

The Early C-reactive Protein Trend Does Not Have a Role in Monitoring Acute Diverticulitis Progression

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Rezumat

Modificările precoce ale valorilor proteinei C reactive - lipsite de influență în monitorizarea progresiei diverticulitei

Obiectiv: Investigarea variației valorilor markerilor serologici ai inflamației în timpul spitalizării pacienților cu diverticulită acută și evaluarea rolului evoluției lor inițiale în identificarea timpurie a rezistenței bolii la măsurile tratamentului conservator.

Pacienți și metode: Studiarea retrospectivă a fișelor electronice ale pacienților diagnosticați cu diverticulită acută în Spitalul Universitar Oulu, Finlanda pe o perioadă de 2 ani începând cu decembrie 2006. Formele medii de diverticulită acută au fost tratate cu succes prin tratament conservator. Atunci când este nevoie de o intervenție percutană sau chirurgicală în timpul aceleiași spitalizări sau în interval de o lună de la această spitalizare considerăm că diverticulita acută este într-o formă severă. Compararea mijloacelor variabilelor continue a fost efectuată folosind testul T pentru eșantioane dependente.

Rezultate: Am avut acces la informații privind evoluția inițială a markerilor inflamatori în cazul a 139 de pacienți diagnosticați cu diverticulită acută în formă medie. Valoarea medie a proteinei C reactive înregistrează paradoxal o creștere semnificativă în cazurile fără complicații în timp ce numărul leucocitelor a scăzut în primele 24 de ore de spitalizare. Ulterior,

nivelul proteinei C reactive a cunoscut o scădere zilnică semnificativă, mai mică decât nivelul inițial pe tot parcursul spitalizării rămase. Evoluția inițială a markerilor inflamatori în cazul pacienților cu forme severe a bolii nu s-a modificat semnificativ.

Concluzie: O creștere a valorii proteinei C reactive în primele 24 de ore de spitalizare nu trebuie considerată ca semn al deteriorării stării de sănătate. Această evoluție nu are nici un rol în evaluarea timpurie a progresului clinic al diverticulitei acute, putând induce în eroare medicul și ducând la o supratratere.

Cuvinte cheie: diverticulită acută, evoluția proteinei C reactive, monitorizarea bolii, practică clinică

Abstract

Objective: To investigate the variation of the values of the serum inflammation markers during the hospital stay of patients with acute diverticulitis and to evaluate the role of their initial trend in the early determination of the disease resistance to conservative measures.

Patients and Methods: The electronic records of patients presenting with acute diverticulitis at the Oulu University Hospital, Finland during a 2-year period starting from December 2006 were retrospectively reviewed. Acute diverticulitis that was successfully treated conservatively was graded as mild. Severe disease was considered when a percutaneous or surgical intervention was necessitated during the same hospitalization or within the first month. Comparisons of the means of continuous variables were performed using the paired samples T test.

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Results: One hundred and thirty-nine patients with mild acute diverticulitis had available data concerning the initial trends of the inflammation markers. The C-reactive protein (CRP) mean value showed a paradoxical significant increase in uncomplicated cases whereas the WBC count declined within the first 24 hours of hospitalization. Thereafter the CRP levels showed a significant daily decrease below the initial levels for the remainder of the in-hospital duration. The inflammation markers' initial trends in patients with severe disease did not change significantly.

Conclusion: A rise in the CRP value during the first 24 hours of hospitalization should not be necessarily considered as a deterioration of the clinical status. This trend has no role in the early evaluation of the clinical progression of acute diverticulitis as it may mislead the clinician towards potential invasive overtreatment.

Key words: acute diverticulitis, C-reactive protein trends, disease monitoring, clinical practice

Introduction

Acute colonic diverticulitis is caused by the development of inflammation due to the perforation of a diverticulum and it constitutes a commonly encountered condition in industrialized societies (1). Epidemiologic data show increasing incidence and hospitalization rates due to the disease which augment the economic burden created by the related health expenses (1,2,3).

The mild form of acute diverticulitis is successfully treated conservatively with or without hospitalization (2,4). However, patients who present with the severe form of the disease may necessitate a kind of emergent or urgent intervention which includes percutaneous drainage of an abdominal abscess and/or laparotomy or laparoscopic surgery (5,4).

According to the practice parameters published by the American Society of Colon and Rectal Surgeons the patients in need of an operation at emergent settings are those who show obvious signs of generalized peritonitis (6). The remainder will initially be treated conservatively, however a subset of them will develop severe disease determined by the failure to respond to the supportive therapy and will undergo an intervention at a later interval during the same hospitalization (4,5,6). Nevertheless, there is lack of objective parameters in order to precisely define the failure of the conservative treatment.

There has been much investigation concerning the diagnosis and the computed tomography (CT)-staging of the disease (7, 8). Conversely, there is little information regarding the variation of the values of the laboratory inflammation markers such as the white blood cell (WBC) count and the C-reactive protein (CRP) during the hospitalization of a patient with acute diverticulitis and the association to their initial levels. Knowledge concerning the trends of these laboratory parameters and their correlation with the clinical status may assist the

physician in the on-going evaluation of the severity of the disease.

The purpose of this research is to investigate the variation of the values of the WBCs and the CRP during the hospital stay of patients with acute diverticulitis. It is particularly aimed to document the trend of these factors within the first 24 hours following the presentation of the patient at the emergency department and to evaluate its role in the early determination of the disease resistance to conservative measures.

Materials and Methods

This retrospective investigation was carried out at the Department of Surgery of the Oulu University Hospital, Oulu, Finland. All patients with discharge diagnosis of acute diverticulitis during a 2-year period starting from December 2006 were considered for the herein analysis. The patients were identified using a computer-generated search from a register that contains prospective data concerning diagnoses coded according to the 10th revision of the International Classification of Diseases.

Electronic records were reviewed to retrieve the demographics, the clinical information and the laboratory values at the initial evaluation of the patients at the emergency department as well as during the in-hospital stay. Individuals who had a concomitant disease and/or were receiving therapy that potentially affects the inflammation markers' serum levels were excluded from the analysis. Therefore, history or presence of cancer or autoimmune disease, detection of neoplastic disease of the large bowel in the follow-up colonoscopy, and immunosuppressive treatment comprised the exclusion criteria. Also, patients on a pre-hospital antibiotic therapy or with a previous visit to a physician for the same acute episode were not considered.

In this study, acute diverticulitis was defined as mild whenever medical therapy sufficed for the resolution of an attack. Severe disease was considered in patients who necessitated percutaneous intervention for the drainage of an abscess or operative treatment during the initial hospitalization or the first 30 days. Persistent symptomatology or recurrence within a month from the onset of the episode classified the primary incident as severe. Timely distant recurrences or complications were deemed as separate events and therefore not investigated.

The management of acute diverticulitis at our institution followed the practice parameters suggested by the American Society of Colon and Rectal Surgeons (6). Accordingly, patients presenting with generalized peritonitis were served with an emergent operation. The remainder of the patients were initiated on antibiotic therapy and their clinico-laboratory status was followed serially (4, 6). Thus the presence of a small- or a moderate-sized abscess in the abdominal cavity or of contained extra-luminal air at the baseline CT-scan were not deemed as absolute criteria for an emergent operation (3, 4, 9-11). However, those who were unresponsive to the initial conservative treatment were subsequently addressed with percutaneous intervention and/or surgery (4). Therefore, patients who did not show improvement of their clinical conditions

ulteriorly underwent a sequential CT-scan or laparotomy in order to document the extension of the disease and guide therapeutic decisions accordingly.

All the patients of this series received antibiotic therapy, although subsequent evidence put in challenge this practice in simple phlegmonous disease (12). All patients with mild disease underwent follow-up colonoscopy or CT-colonography at an average interval of 4-8 weeks after the initial attack in order to verify the presence of diverticula and exclude bowel cancer.

Statistical analysis

The statistical software package SPSS 21.0 was used for the analysis. Cases with missing information concerning both the WBC count and the CRP value within the first 24 hours following the patient's presentation at the emergency department and those who underwent an emergent intervention were omitted from the investigation. The comparisons of the means of continuous variables were performed using the paired samples T test. A p-value less than 0.05 of the 2-tailed test was considered significant.

Results

Data from 191 patients with acute diverticulitis were retrieved. One hundred and eighty-two patients with acute diverticulitis fulfilled the inclusion criteria of this study. One hundred and fifty-nine were mild cases and thus treated conservatively, whereas 23 underwent percutaneous drainage and/or operation.

Patients treated conservatively – Mild disease

One hundred and thirty-nine patients treated conservatively had a sequential blood test obtained within the first 24 hours after their presentation at the hospital regarding the WBCs (120 patients) and/or the CRP (131 patients). Their clinical and demographic data are depicted in *Table 1*. The mean WBC count decreased significantly from $11.7 \times 10^9/L$ [± 0.26 standard error (SE)] at the admission to $8.9 \times 10^9/L$ (± 0.25 SE) within the following 24 hours ($p=0.0001$). Overall, 110 out of

Table 1. Clinical and demographic data of 139 patients with mild acute diverticulitis with available data of the serum inflammation markers' 24-hour trend

Age	57,84 ($\pm 1,17$) years
Male gender	53 (38,1%)
Diabetes	12 (8,6%)
Abdominal tenderness in > 1 quadrant	19 (13,6%)
Guarding	50 (36%)
Urinary symptoms	12 (8,6%)
Recurrent disease	54 (38,8%)
White blood cell count	$11,55 \pm 0,25 \times 10^9/l$
C-reactive protein	$103,64 \pm 4,74$ mg/l
Albumin	$40,99 \pm 0,36$ g/l
In-hospital stay	$3,67 \pm 0,182$ days

Continuous data are shown in means \pm standard error

120 cases (91.7%) showed a decrease in the WBCs.

On the contrary, the CRP showed an initial significant increase of its value followed by a latent decline after the first 24 hours which continued for the remainder of the hospitalization of cases with mild disease. Details regarding the trends of the CRP values are shown in *Table 2*. The 69 patients who displayed a rise of the CRP had an initial mean value of 84.4 mg/l (\pm SE 6.5) and a mean value of 130.8 mg/l (\pm SE 7.7) in the second measurement (46.4 mg/l \pm SE 5.7 of difference).

Patients who underwent urgent intervention - severe disease

From the 23 patients who had a severe episode of acute diverticulitis 11 were operated emergently and the remaining 12 necessitated an urgent intervention at some time during the same hospitalization. From the latter, 8 patients had a sequential value within the first 24 hours for the WBC count and 7 for the CRP, none of which displayed a significant variation compared to their baseline levels. Accordingly, the WBCs' initial mean value was 17.2×10^9 (± 2.4 SE) whereas their the sequential mean value was 16.4×10^9 (± 3.1 SE) ($p=0.369$). The respective values for the CRP were 227.1 (± 46.8 SE) mg/l and 227.6 (± 32.2 SE) mg/l ($p=0.987$).

Discussion

The serum inflammation markers have a substantial role in the clinico-laboratory diagnosis of acute diverticulitis or they can be used as complementary to the imaging findings (6,13,14). Moreover several reports have correlated the baseline values of the CRP to the CT-classification and to the clinical staging of the disease (7,15-17). The herein study dealt with the variation of the inflammation markers' value during the hospitalization of patients with acute diverticulitis as an expression of the evolution of the disease. We documented a significant paradoxical increase of the CRP values in patients with the mild form of acute diverticulitis with a concurrent decline of the WBC count during the first 24 hours of hospitalization. Thereafter the CRP levels showed a significant daily decrease below the initial levels for the remainder of the in-hospital duration. Therefore, the CRP decline in patients with ensuing improvement of their clinical conditions occurred more latently compared to the WBC count. As a result, in this survey the CRP serial measurement failed to accurately monitor the progression of acute diverticulitis at its early stage.

Despite the fact that the CRP is widely used in the daily clinical practice for the diagnosis and the monitoring of inflammatory and infectious processes, to the best of our knowledge two studies so far report its trends in patients with acute diverticulitis. It is noteworthy that these investigations had different primary aims and the variation of the CRP levels were rather depicted with a descriptive significance. Elsing et al investigated the CRP levels in 38 patients with an acute episode of diverticulitis that was treated conservatively

Table 2. C-reactive protein (CRP) trends in conservatively treated acute diverticulitis patients

	24 hrs	48 hrs	72 hrs	96 hrs	120 hrs	144 hrs	168 hrs
Number of Patients	131	126	72	40	28	12	7
Baseline CRP (mean \pm SE)	105.7 (\pm 4.8)	104.4 (\pm 4.8)	109.6 (\pm 7.2)	119.7 (\pm 10.4)	117.4 (\pm 12.9)	120.7 (\pm 18.1)	138.7 (\pm 24.3)
CRP at each time interval (mean \pm SE)	116.7 (\pm 5.0)	87.4 (\pm 5.2)	71.0 (\pm 7.1)	67.1 (\pm 10.4)	61.2 (\pm 11.8)	55.3 (\pm 12.1)	64.3 (\pm 20.4)
CRP value difference (mean \pm SE)	+11.0 (\pm 4.6)	-17.0 (\pm 5.5)	-38.6 (\pm 7.9)	-52.6 (\pm 11.7)	-56.2 (\pm 12.9)	-65.4 (\pm 18.1)	-74.4 (\pm 20.24)
Number of patients with decreased CRP compared to baseline CRP (%)	62 (47.3)	83 (65.9)	54 (75.0)	30 (75.0)	22 (78.6)	9 (75.0)	7 (100%)
P value	0.017	0.003	0.0001	0.0001	0.0001	0.004	0.01

The mean CRP values of each day of hospitalization and their comparison to the mean CRP value obtained at the presentation of the patient at the emergency department (Baseline CRP) are depicted. The latter is tailored to the number of cases available for analysis at each time interval. The CRP values are measured in mg/l.

(18). As in our study, cases with pre-admission antibiotic therapy were excluded so the analysis considered only those patients who primarily presented to the research Institution. Therefore, the baseline CRP levels were measured at the admission to the hospital and then every second day showing a significant consecutive decline. Data regarding the CRP of the first day of hospitalization are not provided, however the findings regarding the subsequent trends of this parameter are in conform with our results.

Furthermore, a prospective trial of oral vs intravenous antibiotic therapy for the clinically diagnosed acute uncomplicated diverticulitis reported the trends of the CRP as a secondary result and found a serially daily decline of its value (19). Thought our result may seem to differ from the latter there are several possible explanations. The above trial was not specifically designed to evaluate the clinical role of the inflammation markers' trend as it did not exclude patients with a running pre-admission antibiotic therapy. Consequently there were cases that primarily presented to a pre-hospital physician resulting in the non-documentation of the original baseline CRP value. In addition, the antibiotics may have influenced the CRP level obtained at the admission to the research Institution which was considered as the initial value in the analysis of that survey. In view of that, it is noticeable that they reported a considerably lower baseline CRP level (68.8 vs 103.6 mg/l of the herein survey) which may reflect a lesser overall inflammation grade at the admission of their uncomplicated cases. Likewise, the inclusion of cases with a delayed referral may have affected the 24-hour CRP trend of the series as this would correspond to a more latent serum measurement from the patients of our and of Elsing's investigation. Finally, it remains unclear up to which degree an eventual early CRP rise constituted a criterium for intervention as no information was provided concerning the complicated cases during the investigation period. In such event, if the authors employed a sensitive threshold for labeling a case as resistant to conservative therapy this would preclude it from the cohort of the "mild disease" group further contributing to the low index CRP of the latter. Conclusively, while the above trial evaluates the effectiveness of the modality of the administration of antibiotics in patients with mild acute diverticulitis, we believe that it cannot address properly the issue of the role of the inflammation markers' variation in the monitoring of the disease, nor it intends to.

According to recent widely accepted practice parameters the patients presenting with acute diverticulitis and absent signs of generalized peritonitis are best served with the initiation of supportive therapy (4, 6). Recent data support the policy of a less aggressive approach at least during the acute phase of the disease with the aim to convert an eventual emergent procedure to an elective one or to seek definite non-operative treatment (3, 4, 20). Various centers have reported an increasing proportion of acute diverticulitis patients with a perforation who are dealt safely with medical therapy alone (9-11, 20). As shown also from this series most of the cases with absent signs of generalized peritonitis will respond to the conservative measures (9, 15, 16). Nevertheless, a subset will eventually necessitate an intervention at the same hospitalization due to lack of signs of improvement (6). Yet, there is not specific evidence to objectively determine the clinical decision of the failure of the conservative treatment (6) and it is apparent that the latter is being affected by personal and local policies often with a potential tendency to overtreatment. It is likely that patients in published series who otherwise could have been treated conservatively may have undergone an unnecessary invasive procedure in part due to a substantial early rise of the CRP. A key to an improved evaluation of the on-going clinical status can be therefore based on the accurate interpretation of the serial clinical and laboratory parameters. Interestingly, a baseline CT-scan obtained at the initial assessment of the patient is a very useful tool for the prediction of a complicated course (7, 15), nevertheless it does not make part of the continuous daily monitoring of the clinical status.

Our investigation emphasizes that the 24-hour trends of the CRP value should not be used as a determinant of the failure of the responsiveness of acute diverticulitis to the conservative therapy. Accordingly, more than half of the patients with mild disease showed an initial rise of the CRP level of at least 45 mg/l. Therefore, even a substantial increase in the CRP value during the first day following the admission does not necessarily indicate worsening of the disease and should not mislead the clinician towards a decision for sequential imaging and/or an interventional procedure. Such case should be evaluated conclusively and in the absence of generalized peritonitis or clear worsening of the clinical examination the patient could be re-assessed on the following day. The latent decline of the CRP confirms the on-going clinical improvement but on the other hand it is not useful as

an early marker of recovery. In addition, this report documented the rapid decrease of the WBC count in patients with mild diverticulitis. However, the latter has a rather descriptive significance in this non-comparative study.

It should be mentioned that there are limitations in the investigation regarding the trends of the laboratory values of the patients who underwent an intervention during the in-hospital stay. Apart from the restrictions created by a retrospective survey, the group of these patients with a complicated clinical course is intrinsically dishomogeneous. Nearly half of the individuals with a severe attack in this series were operated emergently after the admission. Consequently, the exclusion of these cases from the analysis of the 24-hour trends creates a certain bias. For this reason we avoided to extract conclusions concerning the variation of the inflammation markers' level of the patients with severe acute diverticulitis nor to compare them with the corresponding cases of mild disease. It is important to emphasize that the inflammation markers' trend was not studied as an end-point itself but as a parameter that may assist in the interpretation of an on-going clinical situation.

Conclusion

In conclusion, according to the herein investigation the trend of the CRP value in patients with mild acute diverticulitis declines after a paradoxical temporary increase during the first day of hospitalization. Conversely, the WBCs rapidly decrease in these patients. Even a substantial rise in the CRP value during the first 24 hours of hospitalization should not be necessarily considered as a parameter of deterioration of the clinical status. The early CRP trend has no role in the evaluation of the clinical progression of acute diverticulitis and therefore it should not be used as it may mislead the clinician towards potential overtreatment.

We believe that the clinical role of the CRP trends should be investigated more thoroughly. A dedicated prospective study analyzing only primarily-seen patients without pre-hospital antibiotic therapy and employing carefully defined criteria for the decision of the failure of conservative measures is necessary for the validation of our results.

Conflict of interest

The authors declare no conflicts of interest.

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