Early sepsis markers in patients admitted to intensive care unit with moderate to severe diabetic ketoacidosis

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Abstract

Background

Bacterial infections are frequent triggers for diabetic ketoacidosis. In this context, delayed antibiotic treatment is associated with increase morbidity and mortality. Unnecessary administration of antimicrobial therapy might however also negatively impact the prognosis. The usefulness of traditional sepsis markers in diabetic ketoacidosis has not been assessed. Thus, we sought to investigate diagnostic performances of clinical and biological sepsis markers during diabetic ketoacidosis.

Methods

Patients admitted in a single intensive care unit for diabetic ketoacidosis (defined by pH < 7.3 and glycaemia > 13.75mmol/L) were retrospectively analyzed. Clinical and biological markers were evaluated to determine their ability to identify infected from non-infected patients.

Results

Between 2011 and 2018, among 134 episodes of diabetic ketoacidosis, 102 were included (91 patients). Twenty out of 102 were infected. At admission, procalcitonin (median: 3.58ng/mL vs 0.52ng/mL, p<0.001) and presence of fever, defined as temperature > 38°C, (25% vs 2.5%, p=0.007) were different between infected patients and non-infected patients in both univariate and multivariate analysis. Whole blood count, neutrophils count and presence of hypothermia were not different between both groups. The diagnostic performance analysis for procalcitonin revealed an area under the curve of 0.87 with an optimal cutoff of 1.44ng/mL leading to a sensibility of 0.90 and a specificity of 0.76. Combining procalcitonin and presence of fever allowed distinguish infected from non-infected patients. Indeed, all patients with procalcitonin level of more than 1.44ng/mL and fever were infected patients. The presence of one of these 2 markers was associated with 46% of infected patients. No afebrile patient with procalcitonin level less than 1.44 ng/mL was infected.

Conclusion

At admission, combining procalcitonin with a threshold above 1.44 ng/mL and presence of fever may be of value to distinguish infected from non-infected patients admitted in intensive care unit for
Introduction
Diabetic ketoacidosis (DKA) accounts for 4-9% of all hospital discharge summaries among diabetic patients\cite{1, 2}. Despite a 50% drop in mortality since 1980 due to standardized protocols\cite{3}, recent studies still report a mortality rate of about 2-15%, mostly depending on the age of the patients\cite{4, 5}. Therapeutic guidelines on DKA almost only focus on insulin administration and hydroelectrolytic supplementation\cite{6, 7}.

Discontinuation of insulin therapy and infections are the most frequent triggering factors\cite{2, 5, 8}.

Bacterial infections - urinary tract infections in the first place, followed by pneumonia - explain up to 50% of ketoacidosis cases\cite{6, 8, 9}. In the context of DKA, bacterial infections are reported to increase both mortality\cite{10} and length of stay\cite{9}. Then, early detection of bacterial infections associated with adequate antibiotic treatments are key elements to improve patients’ outcomes. DKA itself can however mimic infections\cite{10} and differentiate septic from non-septic inflammatory response may be difficult. Clinical suspicion of infection can hardly be used and many patients are over-treated with antibiotics leading to inadequate treatment costs, side effects and bacteriological resistance. The development of bacteriological resistance is all the more worrying for these patients admitted for DKA knowing that 20 to 40% of them will develop a new episode of infection in the future\cite{3, 5, 11}.

To our knowledge, no study has already assessed the usefulness of traditional sepsis markers in DKA. The constitutive signs of the systemic inflammatory response syndrome are considered to be poorly specific\cite{12}. Tachycardia and polypnea can be easily integrated in DKA pathophysiology. Hypothermia, fever, and white blood cell count abnormalities are usually considered when assessing septic status. However, none of those signs ever attested to be relevant to distinguish infected from non-infected patients during DKA. Procalcitonin (PCT) is actually one of the major relevant markers for the diagnostic of bacterial infections. PCT is daily used for antibiotic decisions in patients with respiratory tract infections and sepsis\cite{13-15}. Nevertheless some preliminary data suggest that compared with non-diabetic, PCT positive threshold could be higher in diabetic patients, especially during hyperglycemic crisis\cite{16, 17}. We therefore conducted a retrospective study in which we
sought to investigate the diagnostic performance of different sepsis markers (including PCT) to predict bacterial infection in the first 2 days of admission in intensive care unit (ICU) for DKA.

Materials And Methods
Design and Patients: This is a retrospective study performed in the ICU of Avicenne hospital, a French tertiary hospital, in Paris area. All consecutive patients hospitalized for moderate to severe DKA between January 2011 and March 2018 were included. DKA was defined as a glucose concentration $>300$ mg/dL (16.7mmol/L) (either serum or capillary), a pH $\leq 7.25$ or a serum bicarbonate concentration $<15$ mmol/L, and the presence of ketones acetoacetate (either in the blood or the urine) 11, 18. Patients were not included if they had one or more criteria known to increase PCT without any notion of bacterial infection (medullary thyroid carcinoma, small cell lung cancer, cardiac arrest, heat stroke, pancreatitis, malaria, notion of fungal infection, severe trauma) 19.

Ethics: The study was approved by the « Comité d’éthique pour la recherche en Anesthésie-Réanimation » in Paris, France (reference: IRB 00010254 – 2018-029). As a retrospective study of routinely collected and anonymized data, consent was not required, and patients were only informed by letter of their enrollment in the studies.

Data collection: From charts, we extracted the following data at admission (D0): clinical parameters such as history and type of diabetes, comorbidities, diabetes complications, medication, temperature, and biological data such as pH, bicarbonate, first glycaemia available (either by venous or capillary blood punctures), ketonemia, sepsis markers (see below). A follow-up of those parameters was collected on day 2 (D2) when available. Triggering factors of DKA, length of stay in ICU and hospital, and hospital mortality were also collected. Clinical and biological sepsis markers were assessed on D0 and D2. As part of the systemic inflammatory response syndrome, temperature and white blood cell count were collected. Temperature was measured in the armpit area with the addition of a correcting factor (+ 0.5°C). Temperature were then classified: fever ($>38$ °C); apyrexia (36–38 °C) and hypothermia ($<36$ °C) 20. From the whole blood count, white blood cell count (WBC), neutrophil blood count and neutrophils-to-lymphocytes count ratio (NLCR) were extracted. Patients were considered to
have leukocytes abnormalities in case of WBC > 12.0G/L or < 4.0G/L 20. Plasma PCT concentrations were also picked up at D0 and D2. Plasma PCT concentrations were measured using an automated immunofluorescent assay (PCT KRYPTOR®, Thermofisher scientific). PCT concentration was considered normal if below 0.5 ng/mL.

Definition of “Infected Patients”: Patients with a bacteriological documentation on any bacterial sample (urine culture, sputum analysis, blood culture and other specific sample cultures) were classified as “infected patients”. Bacterial samples were only requested in case of suspected infection.

Statistical analysis: A descriptive analysis was performed for all patients and according to infection status: “infected patients” and “non-infected patients”. We performed an univariate analysis to compare these 2 subgroups of patients. Quantitative variables are expressed as median interquartile range (IQR), 25–75% and compared using the Mann-Whitney U test. Categorical variables are expressed as numbers (%) and compared using the Fisher’s exact test. We performed a multivariate logistic regression analysis to assess the relationship between sepsis markers and infection status. Interactions between significant variables during the univariate analysis (threshold of p < 0.05) were tested. As sepsis markers on D0 and D2 are coupled, we used a specific model for each time point.

Receiver operating characteristics (ROC) curves analysis was performed to assess the ability of sepsis markers to predict infection. Optimal cutoff values were chosen to maximize sensitivity and specificity using the Youden index. A P value of ≤ 0.05 was considered to be statistically significant. Statistical analyses were carried out using R version 3.4.1 for Windows® (https://www.r-project.org, accessed June 2019).

Results

Patients: Between January 2011 and March 2018, 134 episodes of DKA (120 patients) were admitted in the ICU. We did not include 32 episodes (29 patients) because of the absence of eligibility criteria, wrong coding diagnosis or missing data (Fig. 1). The remaining 102 episodes (91 patients) were included in the analysis. There were 50 (49.0%) males and 52 (51.0%) females, with a mean age of 46 years (29–58 years) (Table 1). Type 1 diabetes
was the most frequent type of diabetes (n = 60 episodes, 58.8%) and inaugural DKA accounted for 17.6% (n = 18 episodes). Eight patients (8.8%) had recurrent episodes of DKA (2 episodes: 6 patients, 3 episodes: 1 patient, 4 episodes: 1 patient). Triggering factors were poor compliance to antidiabetic treatments and bacterial infection, for 50.0% and 19.6% of the episodes respectively. For 21 episodes (20.6%), no triggering factor was identified. At ICU admission, median pH and bicarbonate were 7.14 [7.05–7.24] and 6.0 mmol/L [3.5–10.4 mmol/L] respectively. On D2, ketoacidosis was corrected as attested by a median pH of 7.41 [7.38–7.43] and glycaemia 6.6 mmol/L [5.2–11.0 mmol/L].
Table 1
Demographic and clinical baseline characteristics of the patients.

| Variables                              | All Cohort (n = 102) | Infected patients (n = 20) | Non-infected patients (n = 82) | p value\(^a\) |
|----------------------------------------|----------------------|----------------------------|--------------------------------|----------------|
| Age, year, median [IQR]                | 47 [29–58]           | 56 [48–64]                 | 41 [28–57]                     | 0.003          |
| Males, n (%)                           | 50 (49.0%)           | 9 (45.0%)                  | 41 (50.0%)                     |                |
| Body mass index, kg/m\(^2\), median [IQR] | 23.65 [20.97–26.54]  | 24.49 [20.89–30.25]        | 23.63 [21.05–26.30]            |                |
| Inaugural diabetes ketoacidosis, n (%) | 18 (17.6%)           | 7 (35.0%)                  | 11 (13.4%)                     | 0.045          |
| Type 1 diabetes mellitus, n (%)        | 61 (59.8%)           | 7 (35.0%)                  | 54 (65.9%)                     | 0.021          |
| Type 2 diabetes mellitus, n (%)        | 23 (22.5%)           | 6 (30.0%)                  | 17 (20.7%)                     | ns             |
| Insulin-dependent diabetes mellitus, n (%) | 72 (70.6%)           | 9 (45.0%)                  | 63 (76.8%)                     | 0.006          |
| Hypertension, n (%)                    | 30 (29.4%)           | 5 (25.0%)                  | 25 (30.5%)                     |                |
| Dyslipidemia, n (%)                    | 19 (18.6%)           | 4 (20.0%)                  | 15 (18.3%)                     |                |
| Ischemic heart disease, n (%)          | 7 (6.9%)             | 2 (10.0%)                  | 5 (6.2%)                       |                |
| Diabetic retinopathy, n (%)            | 27 (26.7%)           | 4 (20.0%)                  | 23 (28.4%)                     |                |
| Chronic kidney disease, n (%)          | 24 (23.8%)           | 5 (25.0%)                  | 19 (23.5%)                     |                |
| Smoking, n (%)                         | 43 (42.2%)           | 5 (25.0%)                  | 38 (46.3%)                     | ns             |
| Alcohol, n (%)                         | 24 (23.5%)           | 4 (20.0%)                  | 20 (24.4%)                     |                |
| Insulin, n (%)                         | 72 (70.6%)           | 9 (45.0%)                  | 63 (76.8%)                     | 0.006          |
| Metformin, n (%)                       | 23 (22.5%)           | 6 (30.0%)                  | 17 (20.7%)                     | ns             |
| Sulfonylurea, n (%)                    | 8 (7.9%)             | 3 (15.0%)                  | 5 (6.2%)                       | ns             |
| No antidiabetic, n (%)                 | 18 (17.6%)           | 7 (35.0%)                  | 11 (13.4%)                     | 0.045          |
| Poor compliance to antidiabetic treatment, n (%) | 51 (50.0%)         |                            |                               |                |
| No triggering factors, n (%)           | 21 (20.6%)           |                            |                               |                |
| Infection, n (%)                       | 20 (19.6%)           |                            |                               |                |
| Others, n (%)                          | 11 (10.8%)           |                            |                               |                |
| pH, median [IQR]                       | 7.14 [7.05–7.24]     | 7.15 [7.02–7.27]           | 7.14 [7.05–7.22]               | ns             |
| Bicarbonate, mmol/L, median [IQR]      | 6.00 [3.50–10.40]    | 8.00 [4.15–10.55]          | 5.90 [3.30–10.30]              | ns             |
| Glycemia, mmol/L, median [IQR]         | 27.5 [26.1–30.6]     | 27.5 [25.1–29.0]           | 27.5 [26.1–30.9]               |                |
| Ketonemia, mmol/L, median [IQR]        | 6.0 [5.1–6.9]        | 5.00 [3.95–5.93]           | 6.1 [5.3–7.0]                  | 0.007          |
| SAPS II, median [IQR]                  | 29 [21–40]           | 45 [35–58]                 | 26 [20–36]                     | < 0.001        |
| Antibiotics treatments, n (%)          | 45 (44.1%)           | 20 (100.0%)                | 25 (30.5%)                     | < 0.001        |
| ICU length of stay, day, median [IQR]  | 2 [1–4]              | 7 [6–12]                   | 2 [1–3]                        | < 0.001        |
| Hospital length of stay, day, median [IQR] | 9 [6–14]           | 20 [12–24]                 | 8 [6–12]                       | < 0.001        |
| Death, n (%)                           | 2 (2.0%)             | 1 (5.0%)                   | 1 (1.2%)                       |                |

\(^a\)Significant difference (p < 0.05) between infected and non-infected patients are reported in the “p value” column. IQR: interquartile range 25–75%, ICU: Intensive care unit, SAPS II: simplified acute physiology score II.

Infections: Among the 102 (19.6%) episodes, 20 were classified “infected patients”. These patients were older...
and have more frequently inaugural DKA compared with non-infected patients (Table 1). On D0, ketonemia was significantly lower and gravity score [simplified acute physiology score II (SAPS II)] was significantly higher for infected patients. On D2, correction of DKA was similar in both groups. Antibiotics were administered to 45 patients: 20/20 (100%) for infected patients versus 25/82 (30.5%) for non-infected patients. Length of stay in ICU and hospital were higher for infected patients (7 vs 2 days, p < 0.001 and 8 vs 20 days, p < 0.001 respectively).

Sepsis markers at ICU admission:

Univariate analysis: On D0, temperature, fever rate and PCT level were significantly higher in infected patients compared with non-infected patients (36.9 [36.2–38.0] °C vs 36.4 [35.7–36.8] °C; 5 (25%) vs 3 (4%) episodes and 3.58 [1.87–11.24] vs 0.52 [0.19–1.38] ng/mL respectively). The other sepsis markers (hypothermia, WBC, neutrophil count, leukocytes abnormalities and NLCR) did not significantly differ between groups (Table 2).

Multivariate analysis: Adjustment for age, type of diabetes, insulin treatment, ketonemia and SAPS II (significant variables during the univariate analysis) revealed that PCT [OR = 1.27, 95% confidence interval (IC95) [1.04–1.63] (p = 0.029) for each point of increase of PCT] and presence of fever [OR = 27.86, IC95 [1.97-887.92] (p = 0.023)] were independently associated with infection.

| Variables                        | Admission                        | Day 2                          |
|----------------------------------|----------------------------------|--------------------------------|
|                                  | Infected patients (n = 20)       | Non-infected patients (n = 82)  | p-value<sup>a</sup> | Infected patients (n = 20) | Non-infected patients (n = 82) | p-value<sup>a</sup> |
| Temperature, °C, median [IQR]    | 36.9 [36.2–38.0]                 | 36.4 [35.7–36.8]                | 0.032                | 38.4 [37.1–39.0]            | 37.0 [36.8–37.3]            | <0.001        |
| Fever, n (%)                     | 5 (25.0%)                        | 3 (3.6%)                        | 0.007                | 12 (60.0%)                  | 7 (8.5%)                     | <0.001        |
| Hypothermia, n (%)               | 4 (20.0%)                        | 26 (31.7%)                      | 0.410                | 0 (0.0%)                    | 1 (1.2%)                     | 1             |
| WBC, G/L, median [IQR]           | 16.85 [14.25–22.15]              | 15.40 [12.30–22.50]             | 0.606                | 13.05 [8.68–18.23]          | 8.15 [6.68–10.20]            | <0.001        |
| Leukocyte abnormalities, n (%)   | 18 (90.0%)                       | 62 (75.6%)                      | 0.232                | 11 (55.0%)                  | 14 (17.1%)                   | 0.001         |
| Neutrophils count, G/L, median [IQR] | 13.30 [12.01–18.24]             | 13.71 [9.69–20.88]              | 0.673                | 10.79 [7.39–16.64]          | 5.38 [3.60–7.62]             | <0.001        |
| NLCR; median [IQR]               | 14.04 [8.79–19.07]               | 11.40 [5.78–19.27]              | 0.359                | 11.54 [7.63–23.99]          | 2.84 [1.56–4.96]             | <0.001        |
| Procalcitonin, ng/mL, median [IQR]| 3.58 [1.87–11.24]                | 0.52 [0.19–1.38]                | <0.001               | 7.43 [2.63–22.70]           | 0.42 [0.14–1.42]             | <0.001        |

<sup>a</sup>Significant difference (p < 0.05) between infected and non-infected patients are reported in the “p-value” column. bFever: Temperature > 38 °C. cHypothermia: Temperature < 36 °C. dLeukocyte abnormalities: white blood cell count > 12000/mm3 or < 4000/mm3. IQR: interquartile range 25–75%, WBC: white blood cell count, NLCR: neutrophils-to-lymphocytes count ratio.
ROC curves: The area under the curve (AUC) for PCT was 0.87 (IC95 [0.79–0.94]) (Fig. 2A). The optimal threshold was obtained at 1.44 ng/mL leading to a sensibility (Se) of 0.90 (IC95 [0.75-1.00]) and specificity (Sp) of 0.76 (IC95 [0.66–0.84]). The AUC for temperature was 0.66 (IC95 [0.50–0.81]) with an optimal threshold of 36.8°C (Se: 0.65 IC95 [0.45–0.85] ; Sp: 0.65 IC95 [0.56–0.75]) (Fig. 2B).

Performance of PCT and fever (> 38.0 °C) for the diagnosis of infection (Fig. 3): Association of a high PCT level (PCT > 1.44 ng/mL) with or without presence of fever for the diagnosis of infection was then investigated. All patients with PCT level of more than 1.44 ng/mL (defined using ROC curves, see above) and fever were infected patients. The presence of one of these 2 markers was associated with 46% of infected patients. No afebrile patient with PCT level less than 1.44 ng/mL was infected.

Sepsis markers at D2:
Univariate analysis: On D2, more differences appeared between the two groups. Indeed, temperature, fever rate, WBC, neutrophil count, leukocytes abnormalities, NLCR and PCT were significantly higher in infected patients (Table 2). Both groups were also different when looking at any episode of fever during the first 2 days of hospitalization (infected patients: 60.0% vs non-infected patients: 9.1%, OR = 14.3 IC95% [4.0–58.0], p < 0.001). In infected patients, between D0 and D2, NLCR and PCT did not change significantly (p = 0.968 and p = 0.283 respectively). Whereas in non-infected patients, NLCR (D0: 13.42 vs D2: 5.37, p < 0.001) and PCT (D0: 0.51 ng/mL vs D2: 0.39 ng/mL, p = 0.005) significantly decreased [see Table S1 and S2 in the Additional file 1].

Multivariate analysis: Adjustment for age, type of diabetes, insulin treatment and ketonemia and SAPS II during the multivariate analysis revealed that only PCT was independently different between both groups [OR = 4.45, IC95 [1.73–39.53] (p = 0.030) for each point of increase of PCT]. Presence of fever and WBC were not different.

ROC curves: The AUC for PCT was 0.91 (IC95 [0.84–0.99] with an optimal threshold at 2.78 ng/mL leading to a Se of 0.74 (IC95 [0.53–0.89] and a Sp of 0.96 (IC95 [0.89-1.00]) [see Figure S1 in the Additional file 1]. The AUC for temperature, WBC, neutrophil count and NLCR were 0.79, 0.78, 0.84 and 0.87 respectively [see Figure S2 in the Additional file 1].

Discussion
This is the first study to assess the diagnostic performance of different sepsis markers to predict infection for patients with DKA, admitted in ICU. Fever and high PCT (threshold above 1.44 ng/mL at D0) at ICU admission may
help to identify patients with bacterial infection in the context of DKA

The only clinical marker was temperature. Presence of fever on D0 and D2 was higher in the infected patients as reported in previous studies [10]. Nevertheless, in non-infected patients, body temperature ranged from 32.9 °C till 38.7 °C on D0. This huge variation may be explained by thermoregulatory function impairment in diabetic patients [21]. Hypothermia (temperature < 36 °C) was equally presented in both groups. In 1978 Gale et al. reported twenty patients with hypothermia during DKA and observed a high mortality rate (60%) [22]. Hypothermia was also associated with infection [23]. In our study, we neither found an increase in mortality nor an association with sepsis for hypothermic patients.

Other classical sepsis markers were also found to be inefficient in our study to differentiate infected patients from non-infected patients. We found a high WBC level on D0 (mostly composed of neutrophil polynuclears) in non-infected patients. Such leukocytosis, as high as 57.0G/L, has already been reported in several case reports [24, 25] and we found a correlation between WBC level and pH. This result leads to reconsider the usefulness of WBC to predict bacterial infection at admission. Recently, the NLCR was proposed to be a more useful diagnostic tool than other blood tests to identify patients with bacterial infection [26]. However, in our study we did not highlight any difference for this marker between both groups at admission.

PCT, a precursor of calcitonin, is amplified as part of the systemic response to bacterial infections [27]. Our study emphasized the interest of PCT to predict infection, with a good predictive value above the level of 1.44 ng/mL at D0. In febrile patients admitted in the emergency department, Hausfater et al. stated that a 0.2 ng/mL cutoff value for PCT had a low Se and Sp to diagnose bacterial infections (0.77 and 0.59%) [28]. Wacker et al. in their meta-analysis [29] focusing on the accuracy and clinical value of PCT for diagnosis of sepsis in critically ill patients reported a Se and Sp of 0.77 and 0.79 respectively. Sager et al. recently summarize the use of PCT to guide sepsis diagnosis [30]. For critically ill patients, bacterial infection was considered to be “likely” when PCT level was 0.5-1.0 ng/mL and to be “very likely” above 1.0 ng/mL. In our study, PCT was accurate at the admission to distinguish infected from non-infected patients with a sensibility of 0.90 and a specificity of 0.76. However, the positive threshold seems to be higher than usual in our study (optimal cutoff on D0: 1.44 ng/mL). Previous studies already reported huge cutoff heterogeneity. For example, Wacker et al. in their meta-analysis [29] reported a median cutoff of 1.1 ng/mL (IQR 0.5-2.0 ng/mL). However, a participation of the hyperglycemic crisis in the
increase of the PCT could not be excluded. Indeed, Aksu et al. had reported a decrease in PCT level following a normalization of glycaemia in patients with acute hyperglycemic crisis [31]. In our study, we also reported a high level of PCT in patients without infection, with a PCT drop following normalization of glycaemia. High PCT levels were recently reported in different case reports or case series focusing on diabetes ketoacidosis without infection [32, 33]. A case series of 5 patients hospitalized for diabetes ketoacidosis reported PCT levels ranging from 6.87 to 30.47 ng/mL. Interestingly, this observation was not found in case of hyperosmolar hyperglycemic syndrome. This led the author to conclude that the augmentation of PCT in acute glycemic crisis may only be found during diabetes ketoacidosis [33].

In early management of DKA, traditional clinical (hypothermia) and biological (WBC, NLCR) signs of bacterial infection proved to be ineffective, probably because of the reported correlation between hyperglycemia crisis and inflammatory response. In non-diabetic patients, induced hyperglycemia led to an amplification of Interleukine-6 (IL-6) and other pro-inflammatory markers [34]. Adding low doses of insulin avoids these alterations even with persistent hyperglycemia [34]. Compared with healthy controls, an induced hyperglycemia in diabetic patients results in a more pronounced secretion of pro-inflammatory cytokines such as Tumor Necrosis Factor-α (TNF-α) and IL-6 [35]. Apart from any bacterial infection, TNF-α is known to induce the release of large amount of PCT in both animals [36] and humans [37]. These data may explain the increase of both PCT and WBC in non-infected patients on D0. Combining PCT and presence of fever may help to be more specific. Indeed, only infected patients presented both signs whereas there was no infected patient in the absence of both signs (Fig. 3). On D2, after administration of insulin and correction of glycaemia, the nearby normalization of PCT and WBC in non-infected patients may be explained by the correction of this inflammatory state, allowing to distinguish two different patterns: infected and non-infected patients. In the former group, episodes of fever occur and high levels of PCT, WBC, neutrophil count and NLCR still persist on D2. In the latter, there is a decrease, if not a normalization, of all the aforementioned markers following the correction of glycaemia. Thus, on D0, infection status should be based on PCT level and presence of fever regardless of WBC or hypothermia occurrence. On D2, after normalization of glycaemia, usual markers recover their discriminating potential and can enable the reassessment of antibiotic prescriptions if started on D0.

This study has some limitations. First, it was a monocentric retrospective analysis which limits the generalizability
of the results. However, PCT and WBC measurement were systematically assessed for every patient admitted for DKA in our center. Second, the sample size is small and may induce bias. Despite these limitations, our study was a “real-life” observation of the population and was consistent with previous studies regarding triggering factors [2], survival rate [4] and increased length of stay in infected patients [9]. Prospective studies will be needed to confirm the interest and the diagnostic thresholds of these markers, before assessing their utility in a strategy to reduce antibiotic exposure.

Conclusions
At admission, our study showed that WBC, neutrophils count and hypothermia should not be taken into account in the diagnosis process of infection in diabetes ketoacidosis patients admitted in intensive care unit. Only fever and PCT (with a higher threshold than usual: 1.44 ng/mL) may help distinguish infected from non-infected patients. By combining those two markers reduction of antibiotic misuse may be possible.

Abbreviations
AUC
Area under the curve
D0
Admission
D2
Day 2
DKA
Diabetic ketoacidosis
IC95
95% confidence interval
ICU
Intensive care unit
IQR
Interquartile range
NLCR
Neutrophils-to-lymphocytes count ratio
PCT
Procalcitonin
ROC
Receiver operating characteristics
Declarations

Ethics approval and consent to participate

The study was approved by the « Comité d’éthique pour la recherche en Anesthésie-Réanimation » in Paris, France (reference: IRB 00010254 - 2018 – 029). As a retrospective study of routinely collected and anonymized data, consent was not required, and patients were only informed by letter of their enrollment in the studies.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

All authors have done substantial contributions to conception and design. FB and JC collected, analyzed and interpreted the data and were the main writers of the manuscript. BP analyzed and interpreted of the data. AP, RC, GVDM, HB, SG, and YC made important intellectual contributions to the manuscript. All authors read and approved the final manuscript.

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Additional File

File name: Additional File 1

File format: PDF .pdf

Titles and descriptions of data:

Table S1: Sepsis markers in infected patients at admission and day 2 (Univariate analysis).

Table S2: Sepsis markers in non-infected patients at admission and day 2 (Univariate analysis).

Figure S1: Receiver operating characteristics curve of procalcitonin on day 2. The area under curve (AUC) was 0.91 with optimal cutoff at 2.78ng/mL leading to a sensibility and specificity of 0.74 (IC95 [0.53-0.89]) and 0.96
(IC95 [0.89-1.00]) respectively. Positive and negative likelihood ratio were 18.5 and 0.25 respectively.

**Figure S2: Receiver operating characteristics curve of whole blood count and temperature on day 2.** Receiver operating characteristics curve of neutrophils-to-lymphocytes count ratio, white blood cell count, neutrophil count and temperature are represented in (A), (B), (C) and (D) respectively. (A) The area under curve (AUC) of the **neutrophils-to-lymphocytes count ratio** was 0.87 (IC95 [0.80-0.95]) with optimal cutoff at 6.81 leading to a sensibility (Se) and specificity (Sp) of 0.80 (IC95 [0.60-0.95]) and 0.83 (IC95 [0.74-0.83]). (B) The AUC of the **white blood cell count** was 0.78 (IC95 [0.65-0.90]) with optimal cutoff at 10.55G/L leading to a Se and Sp of 0.70 (IC95 [0.50-0.90]) and 0.76 (IC95 [0.68-0.85]). (C) The AUC of the **neutrophil count** was 0.84 (IC95 [0.75-0.93]) with optimal cutoff at 6.59G/L leading to a Se and Sp of 0.90 (IC95 [0.75-1.00]) and 0.64 (IC95 [0.53-0.74]). (D) The AUC of the **temperature** was 0.79 with optimal cutoff at 38.2ºC leading to a Se and Sp of 0.60 (IC95 [0.40-0.80]) and 0.96 (IC95 [0.92-1.00]).

**Figures**
Flow Chart of study population and sample size. Shown is the disposition of the trial.
Receiver operating characteristics curve of Procalcitonin (PCT) (A) and Temperature (B) at admission. For PCT, the area under curve (AUC) was 0.87 with optimal cutoff at 1.44ng/mL leading to a sensitivity and specificity of 0.90 (IC95 [0.75-1.00]) and 0.76 (IC95 [0.66-0.84]) respectively. Positive and negative likelihood ratios were 3.75 and 0.13 respectively. For Temperature, the area under curve (AUC) was 0.66 with optimal cutoff at 36.8ºC leading to a sensitivity and specificity of 0.65 (IC95 [0.45-0.85]) and 0.65 (IC95 [0.56-0.75]) respectively. Positive and negative likelihood ratios were 1.86 and 0.54 respectively.
Procalcitonin (PCT) and fever as markers of infection at admission. Results are shown in percent of patients infected over total patients presenting both (100%), either one (46%) or none (0%) of PCT >1.44ng/mL and fever. PCT is expressed in ng/mL. Fever is retained in case of temperature > 38ºC.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.
Additional File 1.pdf