IMPLEMENTATION OF A PROCALCITONIN-GUIDED ALGORITHM FOR ANTIBIOTIC THERAPY IN THE BURN INTENSIVE CARE UNIT

MISE EN PLACE D’UN ALGORITHME BASÉ SUR LA MESURE QUOTIDIENNE DE LA PROCALCITONINE POUR GUIDER L’ANTIBIOTHERAPIE DANS UNE UNITÉ DE SOINS INTENSIFS AUX BRULES

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SUMMARY. The purpose of this study was to examine the hypothesis that an algorithm based on serial measurements of procalcitonin (PCT) allows reduction in the duration of antibiotic therapy compared with empirical rules, and does not result in more adverse outcomes in burn patients with infectious complications. All burn patients requiring antibiotic therapy based on confirmed or highly suspected bacterial infections were eligible. Patients were assigned to either a procalcitonin-guided (study group) or a standard (control group) antibiotic regimen. The following variables were analyzed and compared in both groups: duration of antibiotic treatment, mortality rate, percentage of patients with relapse or superinfection, maximum SOFA score (days 1-28), length of ICU and hospital stay. A total of 46 Burn ICU patients receiving antibiotic therapy were enrolled in this study. In 24 patients antibiotic therapy was guided by daily procalcitonin and clinical assessment. PCT guidance resulted in a smaller antibiotic exposure (10.1±4 vs. 15.3±8 days, p=0.034) without negative effects on clinical outcome characteristics such as mortality rate, percentage of patients with relapse or superinfection, maximum SOFA score, length of ICU and hospital stay. The findings thus show that use of a procalcitonin-guided algorithm for antibiotic therapy in the burn intensive care unit may contribute to the reduction of antibiotic exposure without compromising clinical outcome parameters.

Keywords: antibiotic therapy, procalcitonin-guided, burns

RÉSUMÉ. Le but de cette étude était d’examiner si un algorithme basé sur des mesures de la procalcitonine (PCT) peut permettre la réduction de la durée de l’antibiothérapie, sans être dangereuse, chez les patients brûlés infectés. Tous les patients brûlés nécessitant une antibiothérapie en raison d’une infection bactérienne très probable ou confirmée étaient éligibles. Les patients ont été divisés en deux groupes: groupe à l’étude (durée de traitement guidé par PCT), et groupe de contrôle (durée selon les préconisations actuelles). Les variables suivantes ont été analysées et comparées: durée de traitement, mortalité, le pourcentage de patients avec une surinfection ou une rechute, score SOFA maximum entre J1 et J28, durées de séjour en soins intensifs et à l’hôpital. Un total de 46 patients, hospitalisés en soins intensifs et recevant une antibiothérapie ont été inclus dans cette étude, dont 24 dans le groupe PCT. Ces patients ont reçu une exposition aux antibiotiques inférieure (10,1 ± 4 vs 15,3 ± 8 jours, p = 0,034), sans effets négatifs sur le taux de mortalité et la durée du séjour à l’hôpital. Les résultats montrent que cette méthode peut contribuer à la réduction de l’utilisation des antibiotiques chez les brûlés en soins intensifs, sans compromettre leur avenir.

Mots-clés: antibiothérapie, procalcitonine, algorithme, durée de traitement, brûlés
ditionally, selective antibiotic pressure is a significant factor associated with the emergence of bacterial resistance in critically ill patients.4

In order to reduce the inappropriate or unnecessarily prolonged use of antibiotics, rapid and accurate differentiation of clinically relevant bacterial infections is pivotal. The American Burn Association, in an attempt to improve the current definitions of infectious complications in burns, suggests using procalcitonin (PTC) to define more comprehensively the variations in individual responses to burn injury and infection.3

PTC measurement is now routinely used to confirm bacterial infection in critically ill patients, and also seems to be a useful marker for the detection of septic complications in burn patients.6-10 Besides its role as a marker of infection, PTC has been shown to be helpful in determining the effectiveness and appropriate duration of antibiotic therapy in critically ill patients.11,12 Evidence from clinical trials shows that the use of algorithms based on PCT levels leads to a significant reduction in antibiotic use in critically ill patients.13-15 However, the role of PCT in monitoring the effectiveness of antibiotic therapy and in determining the duration of antibiotic use in critically ill burn patients has not been reported.

In the present study we aimed to assess the benefit of a procalcitonin-based therapeutic strategy in reducing the duration of antibiotic therapy in intensive care unit (ICU) burn patients with suspected bacterial infections.

Methods

Design, inclusion criteria

A single-center study aimed to assess the benefit of a procalcitonin-based therapeutic strategy in reducing the duration of antibiotic therapy in ICU burn patients. All adult patients with suspected bacterial infections admitted to the Burn ICU from October 2012 to April 2014 (intervention period) were included in a prospective, observational study and compared to controls from January 2011 to September 2012. A computer-generated list of potential control individuals was obtained from a historical database of patients attending the same ICU (22 patients from January 2011 to September 2012). The list of potential controls was reviewed for the best possible match, giving a ranking priority of TBSA and SOFA scores, followed by age and sex. Controls were selected based on similarity of the following criteria: age (±10 years), sex, TBSA (±5%), severity of organ dysfunction and failure, an admission SOFA score of ±5 points (calculated within the first 24 hours of ICU admission) with a maximum SOFA score of ±5 points (calculated within first 28 days), and diagnosis of infection during the first 28 days after admission. In the control group of patients the PCT levels had been measured only at the onset of infection, but there were no se-

rial measurements of the PCT levels and the antibiotic treatment was managed irrespective of the PCT levels. For patients in the control group, the decisions of the optimum duration of antibiotic treatment were based upon: a) the current recommendations for duration of antimicrobial treatment for the most frequent infections and b) the physician’s assessment of the clinical course of infection.

Exclusion Criteria

Age lower than 16 years, expected ICU stay of fewer than 3 days, bone-marrow transplantation or chemotherapy-induced neutropenia, infections for which long-term antibiotic treatment is strongly recommended (infective endocarditis, osteoarticular infections, hepatic or cerebral abscesses), nonsurvivable burn (decisions for comfort care on admission and Do Not Attempt Resuscitation orders).

Ethical issues

The approval of the institutional Ethics Committee was obtained. No personally identifiable information was collected in the study.

Data collection

Upon admission to the ICU, data collected were age, sex, pre-existing comorbidities, Total Burn Surface Area percentage (TBSA), presence of inhalation injury, SAPS II score (Simplified Acute Physiological Score II), Sequential Organ Failure Assessment (SOFA) score was assessed on admission, at the onset of infection and daily thereafter for 7 consecutive days. SOFA max (maximum SOFA score) was also estimated during the first 28 days. Need for mechanical ventilation, source of infection when known, results of microbiological cultures, and adequacy of initial empirical treatment were also recorded.

All burn patients requiring antibiotic therapy based on confirmed or highly suspected bacterial infections were eligible.

For patients in the PCT group, two interventions were used to manage the antibiotic therapy:

i) use of PCT concentration to decide whether antibiotic treatment should be continued or changed

ii) use of serial serum PCT concentrations to decide whether antibiotic treatment should be stopped

Our study was based on the use of predefined algorithm4 to guide physicians in discontinuing antibiotic therapy according to serum PCT concentrations. We used both the absolute value of PCT and the changes in PCT levels to guide the antibiotic treatment as was recommended previously.13-15

The guidelines for commencing, continuing or discontinuing antibiotic treatment according to protocol were the following:

– Continuation of antibiotics was encouraged if the
PCT levels decreased by 80% from peak concentration and levels ≥0.5 μg/L.

- Changing antibiotics was strongly encouraged if the PCT levels increased compared with peak concentration and concentration ≥0.5 μg/L.

Discontinuation of antibiotics was:
- i) strongly encouraged in PCT levels < 0.25 μg/L
- ii) encouraged if the PCT levels decreased by 80% from peak concentration or levels ≥0.25 μg/L and < 0.5 μg/L

The final decision with respect to starting and continuing antibiotics was at the discretion of the patient’s physician, irrespective of the PCT levels.

For patients in the control group, the decisions of the optimum duration of antibiotic treatment were based upon:
- a) the current recommendations for duration of antimicrobial treatment for the most frequent infections and b) the physician’s assessment of the clinical course of infection.

For both groups, drug selection was at the discretion of the patient’s physician. Broad spectrum antibiotics were recommended for initial empirical treatment for most severe infections. Antibiotic de-escalation to a narrower-spectrum antibiotic was recommended on the basis of culture results from specimens obtained at the onset of infection.

The study group patients’ PCT levels were measured once they were introduced to the study (at each infectious episode until day 28 of ICU stay) and every morning thereafter until completion of the antibiotic treatment. Serum PCT levels were determined by immunoluminometric assay (Lumitest PCT, Brahms Diagnostica, Berlin, Germany). The lower detection limit was 0.08 ng/ml.

**End points**

Primary end point included systemic antibiotic exposure by measuring two variables:

- i) duration of antibiotic treatment according to infection site, expressed in days
- ii) days without antibiotics, defined as a period of at least 24 hours without antibiotic administration for a given patient (days 1-28)

It has been reported that reducing the duration of antibiotic therapy would alter a number of clinical parameters, such as the percentage of emerging multidrug-resistant bacteria and the relapse or superinfection rate, which would consequently impact on the length of stay, duration of mechanical ventilation, severity of organ failure and mortality rate.13,14 For this reason, the following parameters have been included in the study as the secondary outcome parameters:

- percentage of patients with relapse or superinfection (days 1-28)
- percentage of emerging multidrug resistant bacteria isolated from specimens taken for microbiological assessment (days 1-28)
- number of days without mechanical ventilation (days 1-28)
- maximum SOFA score (days 1-28)
- length of ICU and hospital stay

**Diagnostic criteria**

Diagnosis of sepsis and septic shock was performed according to the current recommendations.5,8,17

**Septic shock** was defined as sepsis with a state of acute circulatory failure characterized by persistent, refractory to intravenous fluid administration hypotension unexplained by other causes.

**Bacteraemia** was defined by the presence of general signs of infection and positive blood culture(s): at least one blood culture (sample taken during a temperature peak) positive to a microorganism known to be a pathogen, two blood cultures in a maximum interval of 48h (sample taken during a temperature peak) positive to one of the following microorganisms: coagulase-negative Staphylococcus, Bacillus sp., Corynebacterium sp., Propionibacterium sp., Micrococcus sp. and Acinetobacter sp.

Diagnosis of localized infections (respiratory tract, burn wound, urinary tract) was defined according to the American Burn Association recommendations as well as by using additional criteria recommended in the bibliography.5,8,19

**Pneumonia** was defined by the presence of a new or progressive infiltrate in addition to at least two out of three clinical features (fever greater than 38°C, leukocytosis or leukopenia, and purulent secretions) plus a positive quantitative culture of samples obtained either by bronchoalveolar lavage, or by protected specimen brush, using diagnostic thresholds of 10³ colony forming units (CFU)/ml and 10⁴ CFU/ml respectively.

**Catheter-associated urinary tract infection (CA-UTI)** was defined by the presence of significant bacteriuria (≥10⁵ CFU/ml) with no more than 2 species of microorganisms in a patient with clinical signs and symptoms relative to the urinary tract infection.

A diagnosis of catheter-related bloodstream infection (CRBSI) required that the same organism grew from at least one percutaneous blood culture and from a culture of the catheter tip, or that two blood samples were drawn (one from a catheter hub and the other from a peripheral vein), and, when cultured, met CRBSI criteria for quantitative blood
cultures or differential time to positivity (DTTP). For quantitative blood cultures, a colony count of microbes grown from blood obtained through the catheter hub that was at least 3-fold greater than the colony count from blood obtained from a peripheral vein defined as CRBSI. For DTTP, growth of microbes from a blood sample drawn from a catheter hub at least 2h before microbial growth was detected in a blood sample obtained from a peripheral vein defined as CRBSI. Growth of >15 colony-forming units (cfu) from a 5cm segment of the catheter tip by semiquantitative (roll-plate) culture reflected catheter colonization.

**Burn wound infection** was characterized by the presence of the following criteria: a) clinical signs of wound infection (purulent secretions, color changes, pain, erythema, unexpected change in the appearance and the depth of the wound, conversion of partial thickness injury to full thickness necrosis, non-viable grafts), and b) burn wound biopsy with $\geq 10^5$ colony-forming units/g tissue, or quantitative swab with counts of $10^6$ bacteria obtained from surface swabsamples or a histological diagnosis of burn wound infection based on the observation of microorganisms invading viable tissue beneath the eschar surface.

**Relapse** was defined as the growth of one or more of the initial causative bacterial strains from a second sample taken from the same infection site at 48h or more after stopping antibiotics, combined with the clinical signs and symptoms of infection.

**Superinfection** was defined as the isolation of one or more pathogens, from the same or another site, different than that identified during the first infectious episodes, combined with signs and symptoms of infection.

Presence of multidrug resistant bacteria was recorded. Multidrug resistance in *P. aeruginosa*, *Stenotrophomonas maltophilia*, or *Acinetobacter* species was defined as a diminished susceptibility to more than one of the following five drug classes: antipseudomonal cephalosporins, antipseudomonal carbapenems, $\beta$-lactam-$\beta$-lactamase inhibitor combinations, antipseudomonal fluoroquinolones, and aminoglycosides. Multidrug resistant bacteria were also defined as one of the following: $\beta$-lactam-producing *Enterobacteriaceae*, high concentration cephalosporinase-producing AmpC *Enterobacteriaceae* and meticillin-resistant *Staphylococcus aureus*.

Acute Kidney Injury was diagnosed according to the current recommendations. Use of renal replacement therapy (RRT) was also recorded.

**Statistical analysis**

The Mann-Whitney test was used in order to test for differences between the distributions of continuous variables, while the chi-square test was employed to test for independence between categorical variables. Univariate analysis was used to correct for confounding factors: age, gender, presence of comorbidities and TBSA. Kaplan-Meier estimates of time to A/B discontinuation were produced for the two study groups. These were compared based on the Cox model risk estimate. P-values less than 0.05 were considered statistically significant. SPSS 21.0 (IBM Inc., Armonk, NY) and STATA 13.0 (StataCorp, College Station, TX) were used for data analysis.

**Results**

A total of 37 burn patients were excluded from the study. The reasons for exclusion were the following: age lower than 16 years (3 patients), expected stay of fewer than 3 days in the intensive care unit (16 patients), bone-marrow transplant or chemotherapy-induced neutropenia (1 patient), infections for which long-term antibiotic treatment is strongly recommended (4 patients), nonsurvivable burns (9 patients). In four patients from the study group (two of whom had secondary infection) the decision was taken to continue the antibiotic treatment irrespective of the PCT levels, therefore, the data of these patients were also excluded from statistical analysis.

Ultimately, a total of 46 Burn ICU patients receiving antibiotic therapy were enrolled in the study (47.7±19 years, 74% males, 35.5±16% TBSA, 10.5±4 APACHE II, 23±10 SAPS II, 3.9 ±2 SOFA score). In 24 patients, antibiotic therapy was guided by daily PCT and clinical assessment. The control group was comprised of 22 patients with a standardized duration of antibiotic therapy. The mortality rates of PCT group and control group patients were 25% and 36%, respectively. Multiple organ failure due to septic complications was the main cause of death. Concentrations of PCT at admission and maximum PCT levels during the infection were 0.69 (0.3-1.4) ng/ml, and 7.8 (0.3-13.9) ng/ml, respectively.

Demographic and clinical data were comparable in both groups (*Table I*). Patients in the control group had a higher incidence of pneumonia diagnosis (20.8% vs. 36%) and were slightly older (42.9±18 vs. 51.1±17, years) than in the investigation group.

The main bacterial strains responsible for infections were Gram-negative bacteria, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumonia*, which had a high percentage of MDR bacteria (47.7%).

Multidrug-resistant strains were isolated in 61% of surviving patients from the investigation group and in 54.5% of the surviving control group patients after the discontinuation of the antibiotics.

The duration of antibiotic therapy was significantly shorter in the PCT-guided therapy group compared to the control group without negative effects on clinical outcome.
The duration of antibiotic therapy was also significantly shorter in patients with pulmonary infection (10.4±2.3 vs. 13.1±6, days, p=0.05). PCT guidance resulted in a smaller overall antibiotic exposure during the first 28 days of ICU stay (Table II). After performing univariate analysis to correct for confounding factors, we found that the presence of comorbidities had influence on the duration of antibiotic therapy with p value of 0.044.

Non-survivors on ICU discharge were older than survivors (66±11 vs. 42±18 years, p=0.014), had a higher percentage of septic shock (91% vs. 15%, p<0.001), and had a higher percentage of acute kidney injury (67 vs. 17.6%.

(Tables I and II).
Thirty-three percent of non-survivors were treated using renal replacement therapy in the form of Continuous Veno-Venous Hemofiltration (CVVH) compared to 6% of survivors.

Kaplan Meyer plots showed a different distribution over time in the number of patients who remained on antibiotic therapy in the PCT group compared to those in the control group (Fig. 1).

Discussion

Infectious complications of burn trauma are associated with high morbidity and mortality and are difficult to diagnose due to the lack of sensitivity and specificity of the clinical diagnostic criteria. Early initiation of appropriate antibiotics and goal-directed therapies reduces mortality in patients with severe infectious complications. Conversely, it is well recognized that overuse of antibiotics and continuing antibiotics longer than necessary for treatment goal can result in antibiotic resistance. This increasing problem of resistance has driven the need to re-evaluate treatment recommendations in terms of diagnoses and duration of therapy.

Recent randomized controlled trials and meta-analyses in a variety of settings concluded that a PCT-based antibiotic treatment algorithm appears to be safe and reduces antibiotic consumption without compromising clinical outcomes. Integration of biomarker-guided antibiotic treatment for guidance of antibiotic treatment may enhance adherence to guidelines since clinicians may be reassured in their decision to discontinue antibiotics by use of objective parameters.

The most common use for PCT in burn patients is related to the diagnosis of infectious complications and to the initiation of antibiotic therapy. Based on the data in non-burn ICU patients, we hypothesized that the length of antibiotic treatment can also be optimized and reduced in burn patients using PCT guidance. To date, there is no evidence in the literature for this approach in burn patients.

We observed significantly shorter durations of antibiotic treatment in the PCT-guided group of patients compared to the standard treatment group (10.1±4 vs. 15.3±8 days). Demographic and clinical data were comparable in both groups of patients except for patients’ age and rate of pneumonia; patients in the control group had a higher incidence of pneumonia diagnosis and were slightly older than in the study group, but the difference was at the edge of statistical significance. Moreover, patients in the PCT-guided group with pulmonary infection also had shorter durations of antibiotic therapy compared to the control group patients with pulmonary infection. We did not observe any differences in main outcome characteristics, such as mortality rate, sepsis-related death, primary infection relapse rate, superinfection rate, ICU length of stay, and length of mechanical ventilation. When referring to the patients’ mortality we observed a higher mortality rate on ICU discharge in patients suffering septic shock, in patients presenting Acute Kidney Injury (AKI), and in patients in whom AKI was treated using renal replacement therapy. The negative impact of AKI on burn patient mortality and morbidity is well established in the literature, and this study’s findings provide further confirmation of the existing data on this issue.

Our results are in accordance with the results from the previous studies in non-burn patients showing reduced duration of PCT-guided antibiotic treatment for critically ill patients. We supposed that the implementation of PCT-guided algorithm therapy had a positive influence on the duration of antibiotic therapy through two main mechanisms: directly, due to its impact on the decision for or against antibiotic therapy and, indirectly, because of physicians’ heightened awareness of the need to continuously re-evaluate the necessity of antimicrobial agents.

We did not observe any increase in the rate of recurrent infections (relapse and superinfection) in patients with PCT-guided treatment. Although the incidence of MDR pathogens cultured after the end of antibiotic treatment was slightly higher in the PCT-guided group, the difference did not reach statistical significance. Conversely, in a study by Chastre and colleagues comparing 8-day and 15-day antibiotic therapy in patients with respiratory-associated pneumonia and systemic sepsis, the rate of recurrent infections with Pseudomonas aeruginosa was higher in patients with short duration of antibiotic therapy, whereas a markedly higher incidence of multi-resistant pathogens was found in the 15-day treatment group.

In the recent study by Layios et al., a PCT-based strategy for the initiation of antimicrobial therapy did not ap-
pear to be helpful in decreasing the antibiotic consumption of ICU patients. It must be emphasized that PCT-algorithms are only a single component in strategies for optimizing antibiotic treatment which should be used together with the institutional complex antimicrobial stewardship program focused on prevention of infection and more rational utilization of antibiotics.

Another finding of our study that is worth mentioning is the extremely low level of de-escalation in our ICU patients. De-escalating antibiotics and avoiding unnecessary antibiotic use prevent the development of resistance and should be a key element within antimicrobial stewardship programs, which should be the focus of our future attention.

This monocentric study is the first attempt to evaluate the potential role of PCT-guided antibiotic treatment in burn patients; however, it clearly has significant weaknesses. The main weaknesses of our study are the single center character and the relatively small number of patients which resulted in the inability to perform relevant statistical analysis of the non inferiority of the PCT-guided therapy versus traditional treatment approach. The small number of patients makes the results of this study susceptible to random errors. The nonrandomized design of our study is also a major limitation. Certainly, only randomization can ensure comparability between study groups and controls. Even though cases and controls were matched for age, sex, severity of organ failure or dysfunction, and TB-SA, there was still selection bias. We found that the presence of comorbidities was a confounding factor altering the duration of antibiotic therapy along with PCT guidance. Additionally, evolution of medical care during the study period might also have influenced our results, even though the diagnostic criteria, the use of antibiotics and other supportive treatment, and routine patient management did not fundamentally change over the period of interest (2011-2014). Another limitation of this study is the inclusion of all types of infections in the statistical analysis. The future studies on this topic should certainly focus on specific infection sites.

Larger scale randomized controlled trials including more patients from different burn centers should be performed to confirm our findings and to explore potential benefits, primarily by reducing antibiotic consumption, and secondarily by decreasing the side effects of antibiotics and reducing antimicrobial resistance. Future research efforts should also be focused on molecular diagnostic techniques to aid in more rapid organism detection, and to allow earlier decisions on therapy appropriateness and de-escalation.

**Conclusion**

The implementation of a procalcitonin-based algorithm seems to reduce antibiotic exposure in ICU burn patients without compromising the main clinical outcome parameters, such as mortality, duration of mechanical ventilation or duration of ICU stay. Taking into account the limitations of this study, future large-scale trials establishing the potential benefits and cost-effectiveness of the use of the procalcitonin-guided treatment protocol in burn patients are warranted.

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**BIBLIOGRAPHY**


