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Biomarkers as a guide for antimicrobial therapy

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Abstract

The use of biomarkers might help to avoid antibiotic misuse and overuse and to curb the rising incidence of microbial resistance. Among >100 biomarkers proposed for use as infection/sepsis markers, procalcitonin is the most frequently evaluated. It has been tested in 11 randomized controlled trials with more than 3500 patients and resulted in a considerable 35–70% reduction in antibiotic use without an apparent negative impact on patient outcome. Testing was carried out in hospital, intensive care unit, emergency and primary care settings; most of the patients had lower respiratory tract infections and only smaller studies exist in surgical patients with infectious complications, immunocompromised patients and patients with sepsis. There are, however, concerns – trials designed to show non-inferiority of procalcitonin to standard management allowed rather large differences for mortality rates, in the range of 7.5–10%, thus clinically relevant excess mortality by procalcitonin-guided antibiotic therapy cannot be completely ruled out. Marker panels derived from transcriptomic or proteomic profiling hold promise in overcoming the limitations of procalcitonin for differentiating non-infectious from infection-associated inflammation. However, the utility of these novel diagnostic tools in the clinical setting remains to be proven.

Keywords:

Antimicrobial therapy

Antibiotic stewardship

Procalcitonin

Biological marker

Infection

1. Introduction

Infection and sepsis are among the most common causes of death in hospitalized patients, and their incidence is increasing continuously at a rate of approximately 5–10% per year. Early and adequate antibiotic therapy is mandatory for successful sepsis therapy, irrespective of the type of organism, portal of entry, age of the patient or the occurrence of shock [1–3]. Rapid diagnosis of infection and sepsis is of outstanding significance, as each hour of delay of appropriate antimicrobial therapy increases mortality by 5–10%. As a result antibiotics are started, without a definitive microbial result, based on clinical signs and routine laboratory parameters such as white blood cell count and C-reactive protein, which have high sensitivity but lack specificity.

Diagnostic uncertainty is compensated for by the liberal use of broad-spectrum antibiotics, with the resulting resistance an increasing public health problem. Antimicrobial resistance has emerged as a major factor affecting patient outcomes and overall resources in intensive care units (ICUs). We are now heading towards extreme drug resistance, especially among Gram-negative bacilli. Two key factors associated with the emergence of bacterial resistance are insufficient infection control measures and selective antibiotic pressure. Compelling evidence that the use of antibiotics causes resistance has led to calls to stop inappropriate prescription of antibiotics.

Antimicrobial consumption in the ICU can be substantially reduced if antibiotics are administered only to patients with true bacterial infections and if treatment duration for those needing antibiotics is shortened. One approach would be to individualize the duration of antibiotic exposure according to the patient's response to antimicrobial treatment. Procalcitonin, a calcitonin precursor hormone, is judged to

be a fairly specific marker for severe bacterial infections and has shown some potential to differentiate infectious from non-infectious causes of systemic inflammation [4–7]. We will give an overview of the prospective randomized trials in which the potential of procalcitonin to limit antibiotic overuse has been assessed in different clinical settings such as the emergency department, the ICU, in neonatology, in hospitalized patients in general, and in primary care.

2. Clinical studies with procalcitonin

Highly sensitive procalcitonin measurements embedded in diagnosis-specific clinical algorithms have been shown to markedly reduce the overuse of antibiotic therapy by 30–80% without affecting the clinical outcome of over 3500 patients in 11 randomized controlled trials.

After the first publication that suggested procalcitonin might be useful for diagnosing bacterial infections [8], more than 10 years elapsed before Müller's group published the first randomized controlled trial in which procalcitonin was used for antibiotic stewardship in patients with lower respiratory tract infections, who often receive antibiotics without evidence of clinically relevant bacterial disease [5]. Two hundred and forty-three patients admitted to an emergency department with suspected lower respiratory tract infections were randomly assigned standard care (standard group; $N = 119$) or procalcitonin-guided treatment (procalcitonin group; $N = 124$). On the basis of serum procalcitonin concentrations the use of antibiotics was more or less discouraged ($<0.1 \mu\text{g/L}$ or $<0.25 \mu\text{g/L}$) or encouraged ($\geq 0.5 \mu\text{g/L}$ or $\geq 0.25 \mu\text{g/L}$), respectively. Re-evaluation was possible after 6–24 h in both groups. The primary end point was use of antibiotics and the analysis was by intention to treat.

The final diagnoses were pneumonia ($N = 87$; 36%), acute exacerbation of chronic obstructive pulmonary disease ($N = 60$; 25%), acute bronchitis ($N = 59$; 24%), asthma ($N = 13$; 5%) and other respiratory disease ($N = 24$; 10%). Serological evidence of viral infection was recorded in 141 of 175 tested patients (81%). Bacterial cultures were positive from sputum in 51 patients (21%) and from blood in 16 (7%). In the procalcitonin group, the adjusted relative risk (RR) of antibiotic exposure was 0.49 (95% confidence interval [CI] 0.44–0.55; $P < 0.0001$) compared with the standard group. Antibiotic use was significantly reduced in all diagnostic subgroups. Clinical and laboratory outcome was similar in both groups and favourable in 235 patients (97%). The authors concluded that in view of the current overuse of antimicrobial therapy in often self-limiting acute respiratory tract infections, treatment based on procalcitonin measurement could have important clinical and financial implications [5].

In a second randomized controlled trial this group evaluated the same algorithm in selected cases of chronic obstructive pulmonary disease (COPD) exacerbation [9]. A total of 208 consecutive patients requiring hospitalization for COPD exacerbation were randomized at the index exacerbation to procalcitonin-guided or standard antibiotic therapy. Patients receiving procalcitonin-guided therapy were treated with antibiotics according to serum procalcitonin levels; standard-therapy patients received antibiotics according to the attending physician. The primary outcome was antibiotic exposure for the index exacerbation and for subsequent COPD exacerbation within 6 months. Secondary outcomes were clinical recovery, symptom scores, length of hospitalization, ICU stay, death, lung function, exacerbation rate, and time to next exacerbation.

The authors found that at the index exacerbation, procalcitonin guidance reduced antibiotic prescription (40 vs 72%, respectively; $P < 0.0001$) and antibiotic use (RR 0.56; 95% CI 0.43–0.73; $P < 0.0001$) compared with standard therapy. Moreover, procalcitonin guidance at the index exacerbation allowed a significant sustained reduction in total antibiotic use for up to 6 months (RR 0.76; 95% CI 0.64–0.92; $P = 0.004$). Clinical outcome and improvement in FEV₁ at 14 days and 6 months did not differ between groups. Within 6 months the exacerbation rate (0.62 vs 0.64, respectively), the rehospitalization rate (0.21 vs 0.24, respectively) and mean ($\pm$ SD) time to the next exacerbation (70.0 ± 46.1 vs 70.4 ± 51.9 days, respectively; $P = 0.523$) were similar in both groups. The authors concluded that procalcitonin guidance for exacerbations of COPD offers a sustained advantage over standard therapy in reducing antibiotic use for up to 6 months.

Similar results were seen in a randomized intervention trial by the same group [6]. The study comprised 302 consecutive patients with suspected community-acquired pneumonia (both groups being similar regarding clinical, laboratory and microbiology characteristics, and Pneumonia Severity Index). Procalcitonin guidance reduced total antibiotic use (RR 0.52; 95% CI 0.48–0.55; $P < 0.001$), antibiotic prescriptions on admission (85 vs 99%; $P < 0.001$) and antibiotic treatment duration (median 5 vs 12 days; $P < 0.001$) compared with patients treated according to guidelines. After adjustment for Pneumonia Severity Index, the hazard ratio of antibiotic discontinuation was higher in the procalcitonin group than the control group (3.2; 95% CI 2.5–4.2). Outcome was similar in both groups, with an overall success rate of 83%.

In a preliminary study in patients with severe sepsis and septic shock [7], Nobre et al. tested the potential of a modified procalcitonin-based algorithm. In patients

randomly assigned to the intervention group, antibiotics were stopped when procalcitonin levels had decreased 90% or more from the initial value (if clinicians agreed) but not before day 3 (if baseline procalcitonin levels were $<1 \mu\text{g/L}$) or day 5 (if baseline procalcitonin levels were $\geq 1 \mu\text{g/L}$). In control patients, clinicians decided on the duration of antibiotic therapy based on empirical rules. Patients assigned to the procalcitonin group had a median duration of antibiotic therapy for the first episode of infection 3.5 days shorter than control subjects (intention-to-treat, $N = 79$, $P = 0.15$). In patients in whom a decision could be taken based on serial procalcitonin measurements, procalcitonin guidance resulted in a 4-day reduction in the duration of antibiotic therapy (per protocol, $N = 68$, $P = 0.003$) and a smaller overall antibiotic exposure ($P = 0.0002$). Similar mortality and recurrence of the primary infection were observed in both groups. An ICU stay 2 days shorter was also observed in patients assigned to the procalcitonin group ($P = 0.03$). The interpretation of this study is limited by the small sample size and the fact that a considerable number of patients met exclusion criteria and were not included in the study. A larger randomized controlled trial in severe sepsis patients, which is powered for 1000 patients, is ongoing in Germany [10].

In patients with ventilator-associated pneumonia (VAP), guidelines recommend antibiotic therapy adjustment according to microbiology results after 72 h. In a randomized controlled multicentre trial [11], 101 patients with VAP were assigned to an antibiotic discontinuation strategy according to guidelines (control group) or serum procalcitonin concentrations (procalcitonin group), with an antibiotic regimen selected by the treating physician. The primary end point was antibiotic-free days alive assessed 28 days after VAP onset and analysed on an intention-to-treat basis. Procalcitonin determination significantly increased the number of antibiotic-free days

alive 28 days after VAP onset (13 (2–21) days vs 9.5 (1.5–17) days). This translated into a reduction of 27% in the overall duration of antibiotic therapy in the procalcitonin group ($P = 0.038$). After adjustment for age, microbiology and centre effect the rate of antibiotic discontinuation on day 28 remained higher in the procalcitonin group than in patients treated according to guidelines (hazard rate 1.6, 95% CI 1.02–2.71). The number of mechanical ventilation-free days alive, ICU-free days alive, length of hospital stay and mortality rate on day 28 for the two groups were similar. The authors concluded that serum procalcitonin measurement reduces antibiotic therapy exposure in patients with VAP.

In a primary care setting [12], 53 primary care physicians recruited 458 patients, each with an acute respiratory tract infection and, in the physician's opinion, in need of antibiotics. Patients were centrally randomized to either procalcitonin-guided antibiotic therapy or a standard approach. For patients randomized to procalcitonin-guided therapy the use of antibiotics was more or less strongly discouraged (procalcitonin level ≤ 0.1 or ≤ 0.25 $\mu\text{g/L}$, respectively) or recommended (procalcitonin level > 0.25 $\mu\text{g/L}$). Follow-up data were collected at 7 days by treating physicians and at 14 and 28 days by blinded interviewers. Adjusted for baseline characteristics, the mean increase at 14 days in days on which activities were restricted was 0.14 with procalcitonin-guided therapy (95% CI 0.53–0.81). This met the study criterion of not increasing the number of days in which activities were restricted by > 1 day. With procalcitonin-guided therapy the antibiotic prescription rate was 72% lower (95% CI 66–78) than with standard therapy. Both approaches led to a similar proportion of patients reporting symptoms of ongoing or relapsing infection at 28 days (adjusted odds ratio 1.0 [95% CI 0.7–1.5]). The authors concluded that, as an adjunct to guidelines, procalcitonin-guided therapy markedly reduced antibiotic use for acute

respiratory tract infections in primary care, without compromising patient outcome. In practice this could be achieved with one or two procalcitonin measurements in patients for whom the physician intended to prescribe antibiotics.

In a randomized controlled multicentre non-inferiority trial in the emergency departments of six tertiary care hospitals in Switzerland, 1359 patients, most of whom had lower respiratory tract infection, were randomized to receive antibiotics based on a procalcitonin algorithm with predefined cutoff ranges for initiating or stopping antibiotics (procalcitonin group) or according to standard guidelines (control group) [13]. Serum procalcitonin was measured locally in each hospital and instructions were web-based. The main outcome measures for non-inferiority were based on the following adverse outcomes: death, ICU admission, disease-specific complications or recurrent infection requiring antibiotic treatment within 30 days (with a predefined non-inferiority boundary of 7.5%), antibiotic exposure and adverse effects from antibiotics. The rate of overall adverse outcomes was similar in the procalcitonin and control groups (15.4% [$N = 103$] vs 18.9% [$N = 130$]; difference -3.5%; 95% CI -7.6–0.4). The mean duration of antibiotic exposure in the procalcitonin vs control groups was lower in all patients (5.7 vs. 8.7 days; relative change -34.8%; 95% CI -40.3 to -28.7) and in the subgroups of patients with community-acquired pneumonia ($N = 925$, 7.2 vs 10.7 days; -32.4%; 95% CI -37.6 to -26.9), exacerbation of COPD ($N = 228$, 2.5 vs 5.1 days; -50.4%; 95% CI -64.0 to -34.0) and acute bronchitis ($N = 151$, 1.0 vs 2.8 days; -65.0%; 95% CI -84.7 to -37.5). Antibiotic-associated adverse effects were less frequent in the procalcitonin group (19.8% [$N = 133$] vs. 28.1% [$N = 193$]; difference -8.2%; 95% CI -12.7 to -3.7).

Kristoffersen et al. evaluated the effect of a single procalcitonin measurement on antibiotic use in suspected lower respiratory tract infections (LRTI) [14]. Two hundred and twenty-three adult patients admitted to the hospital because of suspicion of LRTI were included and 210 were available for analysis. Patients were randomized to either procalcitonin-guided treatment or standard treatment. Antibiotic treatment duration in the procalcitonin group was based on the serum procalcitonin value at admission. The cutoff point for recommending antibiotic treatment was procalcitonin ≥ 0.25 $\mu\text{g/L}$. Physicians could overrule treatment guidelines. The mean duration of hospital stay was 5.9 days in the procalcitonin group vs 6.7 days in the control group ($P = 0.22$). The mean duration of antibiotic treatment during hospitalization in the procalcitonin group was 5.1 days on average, compared with 6.8 days in the control group ($P = 0.007$). In a subgroup analysis of COPD patients, the mean length of stay was reduced from 7.1 days in the control group to 4.8 days in the procalcitonin group ($P = 0.009$).

In a smaller single-centre study [15], Hochreiter et al. assessed the impact of procalcitonin monitoring on the duration of antibiotic therapy in intensive care patients. In this study all patients requiring antibiotic therapy were eligible, based on confirmed or highly suspected bacterial infection and at least two concomitant systemic inflammatory response syndrome criteria. Patients were randomly assigned to either a procalcitonin-guided (study group) or a standard (control group) antibiotic regimen. Antibiotic therapy in the procalcitonin-guided group was discontinued if clinical signs and symptoms of infection improved and procalcitonin decreased to < 1 ng/mL or the procalcitonin value was > 1 ng/mL but had dropped to 25–35% of the initial value over 3 days. In the control group, antibiotic treatment was applied as standard regimen over 8 days. A total of 110 surgical intensive care patients

receiving antibiotic therapy for a confirmed or highly suspected infection were enrolled. In 57 patients antibiotic therapy was guided by daily procalcitonin and clinical assessment and adjusted accordingly. The control group comprised 53 patients. Demographic and clinical data were comparable in both groups. In the procalcitonin group the duration of antibiotic therapy was significantly shorter compared with controls (5.9 ± 1.7 vs 7.9 ± 0.5 days, $P < 0.001$), without negative effects on clinical outcome.

Most recently, the usefulness of procalcitonin to reduce patients' exposure to antibiotics in ICUs was evaluated in a multicentre prospective parallel-group open-label trial [16]. Patients were randomly assigned in a 1:1 ratio to procalcitonin ($N = 311$ patients) or control ($N = 319$) groups; investigators were masked to assignment before randomization but not after. For the procalcitonin group, antibiotics were started or stopped based on predefined procalcitonin cutoff ranges; the control group received antibiotics according to current guidelines. Drug selection and the final decision to start or stop antibiotics were at the discretion of the physician. Patients were expected to stay in the ICU for >3 days, had suspected bacterial infections and were aged ≥ 18 years. Primary end points were mortality at days 28 and 60 (non-inferiority analysis) and number of days without antibiotics by day 28 (superiority analysis). Analyses were on an intention-to-treat basis. The margin of non-inferiority was 10%. Three hundred and seven patients in the procalcitonin group and 314 in the control group were included in the analyses. The mortality of patients in the procalcitonin group seemed to be non-inferior to those in the control group at day 28 (21.2% [65/307] vs 20.4% [64/314]; absolute difference 0.8%, 90% CI -4.6–6.2) and day 60 (30.0% [92/307] vs 26.1% [82/314]; absolute difference 3.8%, 90% CI -2.1–9.7). Patients in the procalcitonin group had

significantly more days without antibiotics than those in the control group (14.3 ± 9.1 days vs 11.6 ± 8.2 days; absolute difference 2.7 days, 95% CI 1.4–4.1, $P < 0.0001$). The authors concluded that a procalcitonin-guided strategy to treat suspected bacterial infections in non-surgical patients in ICUs could reduce antibiotic exposure and selective pressure with no apparent adverse outcomes.

Diagnosis of neonatal early-onset sepsis is difficult because clinical signs and laboratory tests are non-specific. Early antibiotic therapy is crucial for treatment success. In a prospective randomized single-centre intervention study [17], Stocker et al. evaluated the effect of procalcitonin-guided decision-making on duration of antibiotic therapy in suspected neonatal early-onset sepsis. All term and near-term infants (gestational age ≥ 34 weeks) with suspected early-onset sepsis were randomly assigned either to standard treatment based on conventional laboratory parameters (standard group) or procalcitonin-guided treatment (procalcitonin group). Minimum duration of antibiotic therapy was 48–72 h in the standard group, whereas in the procalcitonin group antibiotic therapy was discontinued when two consecutive procalcitonin values were below the predefined age-adjusted cutoff value. One hundred and twenty-one newborns were randomly assigned either to the standard group ($N = 61$) or the procalcitonin group ($N = 60$). The two groups were similar for baseline demographics, risk factors for early-onset sepsis, likelihood of infection as assessed by the attending physician and early conventional laboratory findings. There was a significant difference in the proportion of newborns treated with antibiotics for ≥ 72 h between the standard group (82%) and the procalcitonin group (55%) (absolute RR 27%; odds ratio 0.27 (95% CI 0.12–0.62), $P = 0.002$). On average, procalcitonin-guided decision-making resulted in a reduction of 22.4 h in the duration of antibiotic therapy. Clinical outcome was similar and favourable in both

groups but the sample size was insufficient to exclude rare adverse events. The authors concluded that serial procalcitonin determinations allow physicians to shorten the duration of antibiotic therapy in term and near-term infants with suspected early-onset sepsis, but before this procalcitonin-guided strategy can be recommended its safety has to be confirmed in a larger cohort of neonates.

3. Discussion

The concept of procalcitonin-guided antibiotic stewardship and the studies that support it face a number of criticisms. The main concern is that these studies aimed to demonstrate non-inferiority within a rather large range of 7.5–10% difference in mortality between procalcitonin-guided and control groups. Such high cutoffs have been questioned, since no study in an ICU setting has ever shown such a dramatic difference in mortality. Furthermore, Bouadma et al. found a 3.8% higher 28- and 60-day mortality rate in the procalcitonin-guided group, which was not statistically significant, but the design and the power of the trial implies that a negative impact on mortality attributable to the procalcitonin strategy cannot be definitively excluded. To exclude a true excess mortality of 4%, similar to that seen in the trial, would require about 4220 patients; a study to exclude an excess mortality of 2% would need to be powered for 16 500 patients [18,19]. In their response to this criticism Bouadma et al. pointed to the fact that random allocation at ICU admission resulted in slight imbalances in terms of higher disease severity scores for the procalcitonin group [20].

In a recent review Schuetz et al. [21] summarized the results of 11 randomized controlled trials on procalcitonin-guided antibiotic therapy that have been performed in adult patients. A total of 3691 patients were enrolled; 166 patients died in the control arms and 159 in the procalcitonin arms. Although there remains some

uncertainty on the safety of procalcitonin-guided antibiotic therapy the evidence in favour of this concept is increasing. But a number of open questions remain. Most of the higher-quality studies that were performed were in patients with pneumonia and LRTIs. There is only one smaller study in severe sepsis patients. Studies in post-surgical ICU patients and immunocompromised patients are also warranted as it is well known that procalcitonin is far from being an ideal infection marker. The user has to know that surgical trauma or cardiopulmonary bypass may result in procalcitonin increases without concomitant infection. Likewise, there are a number of other non-infectious causes that may induce elevated procalcitonin serum levels. This was observed in patients treated with anti-T-cell antibodies, alemtuzumab, interleukin 2 or granulocyte transfusions, and patients with acute graft-vs-host disease or liver metastasis [22–24]. It has also been argued that less costly biomarkers such as C-reactive protein have shown test characteristics similar to procalcitonin when assessed in an outpatient population [25,26]

4. Perspectives and conclusions

Recent data from transcriptomic and/or proteomic profiling suggest that marker panels derived from transcriptomic or proteomic profiling are superior to single genes or markers in differentiating non-infectious from sepsis-associated systemic inflammation [27,28] and thus may overcome some of the limitations of procalcitonin. However, among the >100 sepsis and infection markers that have been proposed, procalcitonin is to date by far the most widely evaluated and used marker and there are ongoing trials to assess its clinical utility and safety as guide for antibiotic therapy in settings such as sepsis.

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