Novel biomarkers in severe community-acquired pneumonia

Novos marcadores biológicos na pneumonia comunitária grave

Lígia Sarmet Cunha Farah Rabello[1], Melissa Tassano Pitrowsky[1], Márcio Soares[1], Pedro Póvoa[2,3], Jorge Ibrain Figueira Salluh[1]

1. D'Or Institute of Research and Education – IDOR – Rio de Janeiro (RJ), Brasil.
2. Polyvalent Intensive Care Unit, Hospital de São Francisco Xavier, Centro Hospitalar de Lisboa Ocidental CHLO – Lisboa, Portugal.
3. CEDOC, Faculty of Medical Sciences, New University of Lisboa – Lisboa, Portugal.

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Corresponding author:
Jorge Ibrain Figueira Salluh
Rua Diniz Cordeiro, 30 - Botafogo
Zip Code: 22281-100 - Rio de Janeiro (RJ), Brazil.
Phone: +55 (21) 2538-3541 / Fax: +55 (21) 2538-3555
E-mail: jorgesalluh@gmail.com

ABSTRACT

Community-acquired pneumonia (CAP) is the most common infectious disease requiring admission to intensive care units (ICUs), and achieving an early and precise diagnosis of CAP remains a challenge. Biomarkers play an important role in improving clinical judgment in the emergency room and are adjuvant in evaluating treatment responses. Novel biomarkers, such as cortisol, pro-adrenomedullin and endothelin-1, have been shown to be associated with disease severity and short-term outcomes. This review article focuses on the clinical use of novel biomarkers, severity prediction and treatment monitoring as well as future directions of the field.

Keywords: Biological makers; Pneumonia/drug therapy; Community-acquired infections/drug therapy; Community-acquired infections/prevention & control

INTRODUCTION

Community-acquired pneumonia (CAP) is the most common infectious disease requiring admission to intensive care units (ICU).[1] Mortality is elevated, and the hospital length of stay is long, especially in the elderly and those requiring advanced life support measures.[2] However, achieving an early and precise diagnosis of CAP remains a challenge. General scoring systems, such as the Pneumonia Severity Index (PSI)[3] and CURB-65 (Confusion, Blood Urea Nitrogen>19mg/dl, Respiratory Rate ≥30 breaths per minute, Systolic blood pressure < 90mmHg or Dyastolic blood pressure ≤ 60mmHg and Age ≥65 years)[4] are usually employed to predict prognosis in severe CAP, but their accuracy for predicting outcomes is questionable.[2,5] Thus, there is increasing interest in new risk factors and biomarkers that confer additional prognostic information.[6,7] The present review examines the role of novel biomarkers in the assessment of patient outcome and risk stratification in CAP.

New biomarkers predict outcome in severe CAP

Cortisol

The hypothalamic-pituitary-adrenal axis plays a major role in regulating a patient´s response to infection, and a strong association between elevated cortisol levels, illness severity and the risk of death has been demonstrated.[8]

In previously healthy subjects, cortisol plasma levels have had a direct correlation with acute disease severity. The high cortisol levels occur as a well-described physiologic response to stress that aims to restore homeostasis and counterbalance excessive inflammation.[9] Christ-Crain et al. studied a prospective cohort of 278 patients presenting to the emergency department with non-ICU CAP and found a good correlation between disease severity (as stratified by PSI class) and cortisol levels.[10] Interestingly, in this study, free cortisol was not a better predictor of hospital mortality compared with total plasmatic cortisol. Recently, Salluh et al. investigated patients with severe CAP requiring ICU admission, and the results showed that baseline cortisol levels were better outcome predictors than commonly employed scores, such as Acute Physiologic Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) and CURB-65 and other routine laboratory tests (e.g., C-reactive protein (CRP), leukocyte count and d-dimer).[11]

Although cortisol plasma levels are biologically plausible and easy, Critical Illness-Related Corticosteroid Insufficiency (CIRCI) was not shown to be a good predictor of mortality in patients with severe CAP.[11] Moreover, even if elevated cortisol levels are useful for predicting mortality in these patients, the administration of corticosteroids did not improve survival nor reverse shock in patients with septic shock.[12] Beale et al. analyzed the PROGRESS study database, a large cohort study of severe sepsis patients, and compared the baseline characteristics and clinical outcomes of patients treated with or without low-dose corticosteroids.[13] A total of 79.8% (7160/8968) of patients received vasopressors, and 34.0% of patients (3051/8968) received low-dose corticosteroids. Despite the absence of evidence for shock, 14.2% of patients received low-dose corticosteroids. Patients receiving low-dose corticosteroids spent longer in the ICU than patients who did not (median of 12 vs. 8 days, $p<0.001$) and had a greater overall hospital mortality rate (58% vs. 43%, $p<0.001$).[13] Considering these results, the use of low-dose corticosteroids in septic shock patients should not be routinely applied in this scenario. However, cortisol may be a useful biomarker for assessing risk in patients with severe CAP in the emergency room, where elevated cortisol levels (especially those above 26 mcg/dL) are associated with disease severity and a higher risk of death.[8]

Pro-adrenomedullin

Among novel biomarkers, adrenomedullin (ADM) is a peptide produced by multiple types of tissue during physiologic stress and has a pluripotent function, including vasoregulatory, antimicrobial and anti-inflammatory activity.[14] This biomarker looks promising, although its reliable measurement is challenging because it is rapidly cleared from circulation.[15] Midregional pro-ADM (MR pro-ADM) is a biomarker of interest because it is a more stable, easier to measure, stoichiometrically equivalent, midregion fragment of the parent precursor of ADM.[14] Two primary mechanisms have been postulated as being responsible for increasing circulating MR pro-ADM levels in infections. First, as a member of the calcitonin gene family, ADM is widely expressed and extensively synthesized during severe infections (translated into sepsis), similar to other calcitonin peptides, such as pro-calcitonin and calcitonin gene-related peptides.[16] Bacterial endotoxins and pro-inflammatory cytokines up-regulate ADM gene expression in many tissues, both *in vitro* and *in vivo*, in rodents and humans.[17,18] In addition, the decreased clearance by the kidneys may be partially responsible for the increased pro-ADM levels in infections.[19] This hypothesis has also been supported by the significant correlation between pro-ADM and creatinine levels in patients enrolled in a previous observational study.[15]

The same authors investigated the value of pro-ADM levels for severity assessment and outcome prediction in CAP. Pro-ADM levels, in contrast to CRP and leukocyte count, increased with increasing non-ICU CAP severity, classified according to PSI scores.[15] Subsequently, Huang et al. conducted a multicenter, prospective cohort study to describe the pattern of MR pro-ADM, confirm its prognostic role and compare its performance with PCT in patients with CAP.[14] MR pro-ADM levels at emergency department (ED) admission correlated with increasing illness severity and death, which confirmed the prognostic value of this biomarker. The MR pro-ADM and PCT values were generally concordant, and the 30-day mortality area under ROC curve (AUROC) for MR pro-ADM was higher than for procalcitonin (PCT) (0.76 vs. 0.65, respectively, $p<0,001$).[14] Schuetz et al. validated the usefulness of five pro-hormones for predicting serious complications in patients at ED admission with CAP and other low respiratory tract infection (LRTI) enrolled in the multicenter ProHOSP study.[20] The primary endpoint of this study was serious complications, defined as death from any cause, ICU admission, or disease-specific complications. Disease-specific complications were defined as local or systemic

complications from LRTI, including persistence or development of pneumonia, lung abscess, empyema or acute respiratory distress syndrome within 30 days after inclusion. The discriminatory power of biomarkers for predicting serious complications in CAP patients was only moderate, as assessed by AUROC, ranging from 0.66 for pro-ANP to 0.72 for pro-ADM and pro-ET1. However, the best biomarkers had a better performance, as shown by a higher AUROC than CURB-65 score (AUROC=0.66), PSI score (AUROC=0.69) and all of the individual covariates included in these scores. A combination of pro-ADM in a logistic regression model with either the CURB-65 or PSI scores for the prediction of serious complications yielded significant improvement in the predictive ability of pro-ADM ($p<0.001$).[20]

Recently, Albrich et al. proposed a practical algorithm combining the CURB-65 score with pro-ADM levels in patients with CAP and non-CAP-LRTI.[21] The new CURB-65-A risk score combining CURB-65 risks classes with pro-ADM cut-off values accurately predicted adverse events and mortality in patients with CAP and non-CAP-LRTI. Patients in the lowest CURB-65 groups and with pro-ADM levels less than 0.75 nmol/l were at a very low risk for both adverse events and mortality (CURB-65-A risk class I). Conversely, patients in the highest CURB-65 and pro-ADM groups (CURB-65-A risk class III) had a high risk for adverse events and mortality. Finally, patients in CURB-65 class 2 with pro-ADM levels less than 1.5 nmol/l or CURB classes 0-1 with pro-ADM levels between 0.75-1.5 nmol/l had intermediate risks (CURB-65-A risk class II).[21]

New studies should evaluate the performance of this biomarker in monitoring treatment responses and long-term outcome to clearly establish their role and usefulness in clinical practice.

D-Dimer and coagulation parameters

To date, several studies using natural anticoagulants to treat sepsis have shown conflicting results regarding mortality.[22] Although there is strong biological rationale for the use of anticoagulants in sepsis, better patient selection might be required, including a subgroup of more homogeneous septic patients.[22] First, a placebo-controlled PROWESS study analyzed the effect of drotrecogin alfa on 28-day mortality in patients with severe sepsis. When the study population was divided by infection site, the pulmonary infection subgroup showed a greater reduction in 28-day mortality (33,6% vs. 25%).[23] In the placebo-controlled OPTIMIST trial using tifacogin in severe sepsis, no improvement was found in overall mortality when comparing the two groups.[24] However, the subgroup analysis revealed a trend towards a benefit for patients with pro-calcitonin levels of 2 ng/ml or greater and those with high baseline markers for activated coagulation.[25] A retrospective subgroup analysis suggested that patients not receiving heparin and/or with microbiological evidence for pneumonia appeared to benefit from tifacogin.[24] Nonetheless, the recent CAPTIVATE trial did not show any survival benefits for this treatment; however, no biomarker-based stratification was applied.[26]

Several coagulation markers have been evaluated in severe CAP. One of the most studied, d-dimer, results from the fibrin breakdown after fibrinolytic system activation.[27] Circulating d-dimer levels can be easily measured, and elevated levels have been detected in patients with disseminated intravascular coagulation, severe sepsis, thromboembolic events, pregnancy, liver disease, surgery and trauma.[28] In patients without clinical or overt evidence of coagulopathy, high d-dimer levels may indicate microvascular thrombosis and therefore disease severity.[29] First, Shilon et al. assessed the value of a rapid quantitative d-dimer assay at admission as a marker of disease severity and prognosis in CAP patients.[30] A prospective observational study was conducted evaluating 68 CAP patients presenting to an ED. D-dimer levels were positively correlated with the APACHE II ($r=0.44$, $p=0.0002$), Pneumonia Patient Outcome Research Team (PORT) scores ($r=0.36$, $p=0.002$) and the length of hospital stay ($r=0.24$, $p=0.046$), which demonstrated that d-dimer is associated with disease severity and clinically relevant outcomes. The mean d-dimer levels of hospitalized patients were significantly higher than those of patients for whom hospitalization was not recommended (1.47 ± 1.05 μg/ml and 0.71 ± 0.79 μg/ml, respectively; $p=0.006$).[30]

Querol-Ribelles et al. examined the relationship between d-dimer levels and outcome in a prospective observational study with CAP patients.[26] In nonsurvivors, the mean d-dimer plasma level was 3.786 ng/ml, while in survivors, the mean level was 1.609 ng/ml ($p<0.0001$). A significant association was found between the presence of elevated d-dimer levels and PSI and APACHE II scores.[26] Milbrandt et al. observed in a recent large cohort study that coagulation abnormalities frequently occurred in patients with CAP

requiring hospitalization, and d-dimer levels were again correlated with disease severity and survival.[31]

Recently, Salluh et al. prospectively evaluated the frequency of early coagulation abnormalities and their impact on outcome in 90 patients with severe CAP requiring ICU admission.[32] The baseline d-dimer levels were significantly higher in non-survivors than in survivors. In addition, d-dimer levels at ICU admission were good predictors of outcome compared with the usually employed severity scores (APACHE II and SOFA) and performed better than laboratory markers for CRP. Interestingly, the addition of d-dimer increased the predictive ability of traditionally employed scoring systems, such APACHE II and SOFA.[32]

Although several studies have been conducted, it is not entirely clear how coagulation markers should be incorporated into daily clinical care. However, the evaluation of coagulation markers as risk stratification tools or clinical trial entry criteria is promising.

Endothelin-1

Endothelin-1 (ET-1) is a potent vasoconstrictor agent primarily synthesized by endothelial cells. In humans, elevated plasma levels of mature ET-1 are found during systemic infections, and increased plasma ET-1 levels correlate with mortality risk. The mature form of ET-1 is unstable at room temperature and rapidly cleared from circulation, limiting its ability to be evaluated in clinical conditions. Nonetheless, precursor peptides can be detected for hours in circulation; thus, these peptides can be used to indirectly measure the release of mature ET-1 in physiological and pathological conditions.[33] Schuetz et al. assessed the diagnostic and prognostic value of pro-ET-1 in a prospective cohort of septic CAP patients.[33] In these patients, circulating ET-1 precursor peptide levels had a good correlation with the severity of CAP, as assessed by PSI and CURB-65 scores. Pro-ET-1 levels decrease during recovery of illness and may help predict the occurrence of bacteremia in CAP patients. Pro-ET-1 levels at admission were independent predictors of short-term mortality and the need for ICU admission, with a moderate but superior prognostic accuracy compared with the commonly measured laboratory parameters. The discriminatory ability of pro-ET1 to predict death and ICU admission (AUROC=0.64 [95% CI 0.53-0.74] and AUROC=0.69 [95% CI 0.61-0.77]) was significantly better than CRP (AUROC=0.51 [95% CI 0.41-0.61] and AUROC=0.58 [95% CI 0.51-0.66]) and leukocyte count (AUROC=0.55 [95% CI 0.44-0.65] and AUROC=0.57 [95% CI 0.49-0.65]) and tended to be better than PCT (AUROC=0.59 [95% CI 0.51-0.67] and AUROC=0.65 [95% CI 0.57-0.72]). Importantly, pro-ET-1 levels can improve the prognostic accuracy CURB-65 scores in predicting adverse outcomes.[33] Nevertheless, one must consider that the predictive ability was only modest (AUROC <0.7) in this study, precluding its incorporation into current risk assessment models.

Pro-ANP and CT pro-AVP

Natriuretic peptides, such as atrial natriuretic peptide (ANP), play an important pathophysiological role in cardiovascular disease.[34] Increased concentrations of ANP or ANP pro-hormone fragment have been reported to indicate cardiovascular dysfunction in septic patients.[35-37] A prospective observational study of 545 patients with LRTI and 50 healthy controls investigated pro-ANP levels at an emergency department to evaluate its prognostic use for the disease severity and outcome. MR pro-ANP gradually increased with increasing CAP severity, classified according to PSI score (p<0.001). MR pro-ANP was comparable to PSI (AUROC=0.69 vs. 0.74, p=0,31) in predicting the survival of CAP patients and better than other biomarkers, such as PCT (AUROC=0.57, p=0,008), CRP (AUROC=0.52, p=0.02) and leukocyte count (AUROC=0.56, p=0.07).[38] However, in severe sepsis or septic shock, the natriuretic peptide clearance pathway, called neutral endopeptidase (NEP 24.11), is altered. In a prospective observational study, NEP 24.11 activity was lower in septic shock than in severe sepsis (0.10 ±0.06 nmole/ml/min vs. 0.50±0.22 nmole/ml/min, p<0.0001).[39] The role of ANP in clinical practice should continue to be investigated.

Arginine-vasopressin (AVP), a hormone released from the posterior pituitary gland, has vasoconstrictor and antidiuretic properties and the potential to restore vascular tone in vasodilatory hypotension.[40] Arginine-vasopressin is derived from a larger precursor (pro-AVP) with 2 other peptides of unknown function, neurophysin II and copeptin, the carboxy-terminal component of the precursor.[41]

Kruger et al. investigated the prognostic value of ANP and AVP compared with CRP, PCT and CRB-65 scores in a well-defined cohort of 589 CAP patients.[42] MR pro-ANP and CT pro-AVP levels increased with increasing CAP severity, classified according to CRB-65 score (p<0.0001). The AUROC used to predict the need for hospitalizing CAP patients was 0.80 for

MR pro-ANP (95% CI 0.76-0.83) and 0.80 for CT pro-AVP (95% CI 0.77-0.84), demonstrating good discriminatory power. The AUROC was 0.74 for CRB-65 (95% CI 0.70-0.77) and 0.70 CRP (95% CI 0.66-0.73), significantly lower than for MR pro-ANP and CT pro-AVP. In multivariable Cox proportional-hazards regression analyses, serum MR pro-ANP and CT pro-AVP levels greater than 116 pmol/l and 28.8 pmol/l, respectively, were the strongest predictors of CAP-related mortality within 28 days, independent of the presence of congestive heart failure, other coexisting illnesses or a CURB-65 score >1.[42] Additionally, when long-term outcomes were evaluated, MR pro-AN and, CT pro-AVP serum levels were good predictors of both 28-day and 180-day mortality from pneumonia, and they were significantly better predictors of 28-day mortality and especially 180-day mortality than CURB-65 scores and PCT, CRP and white blood cells (WBC). MR pro-ANP and CT pro-AVP might become useful additional prognostic markers for long-term CAP assessment and the decision of allocating patients presenting at the emergency department by clearly defining patients in need of intensive care.[42]

Another recent study , Claessens et al.[43] investigated the role of biomarkers in the ED to identify higher risk CAP patients who would likely benefit from in-hospital treatment. In this study, PCT, CRP and ANP were prospectively measured in 12 French hospitals. A total of 549 subjects were evaluated at the ED. ANP performed better at predicting admission than PCT and CRP (AUROC=0.76 [95% CI 0.72 – 0.80], 0.65 [95% CI 0.61 – 0.70] and 0.59 [95% CI 0.54 – 0.64], respectively). A threshold of 135 pmol/L for ANP was found distinguish those in need of hospital admission (positive likelihood ratio of 7.45 [95% CI 4.22-8.16]).[43]

Biomarker roles in evaluating clinical response and the future of biomarkers in severe CAP

Another potential biomarker to assess treatment response is Endothelin-1. Schuetz et al. investigated precursor peptides of endothelin-1 (pro-ET1) at admission and follow-up days 3, 5 and 7 in a prospective cohort of 925 CAP patients. Both admission pro-ET1 levels and relative changes between baseline and day 3 provided significant prognostic information concerning mortality and the need for ICU admission and improved the PSI score classification, while additional pro-ET1 measurements at days 5 and 7 did not add any further prognostic information.[44]

Considering the future use of biomarkers in severe CAP, we believe that theragnostic is a useful concept. Theragnostic is a treatment strategy for individual patients that associates both a diagnostic test that identifies patients most likely to be helped or harmed by a new medication and targets drug therapy based on the test results.[45] Theragnostics has three principal applications:

- Identify the subgroups of patients presenting a profile likely to have a positive response to a given treatment: targeted therapies
- Identify the subgroups of patients at risk of aggravated side effects during treatment: pharmacogenomics
- Monitor the treatment response

Genomics-based knowledge promises to approach each patient as a unique biological individual, thereby completely changing our paradigms and improving efficacy.[45]

Molecular theragnostic tests for infectious diseases are an emerging concept in which molecular biology tools are used to provide rapid, accurate, and more informative diagnostic microbiology assays, thus enabling better therapeutic interventions.[45] As an interesting example, a number of different molecular methods for the rapid detection of methicilin-resistant *Staphylococcus aureus* (MRSA) have recently been described as the *Infection Diagnostic Inc-MRSA* test,[46] IDI-MRSA[47] and polymerase chain reaction.[48] The last test has been demonstrated to be feasible in routine clinical practice and provide quicker results than culture-based screening, leading to a better management of both colonized and infected patients and significantly reducing subsequent MRSA transmission.[49]

Gene expression profiles in patients whose systemic inflammatory response syndrome arose from infection, subsequently leading to sepsis, have been compared with those whose systemic inflammatory response syndrome was due to other causes. In the Affymetrix microarray, the upregulation or downregulation of several hundred genes distinguished between patients whose inflammatory condition was caused by infection and those whose respiratory syndrome was non-infective in origin.[50] However, the clinical validation of this concept is still pending.

Genome-wide transcriptional studies have recently emerged as a powerful investigational tool to study complex disease. Tang et al. performed a systematic review of the genomic data of recent microarray studies in which the transcriptional changes of circulating leukocytes were examined in both experimental and

clinical sepsis in humans. Neither a distinctive pro-/anti-inflammatory phase nor a clear transition from a pro-inflammatory to anti-inflammatory phase could be observed during sepsis.[51]

Genetic factors related to cytokine expression may also influence outcome.[50] IL-10 is an important anti-inflammatory cytokine that plays a key role in sepsis and particularly, modulating the pulmonary inflammatory response. The A allele of an IL-10 – 1082 A/G promoter region single-nucleotide polymorphism (SNP) is associated with decreased IL-10 production by peripheral blood mononuclear cells. Wattanathum et al. performed a genetic association study to test the hypothesis that haplotypes of the IL-10 gene are associated with clinical outcome in critically ill patients with pneumonia but not in patients with extrapulmonary sepsis. Of the 550 white patients with sepsis, 158 had pneumonia as the principal cause of their sepsis, and 392 had an extrapulmonary source of sepsis. Patients with pneumonia who carried one or two copies of the CGG haplotype had greater 28-day mortality (51,4%) than patients not carrying this haplotype (29,1%, p=0,007). CGG carriers had significantly more cardiovascular, renal, hepatic and hematologic dysfunction (p<0,005 in each case). Therefore, polymorphisms within the IL-10 gene may be predictors of outcome in patients with sepsis from pneumonia.[52] However, translating this knowledge into medical interventions that may improve outcome remains a considerable challenge.

A recent example of this translation was a controlled biomarker- and immunostimulatory-guided therapy in sepsis. Meisel et al. tested whether granulocyte-macrophage colony-stimulating factor (GM-CSF) reversed monocyte deactivation, a hallmark of sepsis-associated immunosuppression (primary endpoint), and improved the immunological and clinical course of sepsis patients. GM-CSF is a safe and effective measure to restore mHLA-DR expression and cytokine release in patients with sepsis and sepsis-associated immunosuppression. Furthermore, GM-CSF shortened the duration of mechanical ventilation, in-hospital stay and ICU stay.[53]

CONCLUSIONS

Coagulation parameters and other new biomarkers, such as pro-ANP and endothelin, are promising but still require consistent results to be fully incorporated into clinical practice in the decision-making process for severe CAP patients.

Theragnostics is a promising option for an individually based approach to disease staging and treatment. This may result in the ability to prescribe antimicrobials and immunomodulatory agents based on genetic profiles and protein expression as well as immune response patterns and cytokines.

RESUMO

A pneumonia adquirida na comunidade é a doença infecciosa que mais comumente exige internação em unidades de terapia intensiva e o diagnóstico precoce e preciso da pneumonia adquirida na comunidade ainda é um desafio. Os biomarcadores desempenham um importante papel auxiliando no julgamento clínico no Serviço de Emergência e são adjuvantes na avaliação da resposta terapêutica. Novos biomarcadores como cortisol, proadrenomedulina e endotelina-1 demonstraram estar associados a gravidade da doença e a evolução em curto prazo. Este artigo de revisão irá se basear no uso clínico de novos biomarcadores, na sua capacidade de predizer gravidade e de monitorar a resposta ao tratamento empregado.

Descritores: Marcadores biológicos; Pneumonia/quimioterapia; Infecções comunitárias adquiridas/antibioticoterapia; Infecções comunitárias adquiridas/prevenção & controle

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