Editorial

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Secondary peritonitis in cirrhosis: "Oil in fire"

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Spontaneous bacterial peritonitis (SBP) is the most common type of infection in cirrhosis and its diagnostic criteria, risk factors, and therapeutic algorithms have been defined by consensus [1]. In contrast, there is large paucity of clinical investigations on secondary peritonitis in liver cirrhosis in the last two decades and diagnostic markers for early suspicion as well as parameters determining outcome are less clear. Peritonitis can be secondary to perforation or acute inflammation of intra-abdominal organs, abdominal wall infections or previous abdominal surgical procedures or trauma. Except for the latter two, in which the precise nature of peritoneal infection usually is obvious, the differential diagnosis between SBP and secondary peritonitis can be very difficult. In this issue of the Journal of Hepatology, Soriano and coworkers present a retrospective investigation performed in two tertiary hospitals in Spain, extending over an observation period of seven years [2] that helps to re-appraise this important but often neglected clinical issue. In fact, the observed mortality of two out of three cirrhotic patients developing secondary peritonitis dying during hospitalization is reported to be significantly higher than in patients with SBP. Mortality found in the latter group (26.4%) is comparable to previous investigations, but could have been improved by more a consequent use of albumin [3]; thus, further emphasizing the differences in severity of disease between the two entities.

With respect to the frequency of secondary peritonitis, in this largest reported cohort so far 1.25 episodes/year are diagnosed and thus represent only 4.5% of all peritonitis in cirrhotic ascitic patients seen at one of the participating institutions. These data confirm the rarity of secondary peritonitis reported earlier [4] although others have reported that up to 15% of cirrhotic patients with peritonitis may have secondary causes [5]. SBP is shown to occur in more advanced stages of disease as compared to secondary peritonitis. This reflects the well-known observation that SBP develops selectively in patients with low ascitic protein levels with increasing incidence dependent on further additional risk factors such as bilirubin >3.2 mg/dL and platelet count <98.000/mm^3 [6,7]. In contrast, secondary peritonitis develops independently from the presence and/or severity of cirrhosis.

The observed mortality in cirrhotic patients developing secondary peritonitis is clearly higher than reports in non-cirrhotic patient groups, usually remaining below 30% [8]. Thus, it needs to be emphasized that underlying cirrhosis sets the stage for fatality. This is due to marked deficiencies in local and systemic host defence mechanisms against bacteria including dysfunction of cellular and humoral immunity in advanced cirrhosis limiting peritoneal bacterial clearance. Moreover, ascites *per se* may contribute to worsen prognosis of any type of peritonitis since in healthy conditions peritoneal host defence mechanisms are very efficient, and i.p. injection of various numbers of single organisms does not cause peritonitis unless adjuvant substances or ascites are present [9]. Finally, increased porto-systemic shunting as well as the hyperdynamic circulation with enhanced susceptibility for hemodynamic instability in case of further vasodilatory stimuli act in concert to determine the course of disease [10].

The finding of exaggerated mortality in secondary peritonitis as compared to SBP is most likely due to the presumably higher bacterial load and the frequently polymicrobial nature induced by secondary causes. For instance, experimental cecal ligation and puncture with prior cecal lavage has been reported to present with a 100% survival rate as compared to animals with normal gut flora, emphasizing the importance of intestinal bacteria in the development of abdominal sepsis [11]. It is tempting to speculate that bacterial overgrowth as a well-known feature in decompensated cirrhosis may additionally contribute to aggravate this scenario in peritonitis due to intestinal perforation. Moreover, bacterial synergism in polymicrobial infection due to interaction of two or more bacterial species produces results which cannot be achieved by an individual bacterial species alone [12]. In accordance with this concept of "dose of bacterial burden", secondary peritonitis was characterized by more leucocyte recruitment to the peritoneal cavity showing up to threefold higher levels of ascitic PMN count as compared to SBP. In this context, the level of pro-inflammatory mediators aimed at activation of leucocytes that enable bacterial clearance are known to correlate with severity of peritonitis as well as severity of critical illness and to be predictive for outcome [13,14]. In fact, when inflammatory response becomes overwhelming antibiotics can

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Abbreviations: AP, alkaline phosphatise; CEA, carcinoembryonic antigen; CT, computed tomography; i.p., intraperitoneal; LDH, Lactat-dehydrogenase; PMN, polymorphonuclear leucocytes; SBP, spontaneous bacterial peritonitis; SOFA, Sequential Organ Failure Ass.

no longer alter outcome in experimental secondary peritonitis [15]. The priming of PMN present in advanced cirrhosis in conjunction with a vast bacterial load in secondary peritonitis may therefore lead to an excessively pronounced, antibiotic-resistant, and ultimately fatal systemic inflammatory response. In other words, secondary peritonitis occurring in a decompensated cirrhotic patient is like pouring oil into the fire.

However, the outcome of secondary peritonitis in contrast to SBP is apparently independent from the severity of underlying liver disease. Despite having major concerns in mind regarding selection bias, the only variables found to predict survival in patients with secondary peritonitis were high blood pressure and high protein concentration in ascites. This clearly points towards the severity of sepsis determining poor outcome as has been indicated many times before. However, the authors unfortunately do not report any scoring system usually applied in intensive care medicine, e.g. Sequential Organ Failure Assessment (SOFA)-based scores. The prognosis in peritonitis has repeatedly been shown to be decisively influenced by the health status of the patient at the beginning of treatment which can be predicted fairly accurately on the basis of SOFA-derivatives [16]. In fact, in critically ill cirrhotic patients the SOFA-score has been demonstrated to exhibit the best predictive ability and to perform better than liver-specific scores such as the Child classification [17]. Therefore, the use of established prognostic ICU-indices is strongly recommended and should be implemented more rigorously in hepatology.

Finally, patients being operated on and particularly those with early intervention tended to have better outcomes. Although not statistically significant and prone to selection bias, it is self-evident and known since 1889 [18] that early and complete surgical resolution of the abdominal septic focus is of upmost prognostic relevance. Soriano et al. indeed observe that all patients with perforated secondary peritonitis not undergoing surgery die during hospitalization. The median time to surgery in the current series of cases was 3.2 ± 2.4 days in survivors (as compared to 7.2 ± 6.1 days in non-survivors). Therefore, unless the patient is in pre-terminal or non-operable conditions, delayed diagnostic work-up is futile, whereas early imaging and surgical intervention increase chances for cure. Conversely, surgical therapy may be accompanied by significant deterioration in the clinical status of cirrhotic patients with SBP and thus, should be avoided.

Therefore, timing and accuracy of diagnosis correctly separating SBP and secondary peritonitis is crucial. Clinical signs and symptoms are clearly not helpful in this regard.

The study by Soriano et al. reinforces suggestions made beforehand that secondary peritonitis should be suspected when one of the following criteria is present: (a) no response to antibiotic therapy; (b) more than one organism isolated from ascites and (c) Runyon's criteria, namely neutrocytic ascites with at least two of three criteria: ascitic fluid total protein >1 g/dl (in contrast to SBP which selectively occurs in low-protein ascites), glucose <50 mg/dl (due to bacterial glucose utilization), or LDH >225 mU/ml (most likely due to more rapid metabolic rate and disintegration of ascitic PMN) [19]. Polymicrobial culture (OR 587.5; 33–10247) followed by Runyon's criteria (OR 61.2; 6–540) were the only independent predictive factors associated with secondary peritonitis. Moreover, although strata are not stated, the extreme separating power reported for these parameters (AUC of ROC curve 0.952) appears to be present at each level of risk. Uniformly, SBP is reported to be monomicrobial in the vast majority of cases (88–100%) and hence, polymicrobial ascites and/or presence of anaerobic bacteria or fungi, usually not acquired during SBP, clearly indicates the presence of secondary peritonitis. However, it needs to be stressed that microbiology results may be obtained too late in the course of disease. Likewise, re-paracentesis for control of therapeutic efficacy is mostly not diagnostic within 12 or 24 h after initiation of antibiotics and thus is recommended on day two with a PMN cell count reduction of less than 25% of the initial value defining lack of response [4]. Therefore, rapid "chemical" parameters available at the day of paracentesis with sufficient sensitivity and positive predictive value are needed for effective screening. Sensitivity of Runyon's criteria has been reported to reach 97% in some cohorts [20] but elsewhere ranges below 68% [2,19] and thus can be optimized. In this regard, Wu et al. have used carcinoembryonic antigen (CEA) present in colonic enterocytes and alkaline phosphatase (AP) occurring throughout the gastrointestinal tract. Ascitic elevations in both are not likely to be result of inflammatory changes but rather specific for intestinal perforation. In fact, ascitic fluid presenting with either AP >240 U/l or CEA >5 ng/ml in 80% of cases reflects peritonitis of secondary origin [21]. Although no data are available on the diagnostic accuracy of combined criteria, fulfilling either Wu's or Runyon's criteria will most likely improve sensitivity. In such cases: (i) antibiotic regimen must include agents against anaerobes and enterococci and (ii) secondary peritonitis has to be ruled out thoroughly. Therefore, we strongly recommend initiation of abdominal computer tomography (CT) as soon as any of these features are present. This appears to be the only approach to ensure timely diagnosis of secondary causes; therefore, enabling appropriate surgical treatment. In this regard, data by Soriano et al. underscore the usefulness of performing CT since it was diagnostic in more than 91% of patients. In cases in which CT will be performed without contrast agent, e.g. in the presence of advanced renal insufficiency, abdominal sonography can clearly add diagnostic power and should be performed.

In summary, secondary peritonitis in decompensated cirrhosis is a rare entity that requires the meticulous vigilance of clinicians. Its occurrence in cirrhosis delivers a devastating prognosis due to the limited pre-morbid reserves combined with a presumably overwhelmingly severe systemic inflammatory response. Since the first parameter cannot be changed the condition *sine qua non* for success is timely diagnosis and surgical intervention to stop delivery of bacteria and adjuvants into the peritoneal cavity.

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