Recurrent Infective Endocarditis of the Native Aortic Valve due to ESBL Producing *Escherichia coli* (*E coli*) after Therapeutic ERCP

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Abstract

We describe the first case of ESBL producing *E coli* endocarditis of the native aortic valve in which prophylaxis was performed according to currently available guidelines. A 75 year-old woman presented at our emergency department with a two week complaint of fever, fatigue, anorexia, diffuse abdominal pain after ERCP therapeutic. The initial laboratory examinations showed increased levels of ESR, CRP, fibrinogen, alkaline phosphatase, gammaGT, aspartate aminotransferase, alanine aminotransferase and direct fraction of bilirubin. Two blood cultures were positive for ESBL-producing *E coli*. The abdominal sonography revealed intrahepatic biliary tree dilation, cholecystectomy and minimal aerobilia in the left liver lobe. A transthoracic echocardiogram showed a small vegetation adherent to the aortic valve and a moderate amount of aortic and mitral regurgitation. Treatment with imipenem/cilastatin for 35 days was performed with a favorable outcome. During this period she underwent endoscopic metal stenting to replace the plastic tube. The patient was discharged after 40 days of hospitalization. **Conclusion:** Patients with high risk also for endocarditis and infections or bowel colonization with multiple drug resistant Enterobacteriaceae such as ESBL-producing *E coli* that have undergone multiple and repetitive therapeutic procedures are at risk for endocarditis with this type of bacteria. Prophylaxis and therapy with appropriate antibiotics must be considered in these patients.

Key words


Introduction

The spectrum of organisms causing native valve endocarditis is changing continuously. Despite the increasing incidence of infections caused by Gram-negative organisms, they remain a rare cause of native valve endocarditis - 1.8% [1]. Patients currently diagnosed with *E coli* endocarditis are older and they are often diabetics with underlying heart disease (degenerative valve lesions). The male/female ratio in confirmed cases of *E coli* native valve endocarditis is 10:26 (72.2% females) although infective endocarditis is more frequent in elderly men. Prosthetic valves are frequently affected (p<0.05); the main source of infection is the urinary tract and surgery is often necessary [2]. Although the mortality rate associated with this type of infection has decreased since 1960, the current 25% rate is still regarded as high [3]. Russo and Johnson proposed the acronym ‘ExPEC’ (extra-intestinal pathogenic *E coli*) as a new inclusive designation for certain strains of *E coli* that cause extra-intestinal infections associated with particular virulence factors. ExPEC strains are now known to belong predominantly to the *E coli* phylogenetic group B2 and, to a lesser extent, to group D, unlike commensal strains, which belong to phylogenetic groups A and B1[4]. Furthermore, ExPEC strains harbor multiple virulence factors that enable them to adhere, invade and escape host defenses or acquire essential nutrients, such as iron.

Case report

We describe the case of a 75-year-old female patient with a history of endocarditis after cholecystectomy in 2003; plastic tube biliary stenting for benign stenosis since 2008; three episodes of cholangitis in the last year treated with ceftiraxone and metronidazole that required 43 hospitalization days and 4 ERCPs and stent exchanges during the infectious episodes for which she received ampicillin prophylaxis. During the second episode of cholangitis she had positive blood cultures with ESBL producing *E coli*.

She presented at our emergency department with a two week complaint of fever, fatigue, anorexia, diffuse abdominal pain. She had pale skin, discreet yellowing of the sclerae,
respiratory rate of 20 breaths per minute, a heart rate of 94 beats per minute, and a blood pressure of 120/80 mm Hg in both arms, a III high-pitched, decrescendo, holosystolic murmur at the apex and a holodiastolic murmur at the lower left sternal border, moderate hepatomegaly. No jugular venous distention, pulmonary crackles, or peripheral edema was present. There was mild discomfort in the right upper abdominal quadrant and no evidence of peripheral stigmata of endocarditis. She denied use of antibiotics during the febrile episode.

The initial laboratory examinations showed increased ESR, CRP and fibrinogen values but normal PCT. The peripheral white blood cell count was 12,000 cells/dL, with a neutrophil count of 46% and 3% band forms. Hematocrit was 35.5 percent. Trombocytes were 549 x10^3/dL. The alkaline phosphatase level was 4,266 U/L, gammaGT 1,454 U/L, aspartate aminotransferase 87 U/L, alanine aminotransferase 75 U/l and total bilirubin 2.35 mg/dL with a conjugated fraction of 1.76 mg/dL. Blood iron level was 37.5 μg/dL. The following tests revealed normal values: total protein, albumin, electrolytes, urinalysis. An electrocardiogram revealed normal sinus rhythm with a normal axis and normal PR interval. There was no cardiomegaly or pulmonary edema on the chest roentgenogram. The abdominal sonography revealed intrahepatic biliary tree dilation, cholecystectomy, minimal aerobilia in the left liver lobe, a common bile duct of 14mm with sludge in the distal part and no abdominal collection. Cholangitis due to biliary stent obstruction was diagnosed and ampicillin/ sulbactam was administered for empiric coverage.

A transthoracic echocardiogram showed a small vegetation adherent to the aortic valve and a moderate amount of aortic and mitral regurgitation (Fig. 1). Left ventricular size and function were normal (55% estimated ejection fraction). Two blood cultures were positive for ESBL producing E coli susceptible to: cefoxitin, carbapenems, colistin and aminoglycosides (Vitek 2Compact, bioMerieux). The isolated E coli strain was molecularly characterized using PCR multiplex as being derived from the phylogenetic group B2. The strain was tested with PCR for harboring virulence genes: pap, sfâ, afa, hly, cnf, aer, fyu A, fim H and it proved to have the fyuA and fimH genes [5].

E coli endocarditis with one major Duck criterion (vegetation) and three minor criteria (blood culture, fever, history of endocarditis) was diagnosed. Antibiotic treatment was switched to imipenem-cilastatin (Tienam, Merck & co.) for 35 days, which improved the patient’s clinical condition. Gentamicin was added for synergy in the first 14 days. During this period she underwent endoscopic metal stenting to replace the plastic tube (Fig. 2).

The patient was discharged after 40 days of hospitalization. Surgical treatment was not considered because of the clinical response to antibiotic therapy, mild regurgitation of aortic valve and a high surgical risk due to co-morbidities.

**Discussion**

We described the first patient with native aortic valve endocarditis, due to ESBL-producing E coli in which all prophylactic measures recommended by currently approved guidelines had been applied. E coli isolated from blood cultures, similarly to other ExPEC, belongs to the B2 phylogenetic group thus explaining its involvement in infective endocarditis. The genotype of our strain could explain the virulence. FimH is an adhesive subunit of type 1 fimbriae expressed by different enterobacterial species. Fimbrial adhesins expressed by bacteria are protein structures able to recognize molecular receptors and to facilitate adherence to specific tissue surfaces in the host. This tip adhesin may also mediate bacterial autoaggregation and biofilm formation on catheter surface [6]. The fyu A gene encodes yersiniabactin, a siderophore (iron uptake system) first identified in HighPathogenicity Islands(HPIs) of Yersinia species strains [7]. Previous research demonstrated that this HPI could also be found in other Enterobacteriaceae such as ExPEC. This could explain the low iron levels found in our patient. The absence of other virulence genes is not surprising because strains resistant to quinolones present less virulence factors than sensitive strains [8].
Both diagnostic and therapeutic ERCP can lead to transient bacteremia, which is not clinically significant in most cases. Variable rates of up to 6.4% have been reported for diagnostic procedures and of up to 18% percent for therapeutic procedures [9]. Acute recurrent cholangitis is caused by biliary stent obstruction. Cholangitis following biliary stenting is a frequent cause of early stent removal and replacement by ERCP. A 25-40% risk of bacteremia is registered during cholangitis.

*E* coli is the most common organism isolated in bile and blood culture in cholangitis and after ERCP (27%, 59%). On the other hand, studies of the biofilm formed on blocked biliary stents revealed *E* coli as the most frequently isolated microorganism followed by *Enterococcus* spp [10]. Infections with resistant strains such as ESBL-producing strains are usually nosocomial. The major risk factors for infections due to ESBL-producing organisms are: advanced age, female gender, diabetes mellitus, underlying urinary tract infection, prolonged hospital stay, duration of ICU stay and prior exposure to cephalosporins, quinolones and three or more courses of antibiotic therapy within the preceding year [11]. The carbapenemers are commonly used as the drugs of choice for severe infections due to ESBL-producing Enterobacteriaceae. Intestine colonization with ESBL producing Enterobacteriaceae increases with: age, comorbidities, prolonged hospitalization and previous antibiotic treatment. Intestinal carriage could precede infections with ESBL-producing bacteria and biofilm formation on the biliary stent [12]. Only two cases of ESBL-producing Enterobacteriaceae endocarditis, both on prosthetic valves have been published [13, 14]. In our patient the source of bacteremia that produced endocarditis was cholangitis after ERCP.

The American Heart Association, European Society of Cardiology, British Society for Antimicrobial Chemotherapy and National Institute for Health and Clinical Excellence revised their guidelines for infective endocarditis prophylaxis. The current recommendations depart significantly from their prior guidelines. A landmark change in endoscopic practice is that the administration of prophylactic antibiotics solely to prevent infective endocarditis is not recommended in patients who undergo GI-tract procedures except for high risk patients, such as our patient. but only for *Enterococcus* spp. bacteremia. There are no recommendations for Gram negative bacteremia because of the low risk/benefit ratio in endocarditis prophylaxis [15].

### Conclusions

The international guidelines for infective endocarditis prophylaxis proved ineffective in our patient. The individual approach of each case could reduce the risk of bacteremia and endocarditis especially in high risk patients. Our case illustrates a number of important points. *E* coli could be considered an important cause of endocarditis in elderly women with recurrent cholangitis after biliary stenting. Prolonged hospital stay, repeated treatment with cephalosporins for cholangitis and for preventing bacteremia after repetitive ERCP could be risk factors for intestinal colonization with ESBL producing *E* coli and further infections with resistant strains. An empiric therapy that covers ESBL-producing bacteria may be required in certain patients with the above-mentioned risk factors and levels of infection severity.

### Conflicts of interest

None to declare.

### References