinovic J, Gillies C, Shaw EJ, Cheater F, Flottorp S, et al. Tailored interventions to overcome identified barriers to change: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev* 2010; Mar 17;(3)(3):CD005470.

13. Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess* 2004; Feb;8(6):iii,iv, 1-72.

14. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003; May;58(5):377-82.

15. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; Jan 23;336(4):243-50.

16. Ramirez JA, Srinath L, Ahkee S, Huang A, Raff MJ. Early switch from intravenous to oral cephalosporins in the treatment of hospitalized patients with community-acquired pneumonia. *Arch Intern Med* 1995; Jun 26;155(12):1273-6.

17. Halm EA, Fine MJ, Marrie TJ, Coley CM, Kapoor WN, Obrosky DS, et al. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. *JAMA* 1998; May 13;279(18):1452-7.

18. Menendez R, Torres A, Rodriguez de Castro F, Zalacain R, Aspa J, Martin Villasclaras JJ, et al. Reaching stability in community-acquired pneumonia: the effects of the severity of

disease, treatment, and the characteristics of patients. *Clin Infect Dis* 2004; Dec 15;39(12):1783-90.

19. Barlow G, Nathwani D, Williams F, Ogston S, Winter J, Jones M, et al. Reducing door-to-antibiotic time in community-acquired pneumonia: Controlled before-and-after evaluation and cost-effectiveness analysis. *Thorax* 2007; Jan;62(1):67-74.

20. Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Vandervoort MK, Feagan BG. A controlled trial of a critical pathway for treatment of community-acquired pneumonia. CAPITAL Study Investigators. Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin. *JAMA* 2000; Feb 9;283(6):749-55.

21. 1. Barlow G, Nathwani D, Myers E, Sullivan F, Stevens N, Duffy R, et al. Identifying barriers to the rapid administration of appropriate antibiotics in community-acquired pneumonia. *J Antimicrob Chemother* 2008; Feb;61(2):442-51.

22. Halm EA, Switzer GE, Mittman BS, Walsh MB, Chang CC, Fine MJ. What factors influence physicians' decisions to switch from intravenous to oral antibiotics for community-acquired pneumonia?. *J Gen Intern Med* 2001; Sep;16(9):599-605.

23. Ziekenhuisopnemane pneumonie (eng. Hospital admissions pneumonia). Accessed 2011 Aug 1, 2011.

24. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. Handleiding kostenonderzoek (eng. Manual cost research) 2010.

## TABLES

**Table 1. Patient characteristics (n=148)**

| | | Timing switch* | | |
|---|---|---|---|---|
| | **Total*** | **≤ day 3** | **> day 3** | **p-value (95% CI)** |
| | 148 (100%) | 64 (43 %) | 84 (57%) | |
| **Demographic data** | | | | |
| **Age** | 67.0 (± 17.3) | 65.7 (± 19.3) | 68.0 (± 15.6) | 0.423 (-7.974-3.364) |
| **Female** | 71 (48.0) | 29 (45.3) | 42 (50.0) | 0.572 |
| **Comorbidity** | | | | |
| Malignancy** | 18 (12.2) | 6 (9.4) | 12 (14.3) | 0.365 |
| Liver disease** | 2 (1.4) | 1 (1.6) | 1 (1.2) | 1.000 |
| Congestive heart failure** | 17 (11.5) | 8 (12.5) | 8 (10.7) | 0.736 |
| Cerebrovascular disease** | 15 (10.1) | 6 (9.4) | 9 (10.7) | 0.789 |
| Kidney disease** | 9 (6.1) | 6 (9.4) | 3 (3.6) | 0.143 |
| Lung disease | 49 (33.1) | 23 (35.9) | 26 (31.0) | 0.523 |
| ≥1 comorbiditiy | 95 (64.2) | 45 (70.3) | 50 (59.5) | 0.175 |
| **Severity scores and symptoms at presentation*** ** | | | | |
| **CURB-65 at presentation** (min) | 1.5 (± 0.5) | 1.4 (± 1.1) | 1.8 (± 1.2) | **0.046 (-0.759- -0.007)** |
| CURB-65 >2 | 34 (23.0) | 12 (18.8) | 22 (26.2) | 0.286 |
| **Fine score at presentation** (min) | 88.4 (± 32.0) | 83.5 (± 27.9) | 92.2 (± 34.5) | 0.101 (119.174-1.714) |
| Fine score IV | 57 (38.5) | 27 (42.2) | 30 (35.7) | 0.423 |
| Fine score V | 11 (7.4) | 0 | 11 (13.1) | **0.003** |
| Cough | 107 (73.3) | 47 (74.6) | 60 (72.3) | 0.754 |
| Sputum production | 63 (45.7) | 30 (51.7) | 33 (41.3) | 0.223 |
| Dyspnoea | 112 (78.9) | 51 (81.0) | 61 (77.2) | 0.588 |
| Temperature >38°C or < 36°C | 92 (62.2) | 39 (60.9) | 53 (63.1) | 0.789 |
| Pneumonia on auscaltation | 110 (74.8) | 54 (84.4) | 56 (67.5) | **0.019** |

| | | | | |
|---|---|---|---|---|
| Leukocytosis | 102 (69.4) | 44 (68.8) | 58 (69.9) | 0.883 |
| CRP > 30 mg/L | 133 (89.9) | 55 (85.9) | 78 (92.9) | 0.167 |

** n (%) or mean( ± standard deviation) using the Independent-samples T test for ratio variables and the Chi-quadrate or Fishers exact test for nominal variables.*

*** As defined in the Fine score.*

**** Missing data were not used in the calculation*

**Table 2. Outcome measures (n=148)**

| | | Timing switch* | | |
|---|---|---|---|---|
| | **Total*** | **≤ day 3** | **> day 3** | **p-value (95% CI)** |
| | 148 (100%) | 64 (43 %) | 84 (57%) | |
| **Follow up day 3** | | | | |
| **Clinically stable**** | - | - | - | - |
| According to protocol*** | 21 (21.2) | 9 (28.1) | 12 (17.9) | 0.245 |
| According to physician**** | 124 (84.4) | 61 (95.3) | 63 (75.9) | **0.001** |
| **Clinical parameters**** | - | - | - | - |
| Temperature (°C) | 37.0 (± 0.7) | 36.8 (± 0.5) | 37.2 (± 0.8) | **0.000 (-0.698- -0.211)** |
| Oxygen saturation (%) | 95 (± 3) | 94.4 (± 3.7) | 95.4 (± 3.0) | 0.086 (-2.166-0.147) |
| Oxygen administered (yes) | 66 (50.8) | 18 (36.0) | 48 (60.0) | **0.008** |
| Respirtratory rate (per minute) | 20 (± 4) | 18 (± 2) | 21 (± 4) | **0.044 (-5.380- -0.081)** |
| Blood pressure (mmHg) | - | - | - | - |
| Diastolic | 75 (± 12) | 76 (± 14) | 74 (± 11) | 0.343 (-2.212-6.314) |
| Systolic | 137 (± 21) | 138 (± 21) | 136 (± 22) | 0.574 (-5.346-9.604) |
| Heart rate (BPM) | 87 (± 19) | 83 (± 17) | 89 (± 19) | 0.070 (-12.290-0.479) |
| **Day 3 in weekend** | 38 (25.7) | 12 (18.8) | 26 (31.0) | 0.092 |
| **Follow up day 28** | | | | |
| **Stop intravenous agents** (day) | 4.7 (± 2.8) | 2.5 (± 0.7) | 6.4 (± 2.7) | **0.000 (-4.581- -3.219)** |
| **Length of hospital stay** (days) | 8.2 (± 5.5) | 6.0 (± 4.4) | 10.0 (± 5.6) | **0.000 (-5.700- -2.362)** |
| **Readmission** (within 28 days) | - | - | - | - |
| All | 13 (9.3) | 8 (12.7) | 5 (6.5) | 0.208 |
| Pulmonary pathology | 5 (3.6) | 2 (3.2) | 3 (3.9) | 1.000 |
| **Mortality** (within 28 days) | - | - | - | - |
| All | 9 (6.1) | 0 (0.0) | 9 (10.7) | **0.005** |
| Pulmonary pathology | 7 (4.7) | 0 (0.0) | 7 (8.3) | **0.019** |
| **Physician characteristics** | | | | |

| | | | | |
|---|---|---|---|---|
| **Clinical experience (years)** | - | - | - | - |
| Resident (as resident) | 2.2 (± 1.9) | 2.4 (± 2.2) | 2.0 (± 1.6) | 0.320 (-0.309-0.938) |
| Supervisor (as medical specialist) | 10.9 (± 8.1) | 12.2 (± 8.6) | 10.0 (± 7.7) | 0.128 (-0.647-5.085) |
| **Type of admission** | | | | |
| **Lung ward** | 80 (54.1) | 36 (56.3) | 44 (52.4) | 0.640 |
| **University hospital** | 44 (29.7) | 25 (39.1) | 19 (22.6) | **0.030** |

** n (%) or mean( ± standard deviation) using the Independent-samples T test for ratio variables and the Chi-quadrate or Fishers exact test for nominal variables.*

*** Missing data were not used in the calculation.*

**** Patients discharged before day three were excluded here.*

***** Patients discharged before day three were marked as clinically stable according to the physician.*

**Table 3. Criteria applied by the treating physicians (n= 97) when deciding to switch to oral antibiotics**

| Category | Qualitative answers* | Frequency** |
|---|---|---|
| **Clinical course** | | |
| **Clinical judgement** | Clinical improvement (clinical judgement or not specified) | 37.1 (36) |
| **Oral intake** | Able to swallow, no nausea, vomiting or diarrhoea | 20.6 (20) |
| **Temperature** | Fever subsiding | 19.6 (19) |
| | No fever | 37.1 (36) |
| | - At least 1 day | 7.2 (7) |
| | - At least 2 days | 6.2 (6) |
| | Other | 1 .0 (1) |
| **Respiratory** | Dyspnoea subsiding | 16.5 (16) |
| | Less/no need for oxygen administration | 24.7 (24) |
| **Cardiovascular** | Hemodynamically stable | 21.6 (21) |
| | No signs of sepsis | 4.1 (4) |
| **Other** | - | 16.5 (16) |
| **Patient characteristics** | | |
| **Subjective** | Patient feels better | 16.5 (16) |
| **Other** | - | 1.0 (1) |
| **Laboratory parameters** | | |
| **Inflammation parameters** | Decrease in C-reactive protein | 48.4 (47) |
| | Decrease in leucocytes | 12.4 (12) |
| | Other | 2.0 (2) |
| **Culture** | Pathogen known/ culture results available | 11.3 (11) |
| **Practical considerations** | | |
| **Timeline** | Intravenous antibiotics, at least until day 2 | 4.1 (4) |
| | Intravenous antibiotics, at least until day 3 | 17.5 (17) |
| | Intravenous antibiotics, at least until day 4 | 16.5 (16) |
| | Other | 3.1 (3) |

| | | |
|---|---|---|
| **Choice of antibiotics** | A good oral variant is available | 6.2 (6) |
| **Other** | - | 5.1 (5) |

**Answers are displayed in detail if they were provided by 4 physicians or more.*

*** % (number) of physicians that provided this answer.*

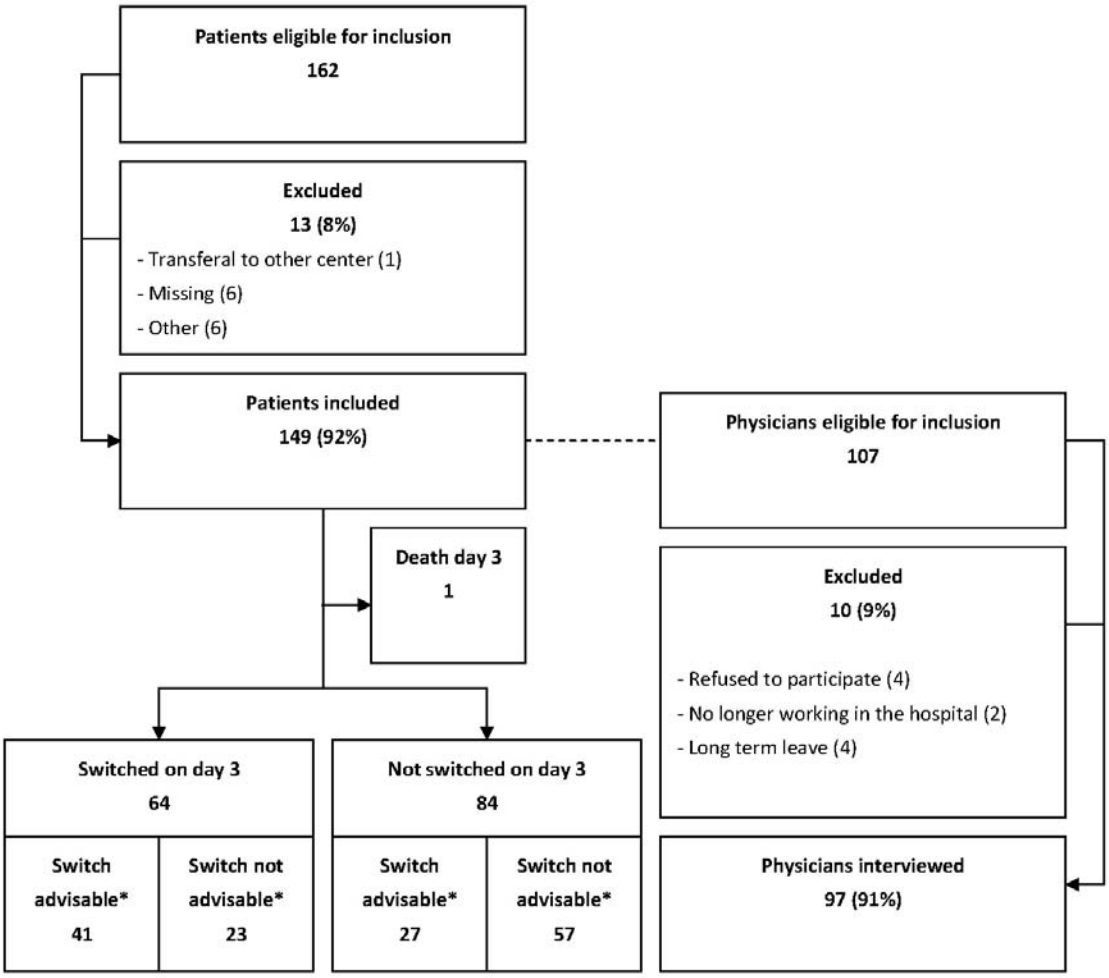
**Table 4. Barriers to an early switch strategy by case (case specific questionnaire n= 27) and in theory (physician specific questionnaire n= 97)**

| **Factors** | | **Frequency*** | |
|---|---|---|---|
| **Category** | **Qualitative answers** | **Case specific** | **Theory** |
| **Physician factors** | | | |
| | Opinion supervisor | 5 (19) | 13 (13) |
| | Forgot | **5(19)** | **2 (2)** |
| | Practice experience/ intuitive | 0 | 9 (9) |
| | Delay due to resident | 0 | 5 (5) |
| | Other | NA | 3 (3) |
| **Patient characteristics** | | | |
| **Patient factors** | Absorption orally not secured** | NA | 37 (38) |
| | Co-morbidity | **1 (4)** | **21 (22)** |
| | Elderly patient (> 75 years) | 0 | 4 (4) |
| | Therapy adherence not secure | 0 | 4 (4) |
| **Clinical course** | Patient very ill at admission | 1 (4) | 7 (7) |
| | Patient still ill | 4 (15) | 23 (24) |
| | Patient feels ill | 1 (4) | 0 |
| | Fever | 3 (11) | 6 (6) |
| | Fever subsided < 24 hours ago | 2 (7) | 0 |
| | Dyspnoea/ oxygen needed | 3 (11) | 1 (1) |
| | Hemodynamically unstable | 2 (7) | 0 |
| **Additional diagnostics** | Elevated CRP | 3 (11) | 3 (3) |
| | High leukocytes | 1 (4) | 0 |
| | Abnormalities on chest radiography | 1 (4) | 1 (1) |
| | Confusion/delirium | 0 | 4 (4) |
| | Empyema/pleural effusion/ abces | 0 | 8 (8) |
| | Secondary infection | 0 | 4 (4) |

| | | | |
|---|---|---|---|
| | Other | NA | 11 (11) |
| **Other hospital staff factors** | | | |
| | Other | NA | 4 (4) |
| **Organisation factors** | | | |
| | Weekend | 5 (19) | 11 (11) |
| | No supervision available | 0 | 4 (4) |
| | Other | NA | 9 (9) |
| **Other** | | | |
| **Antibiotics** | No oral variant for intravenous agent | **1 (4)** | **17 (18)** |
| | Allergy/ toxicity oral variant | 3 (11) | 15 (16) |
| | Recent change in antibiotic regimen | 1 (4) | 1 (1) |
| | Short duration of intravenous therapy | 1 (4) | 0 |
| | Other | NA | 3 (3) |
| **Microbiology** | Culture results still unknown | 3 (11) | 12 (12) |
| | Causative pathogen is atypical | 1 (4) | 10 (10) |
| | Other | NA | 6 (6) |
| **Admission related/ other** | Patient stays admitted/ needs intravenous medication for other reason | 0 | 8 (8) |
| | Other | NA | 2 (2) |

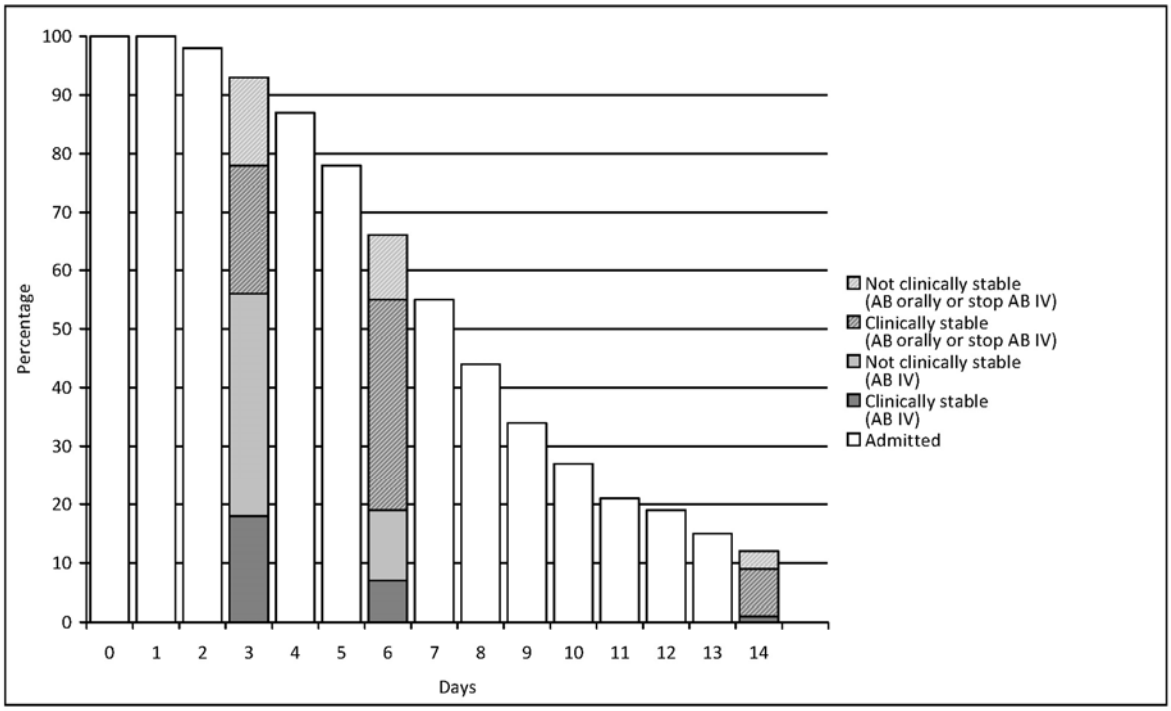
** Number (%) of cases in which an answer was provided or number (%) of physicians that provided this answer. Percentages that differ >10% are in bold printing. Answers mentioned in the physician specific questionnaires only are displayed in detail if they were provided by 4 physicians or more or if they were also provided in the patient specific questionnaire, the remaining answers are provided elsewhere (appendix V).NA: not applicable. ** E.g. not able to swallow, nausea, vomiting.*

**Figure 1. Flow of patients and physicians through the study**




*ICU: Intensive Care Unit*
*CF: Cystic Fibrosis*
*IV: Intravenous*

**Figure 2**


100
90
80
70
60
50
40
30
20
10
0
Percentage
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Days
Not clinically stable (AB orally or stop AB IV)
Clinically stable (AB orally or stop AB IV)
Not clinically stable (AB IV)
Clinically stable (AB IV)
Admitted