

# Guidance of antibiotic therapy with procalcitonin in lower respiratory tract infections

## Insights into the ProHOSP study

Philipp Schuetz,<sup>1,\*</sup> Mirjam Christ-Crain,<sup>1</sup> Werner Albrich,<sup>2</sup> Werner Zimmerli<sup>3</sup> and Beat Mueller,<sup>2</sup> for the ProHOSP Study Group<sup>†</sup>

<sup>1</sup>Department of Internal Medicine; Division of Endocrinology; Diabetes and Clinical Nutrition; University Hospital Basel; Switzerland; <sup>2</sup>Department of Internal Medicine; Kantonsspital Aarau; Aarau, Switzerland; <sup>3</sup>Department of Internal Medicine; Kantonsspital Liestal; Liestal, Switzerland

<sup>†</sup>Members of the ProHOSP Study Group are listed in the appendix

**I**n the recently published ProHOSP trial, we investigated the safety and external validity of procalcitonin (PCT) guidance for antibiotic therapy in patients with different severities of lower respiratory tract infections, mainly pneumonia. In this addendum, we aim to extend the initial report by reinforcing the rationale of the PCT algorithm and by presenting more detailed data on antibiotic therapy in different severities of infection. In milder, mostly viral respiratory infections (i.e., acute or chronic bronchitis) initial prescription of antibiotics was markedly reduced by PCT guidance because PCT remained low in most patients. In pneumonia, PCT showed a severity-dependent increase and highest levels in patients with positive blood cultures. Thus, the main effect in pneumonia was a severity- and bacteremia-adapted reduction of the duration of antibiotic courses. In lower respiratory tract infections, PCT guidance had a differential effect on antibiotic exposure depending on the underlying type and severity of respiratory tract infection.

### Introduction

Recently, we demonstrated the safety of procalcitonin (PCT) guidance of antibiotic therapy in a large multicenter trial in Switzerland including patients with different severities of lower respiratory tract infections (LRTIs) ranging from often self-limiting acute bronchitis or acute exacerbation of chronic pulmonary disease

(ECOPD) to possibly life-threatening community-acquired pneumonia (CAP).<sup>1</sup> Importantly, within this trial, antibiotic therapy was markedly reduced overall and resulted in a reduction of antibiotic side effects, including nausea, diarrhea and rash of about 30%. In this addendum, we extend the initial report by reviewing the clinical PCT algorithm and by presenting more detailed data on antibiotic therapy in different severities of CAP. Because of both different kinetics and absolute values in mild and viral as compared to severe and bacterial LRTI, initiation and duration of antibiotic courses are affected by PCT guidance. Limiting overall antibiotic exposure by both, reducing initiation and by shortening duration of treatment, respectively, is important for lowering antibiotic-associated costs, side effects and minimizing selection pressures for resistant organism.<sup>2</sup>

### Clinical Algorithm for PCT Guidance

PCT concentrations most markedly increase upon inflammation in the context of severe bacterial infections and show a log-normal decrease upon recovery. For this reason, PCT concentrations can help physicians to estimate the likelihood for relevant bacterial infections and thus decide upon the need for antibiotic therapy in individual patients as a surrogate biomarker. Importantly, only highly sensitive PCT assays reliably distinguish between bacterial and non-bacterial LRTI

**Key words:** procalcitonin, pneumonia, bronchitis, COPD, antibiotic therapy, bacterial resistance

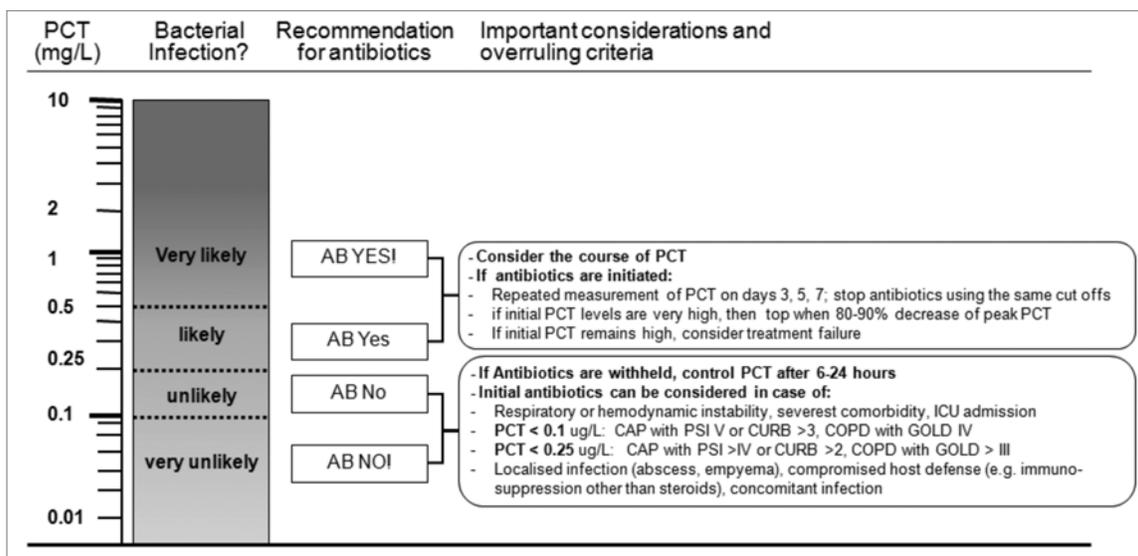
Submitted: 10/30/09

Accepted: 10/30/09

Previously published online:  
[www.landesbioscience.com/journals/virulence/article/10488](http://www.landesbioscience.com/journals/virulence/article/10488)

\*Correspondence to: Philipp Schuetz;  
Email: [SchuetzP@uhbs.ch](mailto:SchuetzP@uhbs.ch)

Addendum to: Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA* 2009; 302:1059–66; PMID: 19738090.



**Figure 1.** Algorithm for Antibiotic Guidance. AB, Antibiotic; PSI, Pneumonia severity index; CURB65, confusion, urea, respiratory rate, blood pressure, age >65 years.

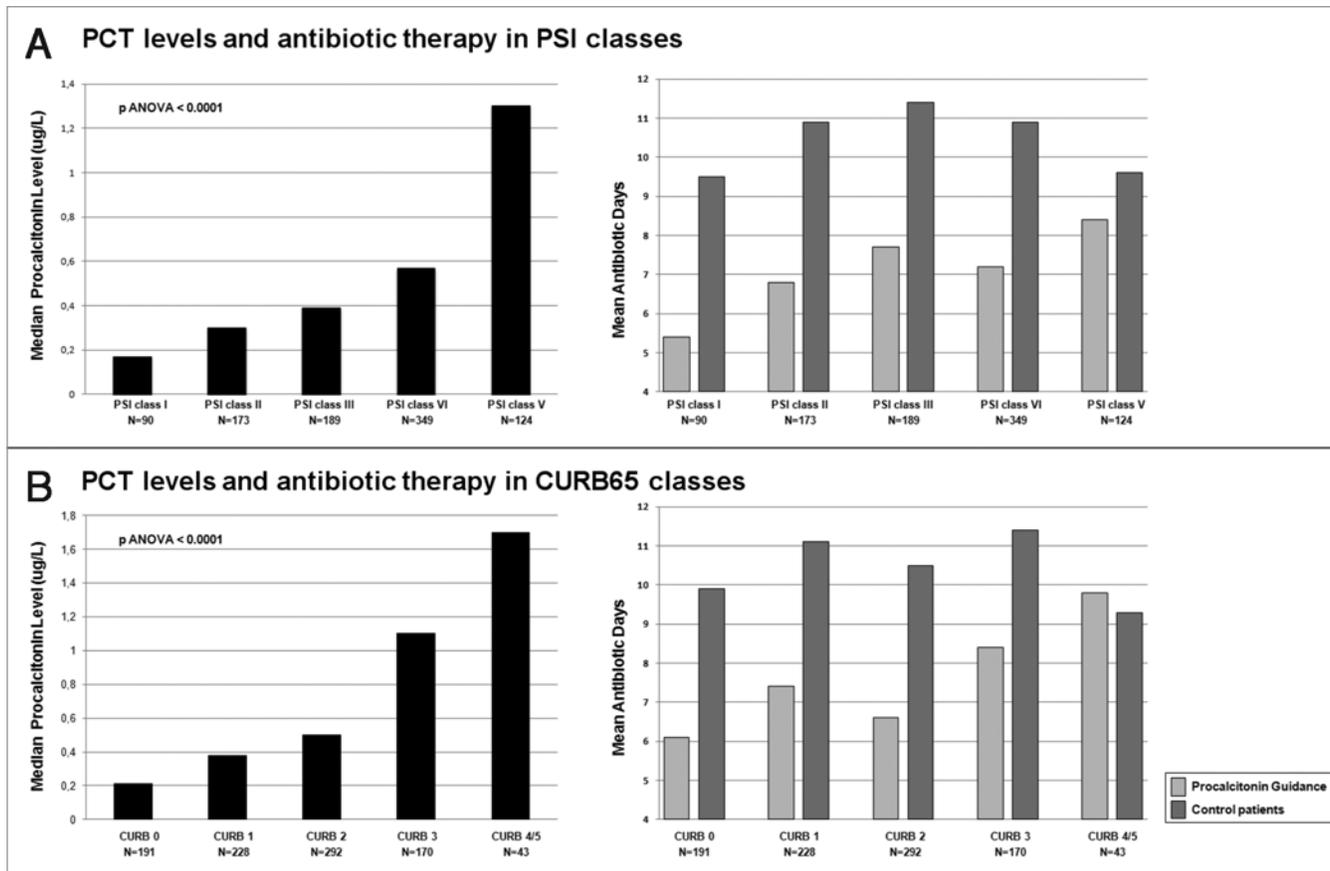
in an Emergency Department setting,<sup>3-6</sup> While observational studies previously tried to assess the diagnostic accuracy of PCT to distinguish bacterial from non-bacterial LRTI, correct interpretation of microbiological analysis in LRTI is hampered by issues like antibiotic pre-treatment, pre-analytic errors, sample availability, co-infection, colonization, persistence of pathogen detectability and most importantly the lack of a diagnostic gold standard. The aetiology of a presumed bacterial cause of fever cannot be detected in 50–80% of patients with suspected bloodstream infections. Therefore, no gold standard exist in LRTI and observational studies remain inconclusive.<sup>7</sup> Meta-analyses of observational studies further stir confusion and cannot resolve the gold standard dilemma.<sup>8,9</sup> Thus the ultimate proof that PCT safely improves clinical decision making must come from intervention studies, in which antibiotic therapy is guided by a PCT algorithm, and in which the primary measure of efficacy is medical outcome. For this purpose a clinical algorithm based on reasonable PCT cut off ranges derived from multilevel-likelihood calculations obtained in observational studies,<sup>10</sup> was proposed and tested in “proof-of-principle” LRTI studies and in different clinical settings.<sup>11-15</sup> The algorithm encourages (>0.5 µg/L or >0.25 µg/L) or discourages

(<0.1 µg/L or <0.25 µg/L) initiation or continuation of antibiotic therapy more or less based on these specific cut-off ranges (Fig. 1). In case antibiotics are withheld, clinical reevaluation and a repeated measurement of PCT is recommended after 6–24 hours in all patients with not improving medical conditions. If PCT values are increased and antibiotic therapy is initiated, repeated PCT measurements are recommended and antibiotics can be discontinued using the same cut-off ranges. In patients with very high PCT values on admission (e.g., >5–10 µg/L), discontinuation of antibiotic therapy is encouraged if levels decreased by more than 80–90% of the initial value. Importantly, to assure the safety of patients, specific “overruling” criteria were defined, which allowed this algorithm to be bypassed. These include all situations where patients are in immediately life-threatening situations (i.e., hemodynamic or respiratory instability or need for ICU admission) and rapid initiation of antibiotic therapy is of utmost importance. Also in patients with high severity CAP as assessed by the Pneumonia Severity Index (PSI) or the CURB65 score, or most severe COPD, respectively, overruling of the algorithm is possible. Interestingly within the ProHOSP study, in around 10% of all patients, the algorithm was overruled based on these pre-specified criteria. For example 3.2 and 8.2% of CAP patients

with immediate need for ICU admission had initial PCT levels below 0.1 µg/L and 0.25 µg/L, respectively. In 9.2% of patients, the algorithm was overruled in violation of the criteria and only based on the judgment of the treating physician. Many physicians in this multicenter study were in the beginning not familiar with the PCT algorithm and were used to giving longer courses of antibiotic therapy. As with any new diagnostic test, changing the behavior of physicians needs continuous education and clinical experience. Interestingly, the overruling rate without prespecified reasons decreased from the first to the second half of the study by over 20% (from 10.5 to 8.2%).

### PCT Guidance in Different Severities of CAP

There are several reasons why tailoring antibiotic therapy in individual patients and thereby shortening the overall duration is important. First, the trend toward greater proportions of pneumococci that are multi-resistant calls for expanded efforts to reduce the unnecessary use of antimicrobial agents.<sup>16</sup> This has been recognized by most professional organisations and societies who developed consensus guidelines restricting the use and duration of antibiotic treatments for this purpose. However, adherence to guidelines is



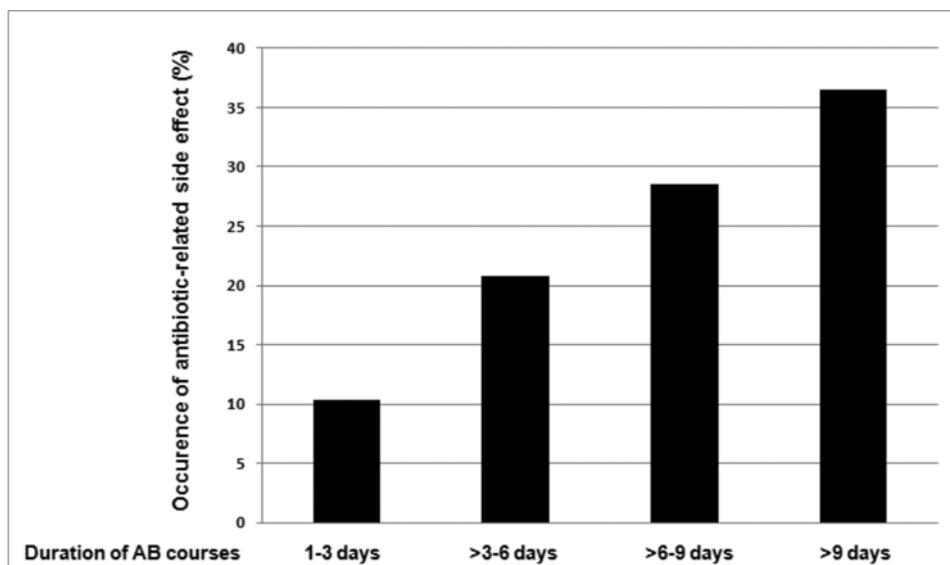
**Figure 2.** Procalcitonin concentrations and Antibiotic Therapy in different severities of CAP. PSI, Pneumonia severity index; CURB65, confusion, urea, respiratory rate, blood pressure, age >65 years.

variable<sup>17,18</sup> and physicians tend to treat longer, especially in elderly patients with co-morbidities and patients with severe pneumonia.<sup>15,19</sup> For example, adherence to guidelines within ProHOSP was moderate with a 24% overruling rate despite the enforced use of a web-based algorithm for all patients. Second, from a pathophysiological perspective, it makes sense that for different severities of LRTI, different durations of antibiotic courses are appropriate. Duration of antibiotic therapy can be guided by clinical signs such as defervescence, decrease of sputum production and coughing, or improvement of general condition. However, the interpretation of the clinical response lacks standardization and validation and is prone to interobserver variability.<sup>20</sup> In this context, most experts agree that readily measurable biomarkers predicting severity and extent of bacterial infection would be helpful. Several biomarkers

have been proposed for this purpose, e.g., s-TREM, C-reactive protein (CRP) and white blood count.<sup>21</sup> However, the reliability of these markers for guiding antimicrobial therapy is limited by their protracted response with late peak levels and a suboptimal specificity, especially in patients with systemic inflammation.<sup>9,21-23</sup> Within ProHOSP,<sup>1</sup> PCT concentrations showed an about 6–8-fold increase with increasing severity of CAP based on both scoring systems, the PSI score<sup>24</sup> and the CURB65,<sup>25</sup> (Fig. 2). Consequently, duration of antibiotic therapy was different in different severities of CAP in the PCT group, while in the control group antibiotic courses were similar. Similarly, as demonstrated in two previous smaller studies<sup>12,14</sup> and in the ProHOSP study, patients with bacteraemic CAP had markedly increased PCT concentrations resulting in a longer treatment of these bacteraemic patients.

### Adverse Outcomes

The aim of the ProHOSP trial was to investigate the safety of PCT guidance in a large and adequately powered sample of patients with LRTI in a multicenter setting. The study was powered for a combined endpoint including mortality, ICU admission, disease specific complications and recurrent LRTI in need for antibiotics within a 30 days follow up. Obviously, mortality is the most important component of this endpoint and 30 days mortality rates were similar in both study arms. Based on the ProHOSP study, the difference of mortality between PCT and control patients was 0.4. The 95% confidence interval of -2.1 to 2.5 excluded a higher mortality of 2.5% in PCT guided patients. The difference of mortality rates between control and PCT patients in all patients (n = 2570) from the previous five LRTI PCT studies<sup>1,11,13-15</sup> is only 0.04% (95%CI—1.0%–1.7%) with 4.7% nonsurvivors (60/1290) in the control group and



**Figure 3.** Antibiotic-related side effects in different treatment durations of LRTI. AB, Antibiotic.

4.6% nonsurvivors (59/1280) in the PCT group. Interestingly, in the ProHOSP study the risk of ICU admission and recurrent infections tended to be smaller in patients allocated to the PCT group. Although there is no definite explanation for this finding, it is conceivable that PCT provides an additional margin of safety for the treating physicians. Because many physicians monitored CRP levels in patients allocated to the control group, CRP with its later peak and slower decrease may have influenced the physicians' decision to transfer patients to the ICU or to suspect recurrent infection. In addition, we found a 42% increase in rates of antibiotic-related side effects including diarrhea, nausea and skin rashes in control group patients (28.1% vs. 19.8%,  $p < 0.001$ ). Antibiotic-related side effects increased threefold in patients with short antibiotic courses (1–3 days) to patients with longer courses (>9 days) (Fig. 3). Importantly, duration of antibiotic courses was the single most important predictor for side effects with an adjusted odds ratio of 1.08 (95%CI 1.05–1.10) after adjustment for randomization arm, type of LRTI, age, gender and total length of hospital stay.

### Future Directions

Procalcitonin-guided antibiotic therapy was repetitively shown to be most effective and efficient to safely reduce the antibiotic overuse in LRTI. Notably, 50% to 75%

of all antibiotic courses are prescribed for LRTI. Thus, it is very likely that if introduced in a larger scale in the medical community it will be associated with a lower risk of emergence of bacterial resistance in clinical practice. All published evidence today, however, was obtained in randomized controlled trials where physicians knew that they were being monitored. Thus physicians may have shown a higher adherence to the PCT algorithm under study conditions as compared to the real-life setting (Hawthorne effect) and data on the efficacy of PCT guidance outside of study conditions are lacking. Because the effect of PCT strongly depends on the adherence to the clinical PCT algorithm future studies should investigate the effect of PCT in real life settings.

For this purpose, we are currently performing a multinational observational quality surveillance study with a target inclusion of at least 1,200 patients in Switzerland, France and the US (ISRCTN40854211). All consecutive adults with LRTI who are seen in hospital emergency departments or general practitioner offices and are being treated in either an ambulatory or hospital setting are being registered and monitored for 30 days after diagnosis. The primary aim is to assess the efficacy of PCT-guided antibiotic guidance for patients with LRTI outside of study conditions; secondary goals include assessment of the adherence

with the PCT algorithm and its safety in a real-life setting. Since some of the currently involved centers participated in the before mentioned trial, it will be interesting to compare these primary and secondary outcomes with the procalcitonin group and the control group within the centers and as pooled results; and further to compare the PCT-naïve centers with those which already have PCT experience. Since like previously noted, controlled studies may show different results from real-life settings,<sup>26,27</sup> it is time to evaluate PCT as the currently best studied and most promising biomarker for antibiotic guidance in LRTIs in larger scale post-study surveillances. We welcome those interested in antibiotic use and resistance issues to join us in these efforts.

### Acknowledgements

This trial is supported in part by a grant from the Swiss National Science Foundation (SNF 3200BO-116177/1), contributions from santésuisse and the Gottfried and Julia Bangerter-Rhyner-Foundation, the University Hospital Basel, the Medical University Clinic Liestal, the Medical Clinic Buergerspital Solothurn, the Cantonal Hospitals Muensterlingen, Aarau and Lucerne, respectively, the Swiss Society for Internal Medicine (SGIM), and from the Department of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Basel.

BRAHMS, the manufacturer of the PCT assay, provided all assay related material, Kryptor® machines if not already available on-site, and kits and maintenance required for 10'000 measurements related to the study.

P.S., M.C.C. and B.M. received support from BRAHMS to attend meetings and fulfilled speaking engagements. B.M. has served as a consultant and received research support from BRAHMS Inc., (major manufacturer of PCT).

The ProHOSP study group consists of the following: Robert Thomann M.D., Claudine Falconnier M.D., Marcel Wolbers Ph.D., Isabelle Widmer M.D., Stefanie Neidert M.D., Thomas Fricker M.D., Claudine Blum M.D., Ursula Schild R.N., Katharina Regez R.N., Rita Bossart R.N., Ronald Schoenenberger M.D., Christoph Henzen M.D., Claus Hoess M.D., Martin Krause M.D., Thomas Bregenzer M.D., Heiner C. Bucher M.D., Ayesha Chaudri, Jeannine Haeuptle, Roya Zarbosky, Rico Fiumefreddo, Melanie Wieland R.N., Charly Nusbaumer M.D., Andres Christ M.D., Roland Bingisser M.D., Kristian Schneider R.N., Christine Vincenzi R.N., Michael Kleinknecht R.N., Brigitte Walz Ph.D., Verena Briner M.D., Dieter Conen M.D., Andreas Huber M.D., Jody Staehelin M.D., Aarau Chantal Bruehlhardt R.N., Ruth Luginbuehl R.N., Agnes Muehleemann Ph.D., Ineke Iambinon and Max Zueger M.D., D. Conen M.D., M. Wieland R.N., C. Nusbaumer M.D., C. Bruehlhardt R.N., R. Luginbuehl R.N., A. Huber M.D., B. Walz R.N. and M. Zueger M.D.

## References

- Schuetz P, Christ-Crain M, Wolbers M, Schild U, Thomann R, Falconnier C, et al. Effect of Procalcitonin-based Guidelines Compared to Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections: The Randomized-Controlled Multicenter ProHOSP Trial. *JAMA* 2009; 302:1059-66.
- Scalera NM, File TM Jr. How long should we treat community-acquired pneumonia? *Curr Opin Infect Dis* 2007; 20:177-81.
- Boussekey N, Leroy O, Georges H, Devos P, d'Escrivan T, Guery B. Diagnostic and prognostic values of admission procalcitonin levels in community-acquired pneumonia in an intensive care unit. *Infection* 2005; 33:257-63.
- Polzin A, Pletz M, Erbes R, Raffenberg M, Mauch H, Wagner S, et al. Procalcitonin as a diagnostic tool in lower respiratory tract infections and tuberculosis. *Eur Respir J* 2003; 21:939-43.
- Hedlund J, Hansson LO. Procalcitonin and C-reactive protein levels in community-acquired pneumonia: correlation with etiology and prognosis. *Infection* 2000; 28:68-73.
- Masia M, Gutierrez F, Shum C, Padilla S, Navarro JC, Flores E, et al. Usefulness of procalcitonin levels in community-acquired pneumonia according to the patients outcome research team pneumonia severity index. *Chest* 2005; 128:2223-9.
- Schuetz P, Christ-Crain M, Muller B. Procalcitonin and other biomarkers to improve assessment and antibiotic stewardship in infections—hope for hype? *Swiss Med Wkly* 2009; 139:318-26.
- Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. *Lancet Infect Dis* 2007; 7:210-7.
- Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis* 2004; 39:206-17.
- Muller B, Becker KL, Schachinger H, Rickenbacher PR, Huber PR, Zimmerli W, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. *Crit Care Med* 2000; 28:977-83.
- Briel M, Schuetz P, Mueller B, Young J, Schild U, Nusbaumer C, et al. Procalcitonin-guided antibiotic use vs. a standard approach for acute respiratory tract infections in primary care. *Arch Intern Med* 2008; 168:2000-7.
- Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *Am J Respir Crit Care Med* 2008; 177:498-505.
- Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Muller C, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest* 2007; 131:9-19.
- Christ-Crain M, Stolz D, Bingisser R, Muller C, Miedinger D, Huber PR, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* 2006; 174:84-93.
- Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 2004; 363:600-7.
- Whitney CG, Farley MM, Hadler J, Harrison LH, Lexau C, Reingold A, et al. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. *N Engl J Med* 2000; 343:1917-24.
- Menendez R, Torres A, Zalacain R, Aspa J, Martin-Villasclaras JJ, Borderias L, et al. Guidelines for the treatment of community-acquired pneumonia: predictors of adherence and outcome. *Am J Respir Crit Care Med* 2005; 172:757-62.
- Aujesky D, Fine MJ. Does guideline adherence for empiric antibiotic therapy reduce mortality in community-acquired pneumonia? *Am J Respir Crit Care Med* 2005; 172:655-6.
- Mandell LA, File TM Jr. Short-course treatment of community-acquired pneumonia. *Clin Infect Dis* 2003; 37:761-3.
- Wipf JE, Lipsky BA, Hirschmann JV, Boyko EJ, Takasugi J, Peugeot RL, et al. Diagnosing pneumonia by physical examination: relevant or relic? *Arch Intern Med* 1999; 159:1082-7.
- Gibot S, Cravoisy A, Levy B, Bene MC, Faure G, Bollaert PE. Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. *N Engl J Med* 2004; 350:451-8.
- van der Meer V, Neven AK, van den Broek PJ, Assendelft WJ. Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. *BMJ* 2005; 331:26.
- Muller B, Gencay MM, Gibot S, Stolz D, Hunziker L, Tamm M, et al. Circulating levels of soluble triggering receptor expressed on myeloid cells (sTREM)-1 in community-acquired pneumonia. *Crit Care Med* 2007; 35:990-1.
- 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; 336:243-50.
- 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; 58:377-82.
- Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004; 351:543-51.
- Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; 341:709-17.