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Title page

Title of manuscript: **Usefulness of serum procalcitonin and point-of-care multiplex PCR gastrointestinal panel in acute diarrhea or colitis in the emergency department**

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Usefulness of serum procalcitonin and point-of-care multiplex PCR gastro-intestinal panel in acute diarrhea or colitis in the emergency department

Abstract (243 words)

Introduction: Acute infectious diarrhea is one of the most common diseases worldwide. Procalcitonin (PCT) is useful for antibiotic stewardship in lower respiratory tract infections but has been poorly studied in infectious diarrhea. Our objective is to describe the PCT concentrations according to diarrhea etiology.

Methods: This is a single-center prospective cohort study involving adults consulting the emergency department (ED) for an acute diarrhea or colitis. Serum PCT was measured and a stool sample was tested with FilmArray® Gastro-Intestinal Panel. The primary endpoint is the PCT concentration according to each type of pathogen identified using Gastro-Intestinal-panel and/or stool cultures at ED admission.

Results: 125 patients were included: 80 had an acute infectious diarrhea, 21 an acute colitis and 24 another illness causing diarrhea. The median (interquartile ranges) PCT values (ng/ml) were 0.13 (0.08-0.28), 0.07 (0.06-0.54), 0.13 (0.09-0.26) and 0.05 (0.03-0.17), respectively if there was a bacteria (n=41), parasite (n=3), virus (n=10) or no pathogen identified and 0.34 (0.13-1.03) if the diarrhea was due to another illness (n=24).

Conclusion: In patients admitted to the ED with an acute infectious diarrhea or acute colitis, PCT remained low when a bacteria was identified. It may not be informative in current practice to guide antibiotic therapy.

Introduction

Acute diarrhea is a major cause of morbidity and mortality worldwide (1) as well as a common reason for admission in the emergency department (ED). Acute colitis usually presents with diarrhea with or without dysentery, abdominal pain, and low-grade fever (2). The etiology of infectious diarrhea or colitis may be viral, bacterial or parasitic (1).

In adults, diagnostic approach in ED includes clinical history and careful examination . Inflammation markers, such as C-reactive protein (CRP) and blood leukocytes count lacks sensibility and specificity to identify a bacterial infection with no cut-off value able to discriminate between bacterial and viral infections (3). Stool culture is usually performed to search for bacteria and parasites, with a result at least 48 hours later and a positivity rate below 50% (4). Consequently, the physician generally has to provide an etiological diagnosis with few elements. This may lead to a prescription of a probabilistic anti-microbial therapy that will be re-evaluated few days later, according to the results of the stool culture.

In the last decade, the development of real-time PCR-based multiplex stool testing displaying a result within one hour, has allowed a fast identification of the main viral, bacterial and parasitic pathogens involved in acute diarrhea. Numerous studies have confirmed PCR interest (5,6), but so far it has not been implemented routinely in the ED.

Procalcitonin (PCT) is assumed to be a pro-hormone of the acute phase of inflammation in response to a systemic bacterial infection, with kinetics faster than that of CRP. In contrast, viral infections result in down regulation of PCT synthesis, which is mediated by interferon-gamma (9). Numerous studies have shown that PCT-driven algorithms substantially reduced antibiotic use, mainly in lower respiratory tract infections (7,8).

To our knowledge, there are few studies about the usefulness of PCT in gastro-intestinal infections in adults (10,11). As PCT appears to be useful for antibiotic stewardship in respiratory infections, the objective of this study is to explore the PCT usefulness in acute diarrhea and colitis. Secondary objectives include the evaluation of feasibility, accuracy and added value of point-of-care real-time PCR-based multiplex gastrointestinal panel compared with stool culture, in the ED.

Methods

Study Design

This is a single-center prospective cohort study involving adult patients admitted for a suspicion of acute infectious diarrhea or acute colitis to the ED of a large 1600-bed academic hospital. The protocol of the study was approved by the ethics committee (comité de protection des personnes (CPP) “Sud Méditerranée” the 7/02/2020) and was registered in Clinical Trials under the number NCT04237181, the 23/01/2020. The research was performed in accordance with relevant guidelines/regulations.

Participant selection

Patients over 18 years old with a social security insurance, were included when attending the ED for acute diarrhea (defined by at least three loose or liquid stools a day for less than 15 days); or for a documented colitis (defined by an abdominal CT scan showing a thickening of at least segmental colonic walls) presumed to be of infectious origin. A written informed consent was signed by each patient.

The patients were excluded if they had an abdominal surgery within the last month, in case of pregnancy, history of inflammatory bowel disease (IBD) or if they were under guardianship, curatorship or unable to express their consent.

Procedures and follow-up

Patients were included after the prescription of the usual blood sampling by the ED physician. The sample was sent analyzed by the hospital central laboratory. PCT measurement (Elecsys® Roche Diagnostics France) was then systematically added without additional blood sampling.

In accordance with usual care, a stool sample was obtained in the ED and sent to the microbiology laboratory for stool culture, to search for *Salmonella enterica*, *Shigella*, *Yersinia*, *Clostridium difficile* and *Campylobacter*. At the same time, the stool sample was tested directly in the ED by a clinical research assistant (CRA), on the BioFire® FilmArray® Torch System with multiplex PCR Gastro-Intestinal (GI)

panel (bioMérieux, Marcy l'Etoile, France). In case no stool could be provided in the ED, a rectal swab was used and tested on the GI panel, which is an off-label use (12,13).

Before receiving the results of the GI panel and PCT, the ED physician taking care of the included patient was asked by the CRA about the decision to start an antibiotic therapy. The same question was asked after the reception of both results, in order to evaluate if PCT and/or GI panel results modified the physician's decision.

Patients received a phone call 15 days after their initial admission in the ED, to assess if there was another final diagnosis other than the one delivered in the ED or a treatment modification. If still hospitalized at the 15th day, the patient's medical chart was consulted.

Data collection

For each patient, we collected the following data:

- From the ED medical electronic file: past medical and surgical history, vital parameters at triage, current medical history
- Biological data through the laboratory information system: usual biological parameters, results of PCT and stool culture
- Filmarray® GI panel results in the ED
- ED physician decision on antibiotic initiation before and after the reception of PCT and GI panel results
- Data on follow-up at 15 days (by phone call): duration of antibiotic therapy and total duration of digestive symptoms

Endpoints

The primary endpoint was the value of PCT concentration according to each type of pathogen identified using GI-panel and/or stool cultures at ED admission.

Secondary endpoints were the positivity rate and distribution of pathogens identified by the GI panel and stool culture; the rate of antibiotic therapy initiated in the ED and in the first 15 days; the number of days of

antibiotic exposure at day 15 and the rate of antibiotics prescription decision before and after results of the GI panel together with PCT.

Statistical analysis

To our knowledge, there were few published studies evaluating PCT measurement in this population and allowing sample size estimation. We decided to include as many patients as possible during 1-year, in order to cover the epidemiological seasonal variations, and to obtain a convenient sample of at least 100 patients. In this manner, we decided to not compare statistically PCT values and to only describe our population.

Clinical and biological data are described, for quantitative variables, as median and interquartile range (IQR) or mean +/- standard deviation (SD) according to the normality of the distribution or as number and percentage for qualitative variables.

Regarding our primary endpoint, PCT concentrations are reported as median and IQR in 5 groups: viral, bacterial or parasitic infection, presumed infectious diarrhea with no pathogen identified by GI panel and/or stool culture, and in diarrhea due to another illness (diagnosis made by the ED physician based on the results of complementary exams: for example, urinary tract infection).

Statistical analysis was performed on R studio, version 1.2.5019.

Results

From March 10th 2020 to December 10th 2021, 125 patients were included (Fig 1). Table 1 presents the baseline clinical characteristics and complementary exams performed in the ED. Mean age was 51 years (+/- 20.5) and 66 (53%) were women. Most patients (76%) had significant past history, mainly cardiovascular (34.7%). For one patient, PCT was inadvertently not prescribed. The other laboratory tests were prescribed at the discretion of the treating physician (Table 1).

Eighty patients (64%) had a diagnosis of acute diarrhea presumed to be of infectious origin, 21 (16.8%) were diagnosed as having an acute infectious colitis, while the remaining 24 (19.2%) had another illness causing diarrhea, like an extra-intestinal infection or an adverse effect of a medication.

The GI Panel was tested point-of-care in all patients during ED stay: on a stool sample for 64 patients (51.2%) and on a rectal swab for 61 patients (48.8%) that were not able to provide a stool sample at ED. Sixty-eight patients (54.4%) had a stool culture either in ED or general wards.

According to the GI-panel, a pathogen was identified for 55 (44%) patients: 41 (32.8%) patients were positive for a bacteria (Table 2), with 11 patients having more than one bacteria identified, 10 were positive for a virus and 3 for a parasite. One patient had both a bacteria and a virus detected by the GI-Panel (Campylobacter and Adenovirus).

The stool culture was positive in 16 patients (23.5% of stool cultures) and the parasitological exam was performed and positive in 2 patients (Table 2). The results were available in a median (IQR) of 3 (3-4) days. All the positive stool culture results matched with the ones found with the GI-Panel.

The median PCT concentration was below 0.25ng/ml in most groups except for diarrhea due to another illness (Table 3 and Fig 2).

In a sub-group of patients diagnosed with an acute diarrhea presumed to be of infectious origin (n=80), there were 24 (30%) bacteria detected, 9 virus (11%), 3 parasite (3,8%) and 44 (55%) patients with no pathogen detected by the GI-Panel and/or stool culture. The median (IQR) PCT concentration (ng/ml) was, respectively, 0.13 (0.08-0.28), 0.13 (0.09-0.26), 0.07 (0.06-0.54) and 0.05 (0.02-0.13).

In a sub-group of patients diagnosed with acute infectious colitis (n=21), 12 had a bacteria (5 Campylobacter, 1 Clostridium, 2 Shigella, 1 Salmonella, 1 Yersinia and 2 E. Coli), while 9 had no pathogen detected. The median (IQR) PCT concentration (ng/ml) was, respectively, 0.14 (0.08-0.30) and 0.14 (0.11-0.18).

The median (IQR) CRP concentration was 66.5mg/l (26.5-94.02) and 19.9(17.26-24.41), respectively, if there was a bacteria or virus detected (Table 3).

Before the reception of both PCT and GI-Panel results, there was a decision to start antibiotics for 38 patients (30.4%). Of these, the antibiotic decision was subsequently stopped for 2 patients because no pathogen was detected on the GI-Panel and for 4 patients the initial antibiotic regimen was modified and

adapted to the bacteria detected. Of the 87 patients (69.6%) with no initial antibiotic prescription, the decision was modified after obtaining the GI-panel and PCT results to initiate antibiotics for 17 patients.

The total rate of antibiotics prescription at ED discharge was 42% (n=53) and the median duration of antibiotics was 7 (3-8) days.

Discussion

We performed a prospective exploratory observational study on 125 patients presenting to the ED with an acute diarrhea. In our population of patients with acute infectious diarrhea and colitis, the serum PCT concentration was low when a bacteria, a parasite or a virus was detected by the GI-Panel which does not support the use of this biomarker in antibiotic stewardship in this setting. Instead, when there was another illness causing diarrhea, like an extra-intestinal infection, cancer or an adverse effect of a medication, median serum PCT was higher than the cut-off of 0.25ng/ml and may alert the ED physician in searching another etiology.

Few studies have evaluated the PCT values in this population. Thia et al (11) evaluated prospectively the usefulness of serum PCT in 81 patients diagnosed with gastroenteritis (GE) confronting the results to both stool and blood culture. Mean PCT concentrations were significantly higher in patients with bacterial GE than in those with undifferentiated GE (ng/ml, 1.81 ± 0.81 vs 0.20 ± 0.03). The difference observed with our results can be explained by the fact that PCT concentration is not normally distributed (14) and should rather be presented as a median (IQR). Otherwise, the reference diagnostic method used was different, with PCR being a much more sensitive technology (5,15). As a result, in the study from Thia et al, there might have been patients classified as having an undifferentiated GE who, with the use of GI-Panel, would have been included in the bacterial group, decreasing the mean PCT concentration in this group.

CRP is the most frequent biomarker used in the ED in patients presenting with acute diarrhea (3). In our study, it seems to be more informative than PCT in antibiotic stewardship as the values were higher in case of bacterial acute diarrhea. Though, no cut-off has been established, helping in the distinction of bacterial and viral infections, its use is still not recommended (12).

That is why new molecular testing, using real-time PCR methods are interesting (5,6,15,16). The results are available in almost 1hour, which is adapted to an ED setting with the possibility of using a rectal swab when no stools are provided (although it is an off-label use (12,13)). Our positivity rate with GI-panel (44%) agrees with the reported literature, ranging from 30 to 70% (5,6,15).

Finally, the rapid identification of a pathogen modified patient care directly in the ED for 23 patients (18%) whom the initial antibiotic molecule was directly adapted to the pathogen detected. This could have avoided another medical appointment at the time of stool culture results and delayed adaptation in antibiotic treatment (6).

Study Limits

Our study has some limitations. First, this is a single-center study and the sample size is limited. As previous data about PCT concentration in the context of acute diarrhea and colitis were lacking, it was not possible to calculate an adequate sample size to test for statistical differences. Second, we only measured procalcitonin levels on admission and did not study procalcitonin kinetic. Our main purpose was to evaluate if a single measurement on admission would accurately help in differentiating between bacterial, parasitical, viral and non-infectious diarrhea.

However, our results provide important message: to our knowledge this is one of the first studies evaluating serum PCT concentrations in adults with acute infectious diarrhea with the added advantage of testing successfully the feasibility and usefulness of point-of-care PCR multiplex GI panel in the ED.

Conclusion

In a population of patients admitted to the ED with an acute diarrhea or acute colitis, serum PCT was low when a pathogen (either bacterial, viral or parasitic) was detected by PCR multiplex GI-Panel and may not be helpful in antibiotic stewardship. Molecular testing like multiplex PCR GI panel, positioned as a point-of-care device may be very useful in the ED setting (integrated with a physician training on the indication of

anti-infectious treatment according to the pathogen identified), with results provided in 1 hour and a high pathogen detection rate able to guide a pathogen-driven treatment.

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