Biomarkers, 2011; 16(8): 637–641

ISSN 1354-750X print/ISSN 1366-5804 online
DOI: 10.3109/1354750X.2011.620629

informa
healthcare

RESEARCH ARTICLE

Bacteremia and MR-proANP changes in mild community-acquired pneumonia

Solweig Guinard-Barbier[1,2], Camille Chenevier-Gobeaux[3], Sophie Grabar[4,5], Laurent Quinquis[4,5], Jeannot Schmidt[6], Pierre Hausfater[7,8], Enrique Casalino[9,10], Stéphanie Huet[1,2], Jean-Louis Pourriat[1,2], Bertrand Renaud[11], and Yann-Erick Claessens[1,2,12]

[1]Department of Emergency Medicine, Groupe Hospitalier Broca Cochin Hôtel-Dieu, Paris, France, [2]Faculté de Médecine, Université Paris Descartes, Paris, France, [3]Department of Biochemistry, Groupe Hospitalier Broca Cochin Hôtel-Dieu, APHP, Paris, France, [4]Department of Biostatistics, Groupe Hospitalier Broca Cochin Hôtel-Dieu, APHP, Paris, France, [5]Faculté de Médecine, Université Paris Descartes, Paris, France, [6]Department of Emergency Medicine, Hospital Gabriel Montpied, Clermont-Ferrand, France, [7]Department of Emergency Medicine, Hôpital Pitié-Salpétrière, APHP, Paris, France, [8]Faculté de Médecine, Université Pierre et Marie Curie, Paris, France, [9]Department of Emergency Medicine, Hôpital Bichat-Claude Bernard, APHP, Paris, France, [10]Faculté de Médecine, Université René Diderot, Paris, France, [11]Department of Emergency Medicine, Hôpital Henri Mondor, APHP, Créteil, France, and [12]Department of Emergency Medicine, Centre Hospitalier Princesse Grace, Monaco

Abstract

Background: Mid-regional pro-atrial natriuretic peptide (MR-proANP) increases with severity in community-acquired pneumonia (CAP). We investigated whether changes of MR-proANP correlated to bacteremia.

Methods: 392 adult patients with CAP visiting emergency department from a prospective observational multicenter study.

Results: MR-proANP levels increased in patients with positive bacteremia (92.8 pmol/L vs. 84.3 pmol/L, $p=0.04$). Performance of MR-proANP to detect bacteremia (0.60) was equivalent to CRP (0.59) but less accurate than PCT (0.69).

Conclusion: MR-ANP poorly predicts bacteremia in CAP patients.

Keywords: Bacteremia, community-acquired pneumonia, C-reactive protein, procalcitonin, mid regional pro atrial natriuretic peptide, emergency medicine

Introduction

Mid-regional pro-atrial natriuretic peptide (MR-proANP) has recently emerged as a promising biomarker (Morgenthaler et al. 2005, Maisel et al. 2010) that better correlates with mortality and morbidity than do procalcitonin (PCT) and C-reactive protein (CRP) in community-acquired pneumonia (CAP; Claessens et al. 2010, Krüger et al. 2010). Severity of CAP depends on underlying conditions. Changes of MR-proANP detect acute and chronic heart failure (CHF; Maisel et al. 2010) whereas prognostic value in CAP is maintained independently to CHF (Krüger et al. 2010). In addition, lipopolysaccharide (LPS) challenge (de Kruif et al. 2008) and pyelonephritis-related bacteremia increase MR-proANP levels (Guinard-Barbier et al. 2011). Therefore MR-proANP could result from severity related to bacteremia, which more frequently occurs in severe CAP (Brown & Lerner 1998).

Here we explored whether MR-proANP levels were associated with bacteremia in patients experiencing mild CAP.

Materials and methods

This was an ancillary analysis of a multicenter, prospective, observational study conducted in 12 French emergency departments (ED; Claessens et al. 2010).

Address for Correspondence: Yann-Erick Claessens, Department of Emergency Medicine, Hôpital Cochin, AP-HP, 27 rue du Faubourg Saint-Jacques, 75679 Paris Cedex 14, France. E-mail: yann-erick.claessens@cch.aphp.fr

(Received 18 May 2011; accepted 01 September 2011)

We evaluated data from mild CAP participants with available blood cultures and measurements of MR-proANP, PCT and CRP.

Methods and statistical analyses have been detailed in a parallel study dealing with pyelonephritis (Guinard-Barbier et al. 2011).

Briefly, we defined CAP as combination of temperature >38°C, acute respiratory symptoms (at least two of the following: fever, cough, sputum production, dyspnea, chest pain, altered breath sounds at auscultation), and new pulmonary infiltrates on chest X-ray. Patients with following conditions were excluded: antibiotic use for at least 3 days during the past month; pregnancy, human immunodeficiency virus infection, active neoplasm, immunosuppressive therapy, prednisone >15 mg/day; septic shock; palliative care; barriers to complete follow-up.

Baseline data consisted in demographic data, underlying disorders, signs and symptoms, usual clinical findings and laboratory tests. Patients were followed for 28 days and classified as outpatients or inpatients by an adjudication committee.

Each center proceeded to automated colorimetric detection of blood cultures. Bacteremia was defined by identification of a bacterial strain in blood culture within 36 h. Positive samples were stained for Gram coloration and subcultured for identification. All bacterial strains were considered pathogenic except *Staphyloccocus saprophyticus*.

Biomarkers measurements have been published elsewhere (Claessens et al. 2010). Blood samples were collected, centrifuged, and stored (–40°C) at a central laboratory until study completion. CRP measurement was performed using an immunoturbidimetric assay (Modular analyzer; Roche Diagnostics, Meylan, France). PCT and MR-proANP concentrations were determined using a sandwich immunoassay based on Time Resolved Amplified Cryptate Emission (TRACE) measurement (Kryptor analyzer; ThermoFischer, Hennigsdorf, Germany).

Results were described by either mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables and by number (percentages) for categorical variables. We applied χ^2 statistics or Fisher's exact tests for qualitative variables and Wilcoxon/Mann–Whitney test for continuous variables with skewed distributions to compare patient characteristics.

Results were analyzed according to the STAndards for the Reporting of Diagnostic Accuracy (STARD) recommendations (Bossuyt et al. 2003). We used area under receiver–operator characteristic curves (AUC) to assess the overall discriminatory power of biomarkers in predicting bacteremia. AUC (95% CI) was estimated for each biomarker and compared by a nonparametric method (Delong et al. 1988). Biomarkers accuracy to predict bacteremia was calculated for the total population.

All tests were two sided. p Values <0.05 were statistically significance. All statistical analyses were performed using SAS software V9.1 (SAS Institute, Cary, NC, USA).

Results

Study population

Among 781 patients included in the main study, 392 (50%) had available data for blood cultures and MR-proANP measurements (Figure 1). Median age was 55 (40–60) years, 221 (56.7%) were men and 75 (19.1%) had chronic heart failure (CHF).

Blood cultures were positive in 38 (9.7%) patients. *Streptococcus pneumoniae* was the main pathogen ($n=16$, 42.1%). Characteristics at presentation did not significantly depend on bacteremia. Most patients had mild CAP, as 77 (19.6%) accounted for PSI IV-V and 82 (20.9%) for CURB-65 ≥ 3. Bacteremia did not alter distribution among severity classes but was significantly associated with a decision of admission ($p<0.01$). All patients survived at 30 days.

MR-proANP measurements and results of blood cultures

MR-proANP levels were 92.8 pmol/l (IQR 76.2–165.4) in bacteremic patients and 84.3 pmol/l (IQR 54.5–130.4) in nonbacteremic patients, merely reaching statistical significance ($p=0.04$). PCT concentrations significantly increased in CAP patients with bacteremia (3.1 vs. 0.4 ng/l, $p<0.01$). This was not observed with CRP (200.9 vs. 135.1 mg/l, $p=0.08$; Table 1).

Accuracy of MR-proANP to predict bacteremia and comparison with PCT and CRP

MR-proANP poorly detected bacteremia (AUC 0.60 [95% CI 0.51–0.69]), preventing determination of accuracy thresholds. CRP did not differ from MR-proANP to detect bacteremia (AUC 0.59 [95% CI 0.46–0.71], $p=0.87$). Accuracy was better for PCT (AUC 0.69 [95% CI 0.59–0.80]) than MR-proANP and CRP ($p<0.001$).

MR-proANP in CAP patients according to the presence of chronic heart failure

Bacteremia was recorded in 7/75 patients with CHF and 31/317 without CHF. AUC of MR-proANP to detect CHF was 0.83 [95% CI 0.78–0.89]. In nonbacteremic patients, MR-proANP levels were more elevated in patients with CHF (167.5 vs. 74.5 pmol/l, $p<0.01$).

In patients without CHF, MR-proANP levels did not depend on bacteremia (87.1 vs 74.5 pmol/l, $p=0.05$; Table 1). Accuracy to detect bacteremia was poor for MR-proANP (AUC 0.61 [95% CI 0.51–0.71]) and CRP (AUC 0.62 [95% CI 0.49–0.75]). PCT better predicted bacteremia (AUC 0.69 [95% CI 0.58–0.80]). None of the biomarkers was significant in patients with CHF because of the sample size.

Discussion

In this study, MR-proANP accuracy for bacteremia was weak, comparable to CRP and worse than PCT, precluding its use at bedside for this purpose.

Bacterial load may contribute to severity of infectious diseases, and biomarkers can be surrogate for microorganism inoculums (van Langevelde et al. 2000, Lisboa et al. 2008). This hypothesis was suggested for PCT that associates to bacteremia (Müller et al. 2010, Guinard-Barbier et al. 2011). PCT levels increase with severity classes in CAP (Krüger et al. 2008) and, therefore, may reflect severity associated to bacteremia. However, performance of PCT to predict requirement of admission is too weak to be translated in daily practice (Huang et al. 2008, Claessens et al. 2010).

MR-proANP adds information about severity in septic patients as it accurately matches severity groups and better predicts mortality (AUC = 0.88 [95% CI 0.77–0.95]) than other parameters including PCT (Morgenthaler et al. 2005). In CAP patients, MR-proANP better correlated with severity than did other variables, such as PCT or CRP. MR-proANP increased with PSI and CURB-65 classes, detected complications (Prat et al. 2007), and predicted short- and long-term mortality (Masiá et al. 2007, Krüger et al. 2010). We observed that MR-proANP increased in CAP inpatients (87.3 vs. 40.5 pmol/l) and better predicted need for admission than did PCT and CRP [4]. In the CAPNETZ study (Krüger et al. 2010), a threshold at 139.7 pmol/l discriminated CAP at low and high risk (sensitivity 65.5%, specificity 73.7%). Therefore, MR-proANP possibly represents a valuable marker of severity and prognosis in CAP.

Impact of comorbidities is paramount to decide admission of CAP patients. Infection can impair renal and heart function and elevation of MR-proANP levels associated with acute heart failure (Maisel et al. 2010). Then increase of MR-proANP in CAP may result from unsteady underlying disorder, especially incipient CHF. Results

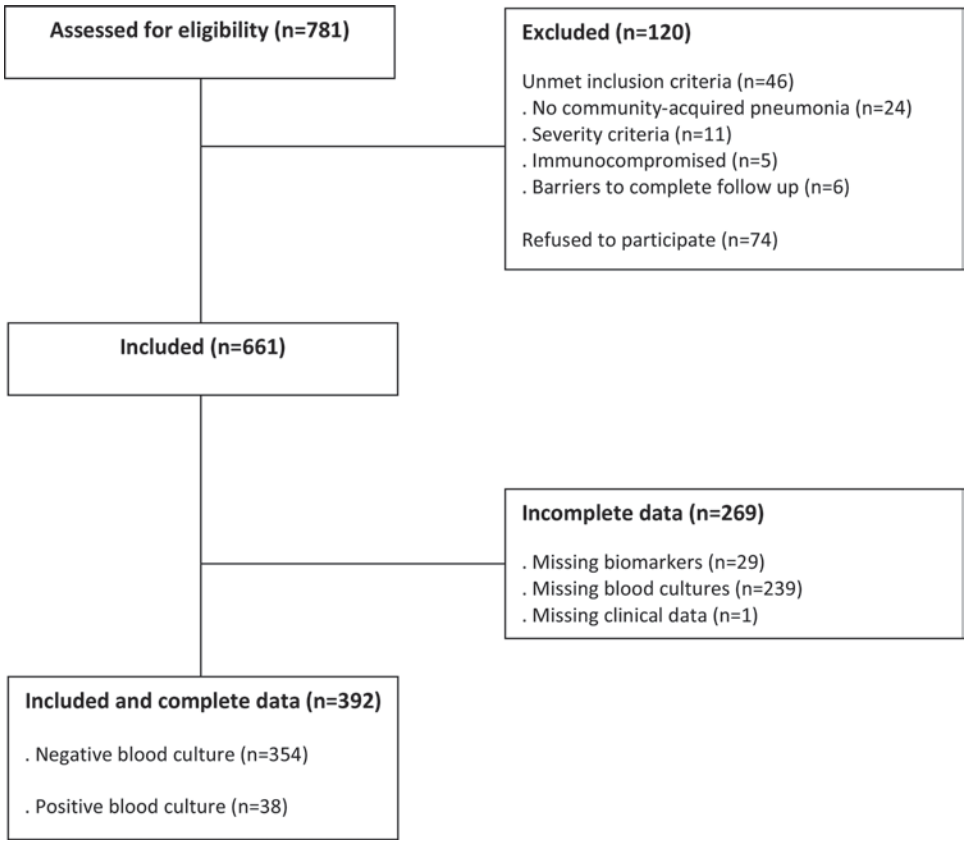

Figure 1. Chart flow of the study population of CAP patients with available blood culture.

Table 1. Concentrations of MR-proANP, PCT and CRP in CAP patients according to results of blood cultures and underlying chronic heart failure.

	Blood Cultures	MR-proANP (pmol/l)		PCT (ng/l)		CRP (mg/l)	
Total Population	Negative (N = 354)	84.3 (54.5–130.4)	p = 0.04	0.4 (0.1–1.8)	p < 0.01	135.1 (67–233.7)	p = 0.08
	Positive (N = 38)	92.8 (76.2–165.4)		3.1 (0.4–12.3)		200.9 (26.3–401.1)	
Without CHF	Negative (N = 286)	74.5 (50.5–109.0)	p = 0.05	0.3 (0.1–1.19)	p < 0.01	139.2 (67.0–237.3)	p = 0.03
	Positive (N = 31)	87.1 (65.9–146.3)		2.3 (0.4–13.3)		202.9 (69.0–414.4)	
With CHF	Negative (N = 68)	167.5 (1161–263.3)	p = 0.15	0.5 (0.2–1.7)	p = 0.07	114.9 (58.7–205.0)	p = 0.57
	Positive (N = 7)	217.6 (167.7–442.2)		5.8 (0.4–12.3)		26.3 (22.3–255.6)	
Total	(N = 392)	86.0 (55.5–140.1)		0.5 (0.1–2.3)		143 (65.4–243.3)	

Results are presented as median (IQR 25–75). p value below 0.05 was statistically significant.
CHF: chronic heart failure.

from the CAPNETZ study suggested that MR-proANP predicted severity of CAP independently to the presence of underlying CHF (Krüger et al. 2010). To note, we were unable to study influence of kidney function on MR-proANP levels as few patients experienced severe kidney failure.

LPS promotes *in vitro* secretion of MR-proANP in macrophages and induces a transient increase in MR-proANP in healthy volunteers (de Kruif et al. 2008). MR-proANP values increase in CAP patients with positive blood cultures (253 pmol/l vs. 130 pmol/l; Müller et al. 2006). These results suggest that changes in MR-proANP may be related to bacteremia in CAP patients. In our study, MR-proANP was higher in bacteremic patients, but differences were statistically low and its poor accuracy to predict bacteremia cannot be converted in clinical practice.

Prognosis signification of bacteremia has been questioned in CAP patients. Bacteremia more frequently occurs in severe CAP and has been associated to mortality (Brown & Lerner 1998). However, approximately half bacteremic CAP patients have mild disease, whereas it may associate with other severity criteria (Lisboa et al. 2009). Bacteremia does not alter clinical improvement, length of stay and mortality (Marrie et al. 2003, Bordón et al. 2008) that mainly depend on initial clinical presentation and underlying diseases (Bordón et al. 2008).

We observed that MR-proANP increases in mild CAP patients with bacteremia, but this elevation was poorly significant. MR-proANP was a prognosis marker for admission that obviously did not predominantly rely on bacteremia. Consequently, MR-proANP elevation in mild CAP could more depend on heart failure, systemic response and adverse events than bacteremia.

Limits

We acknowledge that our results should be interpreted with caution. This is a retrospective analysis of a prospective study. Population was not sized to specifically address association between markers and bacteremia. In addition, blood culture was not specifically requested for our study and was left at the discretion of the physician. Therefore, only half patients had blood culture. However, no differences were detected between patients who had blood cultures and those who did not. Patients enrolled were mainly mild CAP, and results could not be extrapolated to severely ill patients. Finally, we did not assess activity of neutral endopeptidase (NEP). This enzyme is responsible for MR-proADM cleavage, and its activity decreases in more severe infections (Maeshiro et al. 2008). However, more severe patients were excluded from the study population, precluding limited changes in NEP activity.

Conclusion

Here we observed that MR-proANP levels merely increased in bacteremic CAP patients and did not accurately predict bacteremia. This suggested that prognosis value of MR-proANP mainly depends on the host response to the pathogen and significant underlying disorders rather than bacteremia in CAP patients.

Acknowledgments

We are indebted to Prof. Jean-Marc Treluyer, Dr Raphaël Serreau, Mélanie Anoussamy, Cécile Klochendler, Sandra Colas and the staff of the Clinical Research Department (Unité de Recherche Clinique, URC) Cochin-Paris Centre for their valuable technical and logistical support. We would like to thank Dr Romain Lecomte and Brahms Inc. for providing the Kryptor and corresponding reagents to obtain high quality dosages of PCT and ANP. We thank Dr Ohanessian Ekindjian who supervised dosage of biomarkers. We acknowledge Prof. Patrick Gerbeaux, Dr Julien Charpentier and Dr David Boutoille who reviewed each patient's chart for the need of admission. This study was supported by the "Délégation Régionale de la Recherche Clinique," APHP, Paris, France.

BIS Study Group: Cochin (Paris, France): J.C Allo, C. Barbotin, J.C Boulard, Y.E Claessens (P.I), A. Dabreteau, G. Der Sahakian, S. Esain, A. Gayet, C. Ginsburg (P.I), I. Iraqi-Chentouf, J Kansao, F. Lecomte, I. Mazariegos, O. Meyniard, F. Perruche, S. Pineau, R. Ranerison, K. Takun, C. Vartanian, L. Zarnitsky; Pitié-Salpétrière (Paris, France): R. Achkar, K. An, A. Arhan, M. Bendahou, J.F Benezet, P. Bonnet, A. Dardalon, N Delot-ElFakhri, S. Delerm, P. Hausfater (P.I), M.O Josse, J.S Marx, B. Madonna-Py, P. Ray, B. Riou, K. Saighi, B. Wellner; Hôpital Caremeau (Nîmes, France): P.G Claret, J.E de la Coussaye, T. Duclos, J. Flechet, P. Fournier, A. Gache, F. Hernandez, C. Hilaire, F. Jourdan, G. Kayser, S. Louvard, O. Onde, O. Paul, I. Rajeebally, P. Richard, H. Robert (P.I), J. Rousset, E. Vernes, P. Wagner-Kerdranvat; Hôpital Gabriel Montpied (Clermont-Ferrand, France): C. Billault, S. Boizat, A. Bommelaer, J.L Buisson, C. Carrias, M. Entwhistle, E. Jehle, A. Lenat, J. Liotier, T. Mathevon (P.I), C. Perrier, D. Pic, C. Pourrat, C. Rougier, J. Schmidt, F. Vaysse; Hôtel-Dieu (Nantes, France): I. Arnaudet, N. Asseray-Madani, P. Auneau, E. Batard (P.I), J. Dary, S. DiBernardo, D. ElKouri, C. Ferron, I. Gueffet, J. Jenvrin, V. Kuczer, P. Leconte, E. Legeard, C. Longo, J. Lorber, G. Potel, M.D Touze, D. Trewick, F. Vignaud, D. Yatim-Lequeret; Hôtel-Dieu (Paris, France): M. Baud, M.L Catinois, D. Cantin-Bertaux, F. Dumas, T. Jactat, L. Kachout, G. Kierzek (P.I), E. Hinglais, G. LeGuerrroue, J.L Pourriat, F. Trarieux, C. Wertheimer; Hôpital Européen Geoges Pompidou (Paris, France): M. Aitkaci, M.C Ballester, M Bouyx, T.H Cao, A. Davido, A. Gounaropoulos, A. Levy, O. Limaiem-Joumni, R. Masmoudi, C. Moreau, P. Meraud, A. Patzak (P.I), M.P Playe, M.P Sadier, N. Smbach, A. Severin, C. Vidal; Hôpital Bicêtre (Kremlin-Bicête, France): C. Choquet, J. Depret-Vassal, T. Gudj, S. Sarnel; Hôpital Bichat-Claude Bernard (Paris, France): M. Aliouane, E. Casalino (P.I), M. Dimitroff, LB. Rimaud, P. Werner; Hôpital Jean-Verdier (Bondy, France): J. Benkel, B. Bernot, C. Chassaignon,

E. Debuc, G. Lenoir, D. Pateron (P.I), F. Pevirieri; Hôpital Lariboisière (Paris, France): C. Aparicio, J. Boni-Malka, J.P Courret, A. Debatisse, B. Galichon, S. Gallula, P. Gamand, S. Laribi, K. Mezaib, L. Pasgrimaud, F. Penit, P. Plaisance (P.I), F. Renai; Hôpital Louis Mourier (Colombes, France): A. Briere-Savard, P. Brun (P.I), B. Canderan, S. Hirsch, C. Lagarde, C. Leroy, F. Nikpay-Aslie, R. Sadat, F. Tessiere; Hôpital Sainte-Camille (Bry-sur-Marne, France): P. Collet, P. Hamlin, P. Lebrin, C. Loyer, G. Pinello, L.V.P Vong. Hôpital Beaujon (Clichy, France): P. Juvin, L. Lavagna-Perez (P.I).

We are indebted to Prof. Jean-Marc Treluyer, Dr Raphaël Serreau, Mélanie Anoussamy, Cécile Klochendler, Sandra Colas and the staff of the Clinical Research Department (Unité de Recherche Clinique, URC) Cochin-Paris Centre for their valuable technical and logistical support. We would like to thank Dr Romain Lecomte and Brahms Inc. for providing the Kryptor and corresponding reagents to obtain high quality dosages of PCT and ANP. We thank Dr Ohanessian Ekindjian who supervised dosage of biomarkers. We acknowledge Prof. Patrick Gerbeaux, Dr Julien Charpentier and Dr David Boutoille who reviewed each patient's chart for the need of admission. This study was supported by the "Délégation Régionale de la Recherche Clinique," APHP, Paris, France.

Declaration of interest

This study was supported by institutional grants by the French "Programme Hospitalier de Recherche Clinique," 2003. Brahms Inc. freely provided the Kryptor and corresponding reagents to obtain high quality dosages of PCT and MR-proANP.

References

Bordón J, Peyrani P, Brock GN, Blasi F, Rello J, File T, Ramirez J; CAPO Study Group. (2008). The presence of pneumococcal bacteremia does not influence clinical outcomes in patients with community-acquired pneumonia: results from the Community-Acquired Pneumonia Organization (CAPO) International Cohort study. *Chest* 133:618–624.

Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Lijmer JG, Moher D, Rennie D, de Vet HC; Standards for Reporting of Diagnostic Accuracy. (2003). Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD Initiative. *Ann Intern Med* 138:40–44.

Brown PD, Lerner SA. (1998). Community-acquired pneumonia. *Lancet* 352:1295–1302.

Claessens YE, Mathevon T, Kierzek G, Grabar S, Jegou D, Batard E, Loyer C, Davido A, Hausfater P, Robert H, Lavagna-Perez L, Bernot B, Plaisance P, Leroy C, Renaud B. (2010). Accuracy of C-reactive protein, procalcitonin, and mid-regional pro-atrial natriuretic peptide to guide site of care of community-acquired pneumonia. *Intensive Care Med* 36:799–809.

de Kruif MD, Lemaire LC, Giebelen IA, Struck J, Morgenthaler NG, Papassotiriou J, Elliott PJ, van der Poll T. (2008). The influence of corticosteroids on the release of novel biomarkers in human endotoxemia. *Intensive Care Med* 34:518–522.

DeLong ER, DeLong DM, Clarke-Pearson DL. (1988). Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics* 44:837–845.

Guinard-Barbier S, Grabar S, Chenevier-Gobeaux C, Quinquis L, Schmidt J, Kierzek G, Guérin S, Hausfater P, Bernot B, Brun P, Gayet A, Casalino E, Andreotti C, Renaud B, Claessens YE. (2011). Is mid-regional pro-atrial natriuretic peptide (MRproANP) an accurate marker of bacteremia in pyelonephritis? *Biomarkers* 16:355–363.

Huang DT, Weissfeld LA, Kellum JA, Yealy DM, Kong L, Martino M, Angus DC; GenIMS Investigators. (2008). Risk prediction with procalcitonin and clinical rules in community-acquired pneumonia. *Ann Emerg Med* 52:48–58.e2.

Krüger S, Ewig S, Kunde J, Hartmann O, Suttorp N, Welte T; CAPNETZ Study Group. (2010). Pro-atrial natriuretic peptide and pro-vasopressin for predicting short-term and long-term survival in community-acquired pneumonia: results from the German Competence Network CAPNETZ. *Thorax* 65:208–214.

Krüger S, Ewig S, Marre R, Papassotiriou J, Richter K, von Baum H, Suttorp N, Welte T; CAPNETZ Study Group. (2008). Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes. *Eur Respir J* 31:349–355.

Lisboa T, Blot S, Waterer GW, Canalis E, de Mendoza D, Rodriguez A, Rello J; Community-Acquired Pneumonia Intensive Care Units Study Investigators. (2009). Radiologic progression of pulmonary infiltrates predicts a worse prognosis in severe community-acquired pneumonia than bacteremia. *Chest* 135:165–172.

Lisboa T, Seligman R, Diaz E, Rodriguez A, Teixeira PJ, Rello J. (2008). C-reactive protein correlates with bacterial load and appropriate antibiotic therapy in suspected ventilator-associated pneumonia. *Crit Care Med* 36:166–171.

Maeshiro K, Takamori S, Mifune H, Matsuo T, Kimura NY, Honda J, Shirouzu K. (2008). Changes in A-type natriuretic peptide and its receptors induced by a neutral endopeptidase inhibitor in a rat model of sepsis. *Surg Today* 38:130–134.

Maisel A, Mueller C, Nowak R, Peacock WF, Landsberg JW, Ponikowski P, Mockel M, Hogan C, Wu AH, Richards M, Clopton P, Filippatos GS, Di Somma S, Anand I, Ng L, Daniels LB, Neath SX, Christenson R, Potocki M, McCord J, Terracciano G, Kremastinos D, Hartmann O, von Haehling S, Bergmann A, Morgenthaler NG, Anker SD. (2010). Mid-region pro-hormone markers for diagnosis and prognosis in acute dyspnea: results from the BACH (Biomarkers in Acute Heart Failure) trial. *J Am Coll Cardiol* 55:2062–2076.

Marrie TJ, Low DE, De Carolis E; Canadian Community-Acquired Pneumonia Investigators. (2003). A comparison of bacteremic pneumococcal pneumonia with nonbacteremic community-acquired pneumonia of any etiology–results from a Canadian multicentre study. *Can Respir J* 10:368–374.

Masiá M, Papassotiriou J, Morgenthaler NG, Hernández I, Shum C, Gutiérrez F. (2007). Midregional pro-A-type natriuretic peptide and carboxy-terminal provasopressin may predict prognosis in community-acquired pneumonia. *Clin Chem* 53:2193–2201.

Morgenthaler NG, Struck J, Christ-Crain M, Bergmann A, Müller B. (2005). Pro-atrial natriuretic peptide is a prognostic marker in sepsis, similar to the APACHE II score: an observational study. *Crit Care* 9:R37–R45.

Müller B, Süess E, Schuetz P, Müller C, Bingisser R, Bergmann A, Stolz D, Tamm M, Morgenthaler NG, Christ-Crain M. (2006). Circulating levels of pro-atrial natriuretic peptide in lower respiratory tract infections. *J Intern Med* 260:568–576.

Müller F, Christ-Crain M, Bregenzer T, Krause M, Zimmerli W, Mueller B, Schuetz P; ProHOSP Study Group. (2010). Procalcitonin levels predict bacteremia in patients with community-acquired pneumonia: a prospective cohort trial. *Chest* 138:121–129.

Prat C, Lacoma A, Dominguez J, Papassotiriou J, Morgenthaler NG, Andreo F, Tudela P, Ruiz-Manzano J, Ausina V. (2007). Midregional pro-atrial natriuretic peptide as a prognostic marker in pneumonia. *J Infect* 55:400–407.

van Langevelde P, Joop K, van Loon J, Frölich M, Groeneveld PH, Westendorp RG, van Dissel JT. (2000). Endotoxin, cytokines, and procalcitonin in febrile patients admitted to the hospital: identification of subjects at high risk of mortality. *Clin Infect Dis* 31:1343–1348.