Blood biomarkers for personalized treatment and patient management decisions in community-acquired pneumonia

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Purpose of review
In patients with community-acquired pneumonia (CAP), blood biomarkers can help to substantially improve individual decisions involving initiation, (de-)intensification, and cessation of antibiotics, and initial risk stratification, site-of-care assignment (outpatient versus ward versus ICU), and discharge. To illustrate these processes, this review summarizes recent findings from trials investigating the use of two hormokines, procalcitonin (PCT) or proadrenomedullin (ProADM), in personalized treatment and management decisions in CAP patients.

Recent findings
Many biomarkers from distinct pathophysiological pathways have been evaluated in observational studies. However, only few analytes have been tested for efficacy and safety in numerous, large observational studies or in prospective, randomized, interventional trials. Among the latter, PCT has been demonstrated to be well tolerated and highly effective for monitoring and de-escalating antibiotic therapy. ProADM has shown higher accuracy for short-term and long-term adverse outcome prediction and improves prognostic accuracy when combined with current clinical risk scores, that is, Pneumonia Severity Index, the CURB65 (confusion, uremia, respiratory rate, blood pressure, age at least 65 years) score, and Risk of Early Admission to ICU, compared to applying the respective score alone. ProADM use has – in a pilot interventional study – improved site-of-care decisions and tended to shorten length hospitalization.

Summary
Inclusion of biomarker data in clinical algorithms improves individual decision-making in CAP patients. Interventional trials should be conducted to determine these markers' ultimate utility in patient management.

Keywords
antibiotic stewardship, biomarker, community-acquired pneumonia, proadrenomedullin, procalcitonin

INTRODUCTION

In patients with community-acquired pneumonia (CAP), morbidity, mortality, and treatment-related toxicity and costs remain substantial, and have changed little over recent years. In an effort to improve outcomes, current CAP and sepsis management guidelines emphasize an early start of fluid resuscitation and appropriate antimicrobial therapy [1▪,2]. These recommendations are based on convincing evidence that such interventions improve outcomes in CAP patients with hypotension in the emergency department (ED) [3,4]. There is further evidence from a trial including septic shock patients treated with an early resuscitation protocol in the ED that found no mortality increase per hour delay in antibiotic administration after triage, yet significantly higher mortality with a delay in antibiotics until after shock recognition. This finding again demonstrates the importance of rapid recognition of severe bacterial infections and prompt initiation in such cases of therapeutic regimens, like antibiotics [5]. Unfortunately, in real-life practice, such recognition remains challenging, and clinical parameters like the systemic inflammatory response syndrome criteria lack specificity for sepsis etiology and prognosis [6]. Additionally, current

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KEY POINTS

- PCT has been shown in numerous interventional studies to identify and reflect severity of systemic bacterial infection and to safely and effectively guide individualized decisions about initiation and duration of antimicrobial therapy in patients with CAP.
- In patients with respiratory infections, use of PCT protocols has resulted in significantly lower antibiotic exposures without increases in mortality or any adverse patient outcomes.
- Prognostic biomarkers, such as ProADM, have high accuracy to predict short-term and long-term outcomes of patients with CAP and, thus, improve initial risk assessment.
- In the same setting, on the basis of data from multiple observational studies and one pilot interventional trial, ProADM combined with clinical assessment may increase accuracy of risk stratification and improve site-of-care decisions relative to using clinical scoring systems alone.

microbiological diagnostics have low sensitivity and important delays in providing needed information. Specific blood biomarkers for bacterial infections, therefore, may be interesting tools to improve early recognition of severe systemic infection and help guide therapeutic decisions in individual patients.

Current CAP guidelines also recommend using objective measures for outcome prediction, such as the Pneumonia Severity Index (PSI) or the CURB65 (confusion, uremia, respiratory rate, blood pressure, age at least 65 years) score, to improve site-of-care and early discharge decisions [1▪]. Carefully selecting patients for inpatient or outpatient care is important, because hospitalization for CAP increases treatment costs eight-fold to 20-fold [7,8] and carries a higher risk of nosocomial complications such as hospital-acquired disability and infections including *Clostridium difficile*-associated diarrhea [9]. Additionally, many patients prefer outpatient treatment [10]. Yet physician and patient concerns regarding adverse disease course are major obstacles to such care [11]. Consequently, even when there is high-intensity implementation of the PSI, only half of patients in low-medical risk groups as determined by that scoring system are treated as outpatients [12,13]. Hesitancy to follow recommendations based on CAP risk scores may partly be because of the static nature of such scores during follow-up, the considerable variability in outcome within a given risk category, and poor memorizability [14]. Innovative management bundles incorporating accurate prognostic biomarkers and thorough clinical and nursing assessment have great potential to address these issues and so reduce the hospitalization rate and length stay, particularly in low-risk patients [15,16]. In the last years, different prognostic biomarkers have been put forward in observational studies as having the ability to improve site-of-care decisions, and thus patient management. Yet, few of these analytes have had their efficacy and safety evaluated in prospective, randomized controlled interventional trials, the crucial step before biomarkers should be used in clinical practice, much less evaluated in multiple observational studies.

Procalcitonin (PCT) and proadrenomedullin (ProADM) are recently introduced blood biomarkers that respectively may address the diagnostic and prognostic needs described above. They exemplify a class of circulating substances referred to as 'hormokines,' as they normally follow hormonal behavior, that is, expression in neuroendocrine cells and systemic action, but in response to inflammation or other physiological stress follow cytokine behavior, that is, expression in numerous cell types throughout the body and local action [17]. PCT and ProADM also represent biomarkers that can be incorporated into the emerging and increasingly important personalized medicine paradigm [18]. Appreciating the ancient wisdom of *primum nil nocere*, personalized medicine is the concept that owing to potential toxic (side) effects, nosocomial complications, resource constraints, for example limited hospital beds, and potential public health concerns, for example development of antibiotic resistance, interventions should be limited to the patients most likely to truly need them.

The current review uses the examples of PCT and ProADM to illustrate how blood biomarkers can be applied to help identify such patients and individualize treatment and patient management decisions. We summarize recent findings of studies with a particular emphasis on randomized controlled trials (RCTs) investigating the potential of these analytes in personalized medicine in CAP patients. We first focus on PCT, a marker that improves identification of systemic bacterial infection and that provides guidance for therapeutic decisions about initiation, (de-)intensification, and duration of antimicrobial therapy. Second, we discuss ProADM, a prognostic marker that has been shown in numerous observational studies to improve mortality and other adverse outcome prediction and – in a pilot interventional study – improved site-of-care and early hospital discharge decisions in CAP patients.

INDIVIDUALIZED ANTIBIOTIC THERAPY DECISIONS WITH PROCALCITONIN-BASED ALGORITHMS

Effective antibiotic therapy is the cornerstone of therapy and is highly effective for reducing mortality and morbidity in CAP [19]. Still, overexposure to antibiotics, mainly through long treatment durations and application in nonpneumonic or viral respiratory infections, subjects individual patients to the risk of adverse drug reactions without any corresponding therapeutic benefit, and increases the likelihood of development of bacterial resistance [20,21]. Traditional signs and symptoms have low sensitivity and specificity to differentiate self-limited and mild viral infections from more severe bacterial disease. For this reason, physicians are reluctant to abstain from or limit the duration of antibiotic therapy based on clinical grounds only. Blood biomarkers that accurately can indicate the risk for bacterial infection and can be measured within 2 h of a patient's admission can help to fill this gap. PCT in particular has been studied in various settings and its advantages and limitations are well known [22]. This biomarker is upregulated in response to microbial toxins and certain bacterial specific proinflammatory mediators (e.g., interleukin-1b, tumor necrosis factor-α, and interleukin-6), and is downregulated as these substances decrease in the circulation during recovery. Conversely, PCT expression is attenuated by the cytokines typically released in response to a viral infection (e.g., interferon-γ). Therefore, by flagging the presence and tracking the status of systemic bacterial infection, PCT measurements are helpful in determining the necessity and optimal duration of antibiotic therapy [23–27].

The efficacy and safety of PCT-guided decision-making regarding antibiotics has been demonstrated in 14 RCTs in different clinical settings and including infections of varying severity [28,29]. The PCT protocols used were all somewhat similar and relied on the same intuitive concept. Recommendation for or against initiation or discontinuation of antibiotic therapy was based on initial PCT levels, the kinetics of PCT over time, or both [28]. Different PCT cut-offs triggered stronger or weaker recommendations for or against antibiotic therapy (Fig. 1). The cut-offs differed depending on the clinical setting and the patients' acuity. In low-acuity settings (primary care) or lower-acuity patients (e.g., bronchitis), PCT was used, generally in the form of an initial measurement only, mainly to assist in the decision whether or not to prescribe antibiotics (Fig. 1a). Follow-up PCT measurements were only recommended in patients with nonresolving or worsening infection within 1–2 days. In moderate-severity settings (i.e., CAP in the ED), PCT can be used to determine the likelihood of bacterial respiratory infection, and thus the need for antibiotics, as well as for monitoring the course, and the response to antibiotics, of such infection (Fig. 1b). PCT should be measured every 2–3 days, and antibiotics stopped once the patient shows clinical improvement and a drop of PCT into normal values (i.e., less than 0.25 μg/l). Importantly, the algorithm can be 'over-ruled' in patients at high risk for adverse outcome (i.e., high PSI class or immunosuppression). In the highest-acuity settings (i.e., ICU patients with sepsis from CAP), PCT should be used not to determine whether antibiotics should be initiated but, rather, when to discontinue them earlier (Fig. 1c).

The algorithms described above have been tested in different interventional trials, all of which documented significantly reduced antibiotic exposure. More importantly, in none of the trials was there an excess mortality or adverse events rate in patients treated with PCT-guided protocols. These observations were also confirmed in a recent meta-analysis including all patients with respiratory infections from published trials [30▪▪]. In low-acuity patients, PCT guidance resulted in a relative lowering of prescription rates by 69% (from 48 to 15%) in patients with upper respiratory infections and by 64% (from 66 to 24%) in those with bronchitis. In higher-acuity patients, PCT guidance resulted in a relative reduction in the duration of antibiotics by 37% in CAP (from 11.1 to 7.0 days, a 4.1-day absolute decrease) and by 21% in ventilator-associated pneumonia (from 14.6 to 12.2 days, a 2.4-day absolute decrease).

Still, adherence rates to the PCT protocol were variable, particularly for ICU trials [31,32]. With respect to the ICU setting, remaining uncertainty about safety raised by relatively large confidence intervals in adverse outcome rates calls for additional validation studies.

Apart from these randomized trials, the literature contains several reports of PCT use 'in real life', that is, outside of study conditions. First, the results of an observational quality control survey [33] in a former site in a multicenter antibiotic stewardship trial confirmed similar antibiotic exposure rates after the study as compared to rates observed within the RCT [12]. Similarly, the 'Procalcitonin in Real Life conditions' (ProREAL) survey [34▪▪] investigated the effects of PCT use in 1759 patients with lower respiratory infections from 14 centers in Switzerland, France, and the United States. ProREAL found an overall PCT algorithm compliance rate of 68%, with differences based on diagnoses, outpatient versus inpatient status,

A. Low risk or acuity: non-pneumonic respiratory infections				
Evaluation on admission				
PCT threshold	**<0.1**µg/l	**<0.25**µg/l	≥**0.25**µg/l	**>0.5**µg/l
Recommendation on antibiotics	Strongly discouraged	Discouraged	Encouraged	Strongly encouraged
Over-ruling the algorithm	Consider antibiotics if patient are clinically unstable, have strong evidence for pneumonia, are high risk (PSI classes IV–V), need hospitalization			
Follow-up/other comments	Follow-up only needed if no symptom resolution after 1–2 days or clinical situation not improving; Consider antibiotics if PCT increases to ≥**0.25**µg/l		Clinical re-evaluation as appropriate	
B. Moderate risk or acuity: pneumonic infections in the emergency department and inpatients				
Evaluation on admission				
PCT threshold	**<0.1**µg/l	**<0.25**µg/l	≥**0.25**µg/l	**>0.5**µg/l
Recommendation on antibiotics	Strongly discouraged	Discouraged	Encouraged	Strongly encouraged
Over-ruling the algorithm	Consider alternative diagnosis; consider antibiotics if patient are clinically unstable or at high risk for adverse outcome (e.g., PSI classes IV–V) or have strong evidence for bacterial pathogen			
Follow-up/other comments	Reassess patient and re-check PCT after 6–24h if no clinical improvement		Re-check PCT every 2–3 days to consider early stop of antibiotic therapy	
During antibiotic therapy follow-up evaluation every 1–2 days				
PCT threshold	**<0.1**µg/l	**<0.25**µg/l	≥**0.25**µg/l	**>0.5**µg/l
Recommendation on antibiotics	Stop strongly encouraged	Stop encouraged	Stop discouraged	Stop strongly encouraged
Over-ruling the algorithm	Consider continuing antibiotics if patient clinically not stable			
Follow-up/other comments	Clinical re-evaluation as appropriate		Consider treatment failure if PCT does not decrease adequately	
C. High risk or acuity: sepsis in need of intensive care unit admission				
Evaluation on admission				
PCT threshold	**<0.25**µg/l	**<0.5**µg/l	≥**0.5**µg/l	**>1.0**µg/l
Recommendation on antibiotics	Empirical antibiotics strongly recommended in all patients			
Follow-up/other comments	Consider alternative diagnosis; reassess patient ad re-check PCT every 2 days		Reassess patient and re-check PCT every 2 days to consider discharge and early stop of antibiotic therapy	
During antibiotic therapy follow-up evaluation every 1–2 days				
PCT threshold or change	**<0.25**µg/l or **>90% drop**	**<0.5**µg/l **or >80% drop**	≥**0.5**µg/l	**>1.0**µg/l
Recommendation on antibiotics	Stop strongly encouraged	Stop encouraged	Stop discouraged	Stop strongly discouraged
Over-ruling the algorithm	Consider continuation of antibiotics if patient clinically not stable			
Follow-up/other comments	Clinical re-evaluation as appropriate		Consider treatment failure if PCT does not decrease adequately	

FIGURE 1. Procalcitonin for guidance of antibiotic therapy in different clinical settings (adapted from [28]). PCT, procalcitonin; PSI, Pneumonia Severity Index.

experience with the algorithm, and the country. Multivariate adjustment showed antibiotic therapy duration to be significantly shorter if the PCT algorithm was followed versus over-ruled. Importantly, no increase was noted in the risk of the combined adverse outcome endpoint within 30 days of follow-up when the PCT algorithm was followed regarding withholding antibiotics on hospital admission or regarding early cessation of antibiotics, validating earlier results from randomized trials.

PROADRENOMEDULLIN: MORTALITY MARKER AND SITE-OF-CARE DECISION AID?

For the successful and cost-efficient management of CAP, disease severity assessment, outcome prediction, and a well-reasoned site-of-care decision are essential. In an attempt to optimize the appropriateness of admission and to lower rates of unnecessary hospitalization, several international organizations have developed prediction rules and

adopted guidelines to stratify CAP patients based on mortality risk [7,35]. The PSI is a well-validated scoring system from North America that assesses death risk in a two-step algorithm [36]. However, PSI complexity is high and, mainly depending on age as a mortality predictor, it has important drawbacks for routine care. The CURB65 score, a simplified assessment tool developed by the British Thoracic Society, is based on only five predictors [37,38]. Compared to the PSI, CURB65 is easier to calculate, but slightly less prognostically accurate. Both scores were originally validated for 30-day mortality prediction only, lack information on the inflammatory response, and have intraobserver variability of about 10%. Their value in estimating the risks of adverse outcomes other than mortality, that is, CAP complications or need for mechanical ventilation, vasopressors, or ICU admission remains unclear.

Therefore, novel biomarkers as easily measurable, quantitative, objective, and dynamic tools [39–49] are of great interest to improve the accuracy of clinical severity scores and of risk assessment. One promising prognostic marker is ProADM, the mid-regional fragment of the adrenomedullin prohormone. Derived from the endothelium, adrenomedullin is one of the most potent vasodilators, and also possesses immune-modulating, metabolic, and bactericidal properties [50,51]. Adrenomedullin secretion seems to be nonspecifically upregulated by various forms of physiological stress and severe disease [52–56]. However, it is technically challenging to measure mature adrenomedullin, indeed, almost impossible to do so reliably, because this very bioactive peptide is rapidly cleared from the circulation. Because ProADM is apparently biologically inactive, and hence far more stable than adrenomedullin, ProADM is a good surrogate marker for adrenomedullin.

Initial ProADM studies included ICU patients with sepsis wherein CAP was the main focus of infection [57]. In these patients, ProADM concentration increased in tandem with sepsis severity and had a high ability to discriminate survivors from nonsurvivors.

A second prospective study from the same investigators focused on ProADM in CAP patients from the ED [58]. Here ProADM proved to be a useful marker for risk stratification and sensitive in predicting both mortality risk and transfer to the ICU.

Since then, numerous observational cohort studies from a variety of countries have used largely similar protocols to investigate the potential of ProADM for risk stratification of CAP patients, most of whom were hospitalized or presented in the ED (Table 1) [53,59,60▪▪,61–66]. These studies have varied in their duration of follow-up, examining outcomes over times ranging from the hospital stay to 18 months from admission. All have compared ProADM versus one or more of PSI, CURB65 (or its CRB65 variant that excludes urea measurement), or the Risk of Early Admission to ICU (REA-ICU) score, and also compared combining the biomarker with the score versus using the score alone. Additionally, many of the studies have compared ProADM versus other biomarkers such as PCT or C-reactive protein.

Ability to discriminate patients with versus without the given adverse outcome has been measured using the area under the receiver operating characteristics curve (AUC of the ROC curve), or its equivalent, the c-statistic. These variables reflect the probability that the tested predictive method will correctly categorize an individual: the variables are calculated by plotting the true-positive rate (sensitivity) against the false-positive rate (1−specificity) associated with given values according to the predictive method. An AUC or c-statistic of 1.0 means that the predictive method is always correct, whereas a value of 0.5 means that the method is no more accurate than is a coin toss. Values in the neighborhood of 0.7 or greater are considered to be of clinical interest and relevance.

The ProADM studies have had three main patterns of findings. First, ProADM predicted mortality and other adverse outcomes with similar accuracy as did the clinical risk scores. Second, and probably most important, adding ProADM to these scores enhanced such prediction compared to use of the respective scoring system alone, and significantly improved the classification of patients into predefined risk groups [53,58,63,64,65▪]. Importantly, the prognostic accuracy of ProADM was similar in different CAP etiologies and also in nonpneumonic lower respiratory infections [64]. Thus, these data suggest that adding ProADM to clinical severity scores can be extended to other nonpneumonic respiratory infections. Third, ProADM was consistently more prognostically accurate than were the other studied blood biomarkers; for example, the AUC or c-statistic of ProADM was always significantly or numerically higher than was that of PCT.

Interestingly, investigation of ProADM has suggested that use of this biomarker may help to improve timing of ICU admission. Late transfer to the ICU has been recognized to be associated with adverse patient medical outcomes [67,68]. Two studies found ProADM to be helpful in predicting severe CAP needing ICU admission [65▪,66].

It should be kept in mind that most studies on ProADM to date were observational; it remains unclear whether ProADM measurement improves decision-making and patient outcome when used

Table 1. Observational studies evaluating the adverse outcome prediction value of proadrenomedullin in community-acquired pneumonia

First author	Country	Number of patients	Setting	Primary outcome(s) of interest	AUC or c-statistic of ProADM	Main findings
Christ-Crain *et al.* [41]	Switzerland	302	Single-center, CAP	Mid-term 'failure' (mortality + CAP persistence/recurrence)	0.76	ProADM is a useful tool for risk stratification; adding ProADM to the PSI improved failure prediction versus using PSI alone
Huang *et al.* [62]	USA	1653	Multicenter, CAP	Short-term mortality	0.76	ProADM levels correlate with severity of illness and death; offer additional risk stratification in high-risk patients
Krüger *et al.* [59]	Germany	728	Multicenter, CAP	Short-term and mid-term mortality	0.85 (short-term), 0.78 (mid-term)	Of seven studied 'cardiovascular and inflammatory biomarkers,' ProADM best predicted short-term and mid-term mortality
Schuetz[a] *et al.* [53]	Switzerland	925[a]	Multicenter, CAP	'Serious complications' (mortality/ICU admission/ disease-specific complications)	0.76	ProADM showed high prognostic accuracy; adding ProADM to PSI or CURB65 significantly improved adverse outcome prediction versus using respective score alone
Guertler *et al*[b]. [61]	Switzerland	877[a]	Multicenter, CAP	Long-term mortality	0.73	High peak ProADM levels were significantly associated with higher mortality
Albrich[a] *et al.* [60▪▪]	Switzerland	1359[a]	Multicenter, LRTI	'Serious complications' (mortality/ICU admission/ disease-specific complications)	0.73 ('serious complications'), 0.79 (mortality alone)	Adding ProADM to CURB65 score showed significantly improved 'serious complication' prediction versus using CURB65 alone.
Bello *et al.* [64]	Spain	228	Single-center, CAP	Short-term 'complications' (respiratory failure, mechanical ventilation, shock, etc.), short-term, mid-term, and long-term mortality	0.71 (short-term complications), 0.86 (short-term mortality), 0.79–0.83 (mid-term mortality), 0.80 (long-term mortality)	ProADM has high short-term, mid-term, and long-term prognostic accuracy independent of CAP etiology
Suberviola *et al.* [66]	Spain	49	Single-center, CAP with severe sepsis or shock	In-hospital and ICU mortality	0.72	ProADM correlates with increasing severity and death; offers additional risk stratification in high-risk patients
Renaud[a] *et al.* [65▪]	Switzerland	80	Multicenter, early severe CAP	Short-term mortality	ProADM, 0.73; ProADM + REA-ICU, 0.81	Adding initial ProADM to the REA-ICU score improves classification of a substantial proportion of intermediate-risk or high-risk ED patients versus using REA-ICU alone
Courtais *et al.* [63]	France	109	Single-center, CAP	Short-term mortality	0.81	ProADM may be helpful in individual risk stratification of CAP patients with high PSI score

AUC, area under the curve; CAP, community-acquired pneumonia; CURB65, confusion, urea, respiratory rate, blood pressure, age at least 65 years; ED, emergency department; LRTI, lower respiratory tract infection; ProADM, plasma proadrenomedullin; PSI, Pneumonia Severity Index; REA-ICU, Risk of Early Admission to the Intensive Care Unit.
[a]Schuetz, 2010, Guertler, 2011, Albrich 2011, and Renaud 2012 are reports involving the ProHOSP cohort. Schuetz, 2011 reports on the CAP subgroup of the cohort, Guertler, 2011 reports on the hospital survivors among the CAP subgroup, and Renaud, 2012 reports on evaluable patients with early severe CAP among the CAP subgroup.

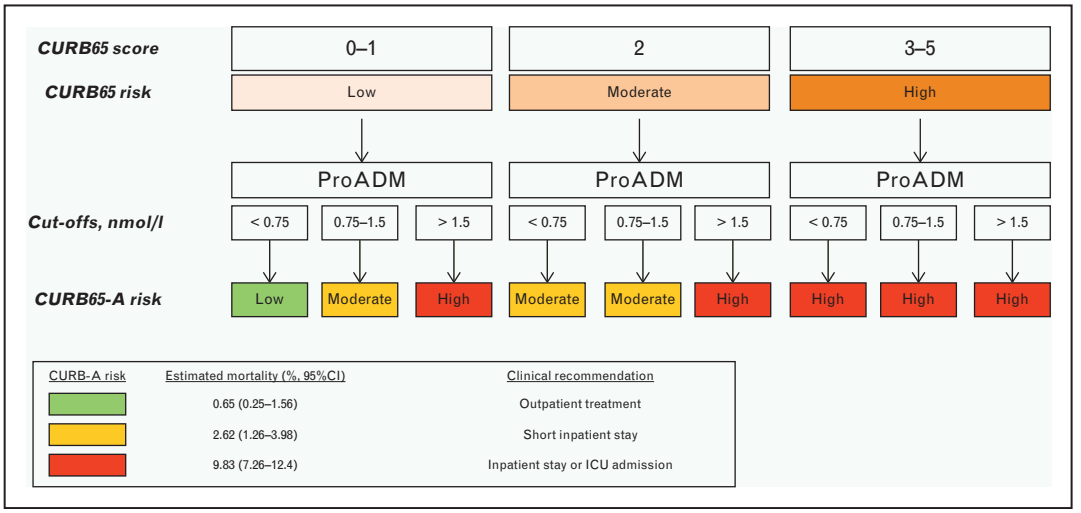

FIGURE 2. Initial ProADM-enriched CURB65 (CURB65A) score for site-of-care decisions. CI, confidence interval; CURB65, confusion, urea, respiratory rate, blood pressure, age at least 65 years; CURB65A, confusion, urea, respiratory rate, blood pressure, age at least 65 years, proadrenomedullin; ProADM, proadrenomedullin. Adapted from [60▪▪].

in an interventional trial. Importantly, such a trial needs to test the benefits of using ProADM integrated into a clinical protocol – with design similar to that of PCT-guided protocols. For this reason, based on data from a previous prospective observational study, Albrich *et al.* [60▪▪] combined the CURB65 score with ProADM cut-offs to create a novel three-level 'CURB65A' risk score (Fig. 2). This score showed higher prognostic potential for predicting adverse outcomes than did CURB65 alone, and tested 'virtually' improved performance for initial triage relative to actual allocation. When CURB65A was validated in an independent observational cohort [69], it again showed high accuracy that was superior to that of CURB65 and better identified patients with truly low medical risk. On the basis of these data, a proof-of-concept interventional RCT was conducted in which the allocation of treatment site and discharge from hospital were guided by clinical criteria combined with serial ProADM levels (manuscript submitted). Clearly, future studies are needed validating this initial effort and investigating the effects of ProADM use in different patient populations and in different countries.

CONCLUSION

Data from PCT and ProADM studies illustrate how biomarkers embedded in clinical algorithms may improve individual decision-making in patients with CAP. Numerous interventional RCTs have demonstrated PCT-guided protocols to be safe and highly effective in appropriately de-escalating or halting antibiotic therapy in patients with CAP. Many prospective observational cohort studies have found that ProADM has a high prognostic accuracy for short-term, mid-term, and long-term outcomes. When combined with current clinical risk scores, that is, PSI, CURB65, and REA-ICU, ProADM significantly improves adverse outcome prediction compared to using the score alone. Moreover, in a pilot study (Optimized Patient Transfer In Medical patients in the Canton Aarau II; OPTIMA), ProADM allowed more appropriate site-of-care decisions and tended to shorten length-of-stay despite organizational challenges. PCT should be further validated for ICU use in interventional studies, and such trials should be conducted to study the ultimate utility of ProADM in site-of-care allocation and discharge decisions. Already, however, these and other biomarkers are ushering in an era of personalized medicine, wherein interventions may be more rapidly and accurately directed to the patients likeliest to benefit.

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Conflicts of interest

P.S., W.C.A., and B.M. reported receiving support from Thermo Scientific Biomarkers, (formerly B.R.A.H.M.S. AG) and bioMérieux Inc. to attend meetings and fulfil speaking engagements. B.M. reported serving as a

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 206–207).

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