

Answering Reviewers

For reviewer 03741310

In this case only the blood cultures were performed arbitrarily. However, we believe that in case of sepsis blood cultures can still provide adequate information for the treatment of sepsis. It would probably be appropriate to do both culture tests, both from the blood and from the bile. Regarding the use of steroids we used it because the patient had an isolated febrile episode, the culture tests were not yet available, to try to reduce the possible inflammatory component on the bile way to try to facilitate the reduction of levels of bilirubin.

For reviewer 00722050

The potential portals of entry for *Aeromonas* bacteria are the gastrointestinal tract, skin lesions, previous surgery or local trauma in an aqueous environment. After adhesion to epithelial cells, *Aeromonas* produces numerous virulent factors that destroy host epithelial barriers and impair immune cells, including exoenzymes, cytotoxic and cytotoxic enterotoxins, hemolysins, proteinases, lipases, agglutinins and various hydrolytic enzymes ^[5]. A wide spectrum of diseases can develop as a result of coming into contact with the bacterium, *e.g.* acute gastroenteritis, bacteremia, pancreatitis, hepatobiliary tract infections, soft tissue infections, indwelling-device-related infections, brain abscesses, meningitis, endocarditis, pleuropulmonary infections, peritonitis, sepsis and HUS ^[6]. Individuals with underlying hepatobiliary diseases are particularly susceptible to the infections, as demonstrated in at least two papers [Serra N, Di Carlo P, Gulotta G, d' Arpa F, Giammanco A, Colomba C, Melfa G, Fasciana T, Sergi C. Bactibilia in women affected with diseases of the biliary tract and pancreas. A STROBE guidelines-adherent cross-sectional study in Southern Italy. *J Med Microbiol.* 2018 Aug;67(8):1090-1095. doi: 10.1099/jmm.0.000787. Epub 2018 Jul 5. PubMed PMID: 29975626. 2: Di Carlo P, Serra N, Gulotta G, Giammanco A, Colomba C, Melfa G, Fasciana T, Sergi C. Bactibilia in diseases of the biliary tract and pancreatic gland in patients older than 80 years: a STROBE-retrospective cohort study in a teaching hospital in Italy. *Eur J Clin Microbiol Infect Dis.* 2018 May;37(5):953-958. doi: 10.1007/s10096-018-3213-y. Epub 2018 Feb 27. PubMed PMID: 29484561] pancreatic head carcinoma rather than gallbladder carcinoma are associated with gram-negative bacterial infections. Moreover, the bacterium type was a positive

predictor of survival time compared to other variables. In patients with hematologic diseases or solid tumors, antineoplastic drugs may induce alteration of gastrointestinal mucosa and allow transmigration of colonized *Aeromonas* species from the bowel into the circulatory system.

Aeromonas veronii biovar *veronii* has rarely been isolated from humans. In our patient, the *A. veronii* biovar *veronii* infection was responsible for monomicrobial cholangitis and was probably caused by the insertion of a percutaneous transhepatic biliary catheter. Few cases of sepsis from *Aeromonas* have been described in Western countries. Dryden and Munro ^[7] described 13 cases of *Aeromonas*-related septicemia (10 from *A. sobria* and 3 from *A. hydrophila*), some of which had biliary tract as the primary site of infection. In the U.S., Clark and Chenoweth ^[8] reported 15 cases of *Aeromonas* infection of the hepatobiliary system but none were related to *Aeromonas veronii* biovar *veronii*. In France, Dudier et al. ^[9] described 2 cases of septicemia caused by *Aeromonas caviae* and *Aeromonas hydrophila* following the placement of transhepatic biliary drainage.

Of note, the routine prophylaxis with ampicillin-sulbactam (or clindamycin and gentamycin for penicillin-allergic patients) before the percutaneous biliary drainage procedure was not done in our patient, an oversight on our part. The patient did not recall having had any contact with potentially contaminated water or food products before admission to hospital, she had not traveled abroad in the recent past, and there were no other cases of this infection in the hospital. The rapid manifestation of symptoms after the second drainage would thus seem to indicate a correlation with the invasive procedure.

The abdominal pain, fever, laboratory alterations in our patient were attributable to sepsis. Although highly improbable, we also considered HUS in the differential diagnosis. Only a few cases of HUS from *Aeromonas* have been described worldwide, with diarrhea as the common feature and sometimes the need for dialysis or hemofiltration. We were unable to confirm or refute HUS because specific laboratory tests for the condition such as polymerase chain reaction assay for shiga-like toxin genes and verotoxin test were not routinely performed.

Patients with *Aeromonas* are susceptible to aminoglycosides, quinolones, co-trimoxazole and aztreonam, but are resistant to broad-spectrum cephalosporins because *Aeromonas* has a propensity to produce at least 3 β -lactamases (1). We initially used levofloxacin because the patient recalled having had a positive allergic reaction to an antibiotic in the past but could not remember its name. However, she had previously taken levofloxacin without problems. In our case *A. veronii* was resistant to amoxicillin/clavulanic acid and moderately sensitive to imipenem. Of note, Sánchez-Céspedes ^[10] reported a resistance to imipenem in case of *A. veronii* biovar *sobria*, which should alert clinicians to the possible emergence of multidrug-resistance.

We describe a case of monomicrobial infection, cholangitis and sepsis caused by *A. veronii* *biovar veronii*, a rare event in humans. In fact, as far as we know, this is the first reported case of sepsis from *A. veronii biovar veronii* following biliary drainage in Western countries. It seems logical to hypothesize that the *Aeromonas* infection in our patient was related to the invasive biliary tract procedure which may have facilitated an ascending infection from intestinal bacteria. Our findings confirm the sensitivity of the bacterium to third-generation cephalosporins, aminoglycosides, quinolones, but the moderate sensitivity to imipenem and piperacillin/tazobactam is potentially indicative of future resistance to these antibiotics.

For reviewer 00722239

The required CT images were produced. Unfortunately, we do not have a picture of the *Aeromonas* blood culture as it is not common practice to do it in our clinical practice and unfortunately we have not been able to find it similar in retrospect. Mettere queste figure 1-4 nel testo a pag 7 dove parlo appunto della TC “A total body CT scan confirmed....”