Usefulness of routine analysis of ascitic fluid at the time of therapeutic paracentesis in asymptomatic outpatients

Results of a multicenter prospective study

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SUMMARY

Aim — The guidelines of the American Association for the Study of Liver Diseases recommend performing exploratory paracentesis on each patient with cirrhosis and chronic ascites. The aim of the study was to evaluate the prevalence of spontaneous bacterial peritonitis and culture-negative neutrocytic ascites in a large population of consecutive asymptomatic cirrhotic ascitic ambulatory patients.

Methods — Patients with cirrhosis and tense ascites hospitalized from January to September 2000 in 5 hepatogastroenterology units prospectively underwent an exploratory paracentesis with cytobiocultural, biochemical and bedside inoculation into aerobic and anaerobic blood culture bottles. Patients studied were not receiving antibiotics except for norfloxacine and had no obvious sign of infection such as fever or hypothermia, chills, unusual abdominal tenderness, de novo or worsening hepatic encephalopathy, recent gastrointestinal bleeding, acute renal failure or marked arterial hypotension.

Clinical and biological findings and ascitic fluid cytological and bacteriological results were evaluated at each exploratory paracentesis. The results are given in mean ± standards deviations with range.

Results — Sixty-seven cirrhotic patients (48M/19F, mean age 59 ± 9 years) had 270 therapeutic paracenteses, preceded by an exploratory aspiration. Fifty-nine patients (88%) had alcoholic cirrhosis. Twenty-five patients (37.3%) received norfloxacine. At first paracentesis 41 (61.2%) and 26 (38.8%) patients were class B and C respectively according to the Child-Pugh classification; the mean Child-Pugh score was 9 ± 1.5. None had suspicion of infection. The mean number of paracenteses was 5 ± 4.3 per patient; 59.6% of the paracenteses (161) were compensated with human albumin. Ascitic protein concentration was 17.5 ± 8.6 g/l, ascitic fluid cell count and number of neutrophils were 127 ± 155/mm³ and 5.9 ± 14/mm³ (0-60), respectively.

No patient had spontaneous bacterial peritonitis nor culture-negative neutrocytic ascites; 10 cases of monomicrobial bacterascites.

Conclusions — In the absence of obvious signs of infection, the prevalence of spontaneous bacterial peritonitis and culture-negative neutrocytic ascites in asymptomatic cirrhotic outpatients with ascites is near 0%. Moreover, for 100 large volume paracenteses, not performing exploratory paracentesis corresponds to a savings of 5,500 euros, without risk for these patients.

RÉSUMÉ

Intérêt de la ponction d’ascite exploratrice chez les malades cirrhotiques ambulatoires sans point d’appel infectieux.

Résultats d’une étude prospective multicentrique

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Objectif — L’American Association for the study of liver diseases (AASLD) (association américaine pour l’étude des malades du foie) recommande de réaliser une ponction d’ascite exploratrice chez tout patient cirrhotique ayant une ascite. Le but de cette étude était d’évaluer la prévalence de l’infection du liquide d’ascite et de l’ascite riche en polynucléaires (ascite neurocytique) chez les malades cirrhotiques ascitiques sans suspicion d’infection, hospitalisés pour ponction d’ascite évacuatrice ambulatoire.

Méthodes — Tous les malades hospitalisés de janvier à septembre 2000 dans 5 services d’hépatogastroentérologie ont eu de façon prospective une ponction exploratrice avec examen cytobactériologique, biochimique et ensemencement au lit du malade sur flacons d’hémocultures aérobie et anaérobie. La suspicion d’infection était définie par les critères suivants : température supérieure à 38° ou inférieure à 36,5°, frissons, douleurs abdominales évoquant une infection, apparition ou aggravation d’une encéphalopathie hérpétique pré-existante, hémorragie digestive datant de moins de 15 jours, insuffisance rénale aigüe, hypotension artérielle (< 80 mmHg) : les malades recevant des antibiotiques en dehors de la norfloxacine étaient également exclus de l’étude.

Les paramètres cliniques et biologiques des malades d’une part, et cytologiques, bactériologiques et biochimiques des ponctions d’autre part, étaient évalués lors de chaque ponction exploratrice. Les résultats sont exprimés en moyenne ± déviation standard avec les valeurs extrêmes.

Résultats — Soixante sept malades cirrhotiques (48H/19M) d’âge moyen 59 ± 9 ans ont eu 270 ponctions évacuatrices, précédées d’une ponction exploratrice. La cirrhose était d’origine alcoolique chez 59 malades (88 %). Vingt-cinq (37,3 %) malades recevaient de la norfloxacine. Lors de la première ponction, 41 (61,2 %) et 26 (38,8 %) malades étaient respectivement classés stade B et stade C selon la classification de Child-Pugh : le score moyen de Child-Pugh était de 9 ± 1,5. Aucun malade n’avait de suspicion d’infection selon les critères pré-établis. Le nombre de ponctions était de

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This work was presented partially at the SNFGE 2001 Liver-Biliary tract and Pancreas Section and at the EASL 2002.
L’ascite neutrocytique chez les malades cirrhotiques ambulatoires est très faible ou nulle, la ponction d’ascite exploratrice pourrait être supprimée dans cette situation sans risque pour les malades en permettant pour 100 ponctions une économie de 5,500 euros.

Introduction

Therapeutic paracentesis is the recommended treatment for patients with ascites resistant or refractory to medical treatment [1]. Many cirrhotic patients with ascites are thus regularly hospitalized for a therapeutic paracentesis. The good clinical practices guidelines of the American Association for the Study of Liver Diseases (AASLD) [2] recommend performing exploratory paracentesis in association with the therapeutic paracentesis in order to search for two serious complications: bacterial peritonitis and neutrocytic ascites [3, 4]. However, except in cases where infection is suspected and/or major liver dysfunction is present [5-7], the usefulness of this approach is not clearly established. In one study including more than 500 paracenteses of ascitic fluid in cirrhotic patients on long-term ofloxacin treatment, the prevalence of bacterial peritonitis was zero [8]. More recently, Jeffries et al. [5], reported a series of 118 ascitic fluid paracenteses in 29 cirrhotic patients free of any signs of infection (treated or not with norfloxacin) and did not find any cases of bacterial peritonitis or neutrocytic ascites. If these results are confirmed in a larger number of patients, substantial savings, both in terms of direct cost and time, would be possible without risk for patients.

The aims of this prospective multicentric study were: 1) to confirm that the prevalence of spontaneous bacterial peritonitis and neutrocytic ascites is low or null in patients free of signs of infection defined by pre-established criteria, and 2) to evaluate, if this is confirmed, the possible savings in terms of direct cost.

Patients and methods

Patients

All cirrhotic patients with chronic ascites attending an outpatient clinic for therapeutic paracentesis in five participating centers were eligible for inclusion in the absence of a priori defined exclusion criteria. Each patient could be included several times. We collected prospectively demographic, clinical and biological data for each patient as well as ascitic fluid cytological, biochemical, and bacteriological data results. All data were collected anonymously in each center. The prevalences of spontaneous bacterial peritonitis and neutrocytic ascites in outpatients not included in this study were noted prospectively in one of the five participating centers [Crelil].

Inclusion and exclusion criteria

All patients aged over 18 years attending an outpatient clinic for therapeutic ascitic fluid paracentesis (apart from emergency situations) were eligible for inclusion in this study. Exclusion criteria were similar to those used by Jeffries et al. [5]: fever > 38 °C, hypothermia < 36.5 °C, chills, abdominal tenderness suggestive of peritonitis, developing or worsening hepatic encephalopathy, gastrointestinal bleeding within the last 15 days, acute renal failure, hypotension (systolic pressure < 80 mmHg), antibiotic treatment at admission except norfloxacin prophylaxis. Corticosteroid treatment in patients with severe alcoholic hepatitis was not an exclusion criterion. Patients with non-cirrhotic ascites (cardiac, carcinomatous, tuberculosis, pancreatitis) were not considered for inclusion in this study.

Methods

ASCITES PARACENTESIS

The usual sterile technique was used for ascites paracentesis. The volume withdrawn was not limited and the type of compensation (type of solution and volume) were determined by each principal investigator in each center. At each paracentesis (figure 1), 40 ml of ascitic fluid were drawn as follows: 10 ml in a sterile bottle for cytological and bacteriological examinations, 10 ml for protein assay and 20 ml for aerobic and anaerobic blood cultures using Bact/ALERT® (Biomerieux, Inc) with bedside inoculation according to the technique described by Runyon [9].

The definitions established by the International Ascites Club [10] were retained for sterile ascites, bacterial peritonitis, neutrocytic ascites, and bacterascitis. Bacterial peritonitis was defined as a polymorphonuclear leukocyte count (neutrophil-count - PMN) > 250/mm³ associated with a germ isolated from the ascitic fluid. Neutrocytic ascites was defined as a polymorphonuclear leukocyte count > 250/mm³ with a negative culture. Bacterascitis was defined as a polymorphonuclear leukocyte count < 250/mm³ with isolation of a unique germ from the ascitic fluid. If bacterial peritonitis or neutrocytic ascites were present, the type of antibiotic treatment and its duration were determined by the investigating physician.

STUDY VARIABLES

The following data were prospectively collected on a pre-established data sheet.

Demographic variables: recruiting center, patient age and gender, number of the paracenteses for patients who had more than one.

Cirrhosis-related variables: etiology (alcoholic, hepatitis B virus, hepatitis C virus, genetic hemochromatosis, other), persistent alcohol intake or not for patients with alcoholic cirrhosis, history of bacterial peritonitis, prothrombin time, serum total bilirubin, serum albumin, Child-Pugh stage [11], presence of moderate or abundant ascites, presence or not of hepatic encephalopathy. The presence of hepatocellular carcinoma and diabetes was also noted.

Ascites-related variables: volume of ascitic fluid withdrawn, compensation (none, human albumin, other solution), treatment or not with a diuretic, primary or secondary prophylaxis with norfloxacin [12, 13] were recorded. For the ascitic fluid, protein content, total cell count and PMN count, and isolation of bacteria were noted. Serum creatinine and
platelet count were also noted since patients with renal failure and/or low platelet counts appear to have a higher prevalence of bacterial peritonitis [14].

Direct cost: The direct cost of a therapeutic paracentesis was considered to include the cost of the cytological, biochemical, and bacteriological tests performed in the present study at the coordinating center. At the time of this study, this direct cost was 55 euros per paracentesis.

Statistical analysis

Results are expressed as mean and standard deviation with range.

Results

From January to September 2000, 67 patients (48 men and 19 women, mean age 59.8 years, age range 38-92) attended outpatient clinics for 270 consecutive therapeutic paracenteses. The direct cost of the examinations of the ascitic fluids was 55 euros \( \times 270 = 14,850 \) euros.

Fifty-nine patients (88%) had alcoholic cirrhosis and eight (12%) had cirrhosis caused by another condition (hepatitis C virus in 4, hepatitis B virus in 1, hereditary hemochromatosis in 1, and an undetermined cause in 2). Habitual alcohol intake persisted during the study period in 20 of the 59 patients with alcoholic cirrhosis (29.8%). Fifty-two patients (77.6%) were taking diuretics and 25 (37.3%) were on norfloxacin prophylaxis. This was a secondary prophylaxis in 4 patients with bacterial peritonitis [13] and primary prophylaxis in 21 patients whose protein content in the ascitic fluid was < 10 g/l [14].

The Child-Pugh classification was stage B for 41 patients (61.2%) and stage C for 26 (38.8%). The mean Child-Pugh score was 9.1 ± 1.5. Thirteen patients (19.4%) had chronic renal failure defined as serum creatinine > 130 nmol/L. Biological data at the time of the first paracentesis are presented in Table I. Five patients (3.5%) had hepatocellular carcinoma. Thirteen patients (19.4%) had diabetes.

The total number of paracenteses was 270, with 5.0 ± 4.3 per patient (range: 1-16). Average volume of ascitic fluid withdrawn per paracentesis was 5.5 ± 3.1 L (range: 2-14). A 20% human albumin solution (8 g per liter withdrawn) was used for compensation for 161 paracenteses (59.6%). Cytology and biochemical results are presented in table II. We did not observe any cases of spontaneous bacterial peritonitis or neutrocytic ascites. Ten patients (3.7%) had normocytic bacterascites, all with commensal germs. During the study period, the center which collected data in patients not included in this study recorded one case of bacterial peritonitis among 143 paracenteses (0.7%) which occurred in a patient scheduled for outpatient care who did not meet the inclusion criteria for this study. This patient had hypothermia, a tender abdomen and acute renal failure, confirming the clinical pertinence of the pre-defined inclusion criteria [5].

To our knowledge, two studies published as pre-review articles [5, 15] and two published in abstract form to date [6, 7] have examined the prevalence of spontaneous bacterial peritonitis and bacterascites in outpatients undergoing therapeutic paracentesis. The results of these studies are summarized in Table IV.

In the study reported by Jeffries et al. [5] which concerned 118 paracenteses in 29 patients, the prevalence of spontaneous bacterial peritonitis was null and the prevalence of bacterascites was 2.3% (3/118). These results are similar to ours (3.7%) although the patients in Jeffries' population had more severe liver disease. Our population was mainly composed of patients with Child B cirrhosis (61%) while Jeffries et al. [5] reported a majority of Child C patients (62%) and 38% of patients on a liver transplantation waiting list. The results of our study are also comparable to those reported by Evans et al. [15] despite certain methodological differences. In their retrospective study of 427 cirrhotic patients seen in a single outpatient clinic, Evans et al. [15] analyzed 427 exploratory paracenteses performed over a 6-year period. Their exclusion criteria were similar to those used by Jeffries et al. [5], however patients receiving primary or secondary prophylaxis with norfloxacin were excluded. In the study by Evans et al. [15] the prevalence of spontaneous bacterial peritonitis was 1.4% and the prevalence of neutrocytic ascites was 2.1% (giving a combined prevalence of 3.9%). The prevalence of bacterascites in this study was 1.9% [15]. In the two studies published in abstract form, the prevalences of spontaneous bacterial peritonitis and bacterascites were 0% in the first study of 78 paracenteses performed in 26 patients [6]. In the second study of 173 paracenteses in 51 patients, the prevalence...
of spontaneous bacterial peritonitis was 0% and that of bacterascites was 2.3% [7]. The results of these four studies in outpatients without suspected infection are thus comparable with a prevalence of spontaneous bacterial peritonitis varying from 0 to 3.9% and of bacterascites varying from 0 to 3.7% (table IV). The highest prevalence of spontaneous bacterial peritonitis and bacterascites was reported by Evans et al. [15]. This higher rate could be explained by 1) the much larger number of patients and paracenteses, 2) the less restrictive a posteriori exclusion criteria due to the retrospective design of the study leading thus to the possible inclusion of patients at risk of infection, 3) the fact that, unlike our study and the study by Jeffries et al. [5], patients receiving norfloxacin were not included, 4) the variable proportion of patients with alcoholic cirrhosis which ranged from 31% [15] to 41% [5] and 88% in our study.

The robustness of the results of the present study is further strengthened by the absence of spontaneous bacterial peritonitis and neutrocytic ascites in an independent population of 30 patients followed since this study in one of the participating centers (Creil) where more than 200 therapeutic paracenteses were performed (data not presented) using the same criteria for suspected infection as those defined before undertaking this study. In addition, Runyon recently reported a 2% prevalence of spontaneous bacterial peritonitis in a series of 400 paracenteses performed in two years in an outpatient setting [16]. Our results should nevertheless be interpreted with caution and can only be applied to a selected population of outpatients. Under these conditions, routine exploratory paracentesis could not be necessary for all cirrhotic patients undergoing therapeutic paracentesis after careful clinical examination. Such routine exploratory examinations could be reserved for patients with a high risk of spontaneous bacterial peritonitis and of course in any doubt of infection. This attitude would enable a savings of 5,500 euros for 100 therapeutic ascites paracenteses without risk for the patients (reduction of direct cost). Furthermore, the time savings for the medical staff and assistants would be substantial (decreased indirect cost not evaluated in this study).

It was recently demonstrated that a urine dip strip could be used for ascitic fluid to detect bacterial peritonitis with a sensitivity of 90 to 100% [17-22]. However, the usefulness of such strip is yet to be established in the setting of ambulatory patients. In the future, it could be possible that reagent strips similar to those used for urine tests could be validated for ascitic fluid allowing more rapid diagnosis of bacterial peritonitis and neutrocytic ascites [17]. Despite use of these low-cost strips is not time consuming and before the validation of their diagnostic accuracy in this setting, routine tests of ascitic fluid will undoubtly be used by most physicians for outpatients with no suspected infection despite the fact that the prevalence of peritoneal infection is rare and the prognosis of such infections is less severe [15]. At the present time however, the use of these strips has not been fully validated. Several studies are currently under way.

In conclusion, the results of our study confirm that spontaneous bacterial peritonitis is rare in asymptomatic cirrhotic outpatients undergoing exploratory paracentesis. In the absence of clinical and/or biological signs suggestive of infection after careful clinical examination, we suggest that exploratory paracentesis would not be necessary in a large number of outpatients. A significant cost savings can be achieved without risk for the patients.

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REFERENCES


Table III. – Cytological and bacteriological characteristics of 10 cases of bacterascites.
Caractéristiques cytologiques et bactériologiques des 10 cas de bactéraoscites.

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Total cell count/mm³</th>
<th>Polymorphonuclear count/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram negative cocci</td>
<td>95</td>
<td>4</td>
</tr>
<tr>
<td>Staphylococcus warneri</td>
<td>90</td>
<td>9</td>
</tr>
<tr>
<td>Staphylococcus epidermidis (1)</td>
<td>208</td>
<td>44</td>
</tr>
<tr>
<td>Staphylococcus epidermidis (2)</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Staphylococcus capitis</td>
<td>59</td>
<td>0</td>
</tr>
<tr>
<td>Coagulase negative Staphylococcus</td>
<td>1230</td>
<td>35</td>
</tr>
<tr>
<td>Staphylococcus stimulis</td>
<td>212</td>
<td>11</td>
</tr>
<tr>
<td>Corynebacterium</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Streptococcus salivarius</td>
<td>80</td>
<td>15</td>
</tr>
<tr>
<td>Streptococcus oralis</td>
<td>32</td>
<td>0</td>
</tr>
</tbody>
</table>

Table IV. – Prevalence of spontaneous bacterial peritonitis and bacterascites in asymptomatic outpatients.
Prévalence de l’infection du liquide d’ascite et des bactéraoscites chez les malades cirrhotiques ambulatoires asymptomatiques.

<table>
<thead>
<tr>
<th>Study first author [Ref.]</th>
<th>Number of patients</th>
<th>Number of paracenteses</th>
<th>Prevalence of bacterial peritonitis (%) n</th>
<th>Prevalence of bacterascites (%) n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeffries [5]</td>
<td>29</td>
<td>118</td>
<td>0 (0)</td>
<td>2.5 (3)</td>
</tr>
<tr>
<td>Stern [6]</td>
<td>26</td>
<td>78</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Kolle [7]</td>
<td>51</td>
<td>173</td>
<td>0 (0)</td>
<td>2.3 (4)</td>
</tr>
<tr>
<td>Romney [present study]</td>
<td>67</td>
<td>270</td>
<td>0 (0)</td>
<td>3.7 (10)</td>
</tr>
</tbody>
</table>

* 69 cytobacteriological examinations, 37 cultures of ascitic fluid


