# Unexpected clinical case of *Pasteurella multocida* infectious endocarditis in a patient with iv drug abuse: why epidemiological history matters

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## Abstract

**Introduction** **Right-sided lesions caused by staphylococci are the most common clinical entity of infectious endocarditis (IE) among iv drug abusers. But some aspects of the epidemiological history are critical in terms of early detection of uncommon pathogens.**

**Case report** **We describe a clinical observation of native aortic valve IE caused by *Pasteurella multocida* in a 37-year-old female with a history of heroin addiction, alcohol abuse and liver cirrhosis.**

**She presented herself at our hospital with acute fever, chills, subconjunctival petechial hemorrhages, traces of scratches on the hands, splenomegaly, peripheral edema, elevated WBC and inflammatory serum markers. Initial transthoracic echocardiography was negative, but the patient was put on oxacillin for suspected right-sided IE. The transesophageal echocardiography revealed vegetation on noncoronary leaflet of aortic valve. Blood culture was positive with the growth of *P. multocida* in 4/4 samples.**

**On detailed questioning, a close domestic contact with cats was revealed. Oxacillin was switched to meropenem and tigecycline with a prompt clinical response. The *P. multocida* isolate was found to be susceptible to penicillins, so the patient was discharged after 3 weeks with recommendations to take amoxicillin for up to 4 weeks. At 3 and 6 months follow-up there were no signs of IE relapse revealed.**

**Conclusions** ***P. multocida* is a rare causative agent of IE. In our case, this pathogen was identified in a patient with injection drug use, where such etiology is not usually assumed. The close contact with cats was not taken into account, which caused late diagnosis and delayed therapy.**

**Keywords** **Infectious endocarditis, *Pasteurella multocida*, injection drug use, liver cirrhosis.**

## Introduction

Infectious endocarditis (IE) is a serious disease distinguished by high in-hospital mortality.[1,2] *Pasteurella multocida* is a rare causative agent of IE. In a recent review, Porter RS et al. described 36 cases of IE caused by *Pasteurella* spp., of which only 24 were related to *P. multocida*.[3] In this regard, the features of IE caused by this pathogen have not been fully determined, and

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there are no uniform guidelines developed for the treatment of such patients.

We present a clinical observation of *P. multocida*-associated native aortic valve IE in a patient with injection drug use (IDU), where both such etiology and localization of the lesions are uncommon. Her epidemiological history, a close contact with pets in particular, was initially underestimated, leading to an incorrect clinical judgment and inadequate therapy. The patient's condition was aggravated by decompensated liver cirrhosis, which, on the one hand, increased the risk of an unfavorable outcome, and, on the other hand, limited our options for treatment.

## Case report

A 37-year-old female, with a BMI of 20.7 kg/m$^2$, unemployed, was admitted to the hospital with complaints of an acute increase in body temperature up to 38.0°C with chills and severe weakness. Her anamnesis was marked by heavy smoking (20 pack-years, current smoker), long-term history of drug abuse, including 3 years of heroin addiction: her last heroin injection had been done 2 weeks before the admission to the hospital. She had been suffering from alcohol abuse for 19 years; in 2019 hepatitis C virus (HCV) infection complicated by liver cirrhosis (class B according to Child-Pugh) was diagnosed. The patient was referred to an infectious disease specialist, where ursodeoxycholic acid, ademetionine, furosemide, spironolactone and carvedilol were initiated; antiviral treatment was not provided. She took medications irregularly.

Three months before the present hospitalization, the patient had had a COVID-19 infection of moderate severity, she was treated as an outpatient, the prescribed medications included ibuprofen and oral antiviral umifenovir. At the time of admission her antibodies against SARS-CoV-2 were as follows: IgM 1.56 OE/mL (n<2), IgG 200.92 OE/mL (n<10).

The patient was married, had four children from four pregnancies and was living with her husband in a one-room rented apartment. Her family history was unremarkable.

About 3 weeks before the hospitalization she noted an increase in body temperature (up to 37.7°C) and a pain in the right hip; due to the suspicion of hip abscess she was examined by a surgeon, ultrasound examination of her hip was performed, no abnormalities were revealed and thus, no treatment was provided. But the patient continued to have episodes of fever, accompanied by chills. There was increasing general weakness reported; 3 days before the hospitalization she noticed abdomen enlargement and subcutaneous hematomas on her arms.

On admission, her condition was considered moderately severe, her axillar body temperature was 38.1°C, blood pressure - 100/60 mmHg, pulse rate - 110 beats/min, respiratory rate - 21/min, on-air oxygen saturation - 96%. Multiple telangiectasias were revealed on the face and the chest. Petechial hemorrhages were seen on the conjunctiva of the lower eyelid, subcutaneous hematomas – on the right thigh, elbows of both arms, forearms. There were traces of scratches seen on the skin of the hands, and bilateral edema of the feet. Percussion and auscultation of lungs was unremarkable, heart sounds were muffled, no murmurs revealed. The abdomen was moderately enlarged due to ascites, soft, moderately painful in the right hypochondrium. Percussion size of the liver was 13×11×9 cm, the edge was painful on palpation, the spleen was enlarged (20×10 cm). A neurological examination revealed no significant pathological changes with the exception of the signs corresponding to a mild hepatic encephalopathy.

The blood tests revealed elevated WBC, moderate anemia, thrombocytopenia, a significant increase in serum C-reactive protein (CRP) - 155 mg/L and procalcitonin >2 ng/mL, elevated creatinine level with MDRD GFR 28 mL/min/1.73 m$^2$. An increase in total and direct bilirubin, a significant decrease in albumin level and prolonged prothrombin time were seen. In urinalysis leukocyturia 500 cells/mqL (n=5-15) and erythrocyturia 300 cells/mqL (n=0-11) were observed. The urine culture upon admission was negative. Toxicological examination of the biological fluids (blood and urine) did not reveal ethanol traces.

Her ECG was normal, chest CT revealed bilateral mild hydrothorax, ultrasound and CT of the abdominal cavity confirmed the presence of ascites, hepatomegaly, splenomegaly and

identified a slight expansion of the portal vein up to 13 mm (n<12 mm). Transthoracic echocardiography (TTE) revealed mitral and tricuspid valve regurgitation of the 1st degree; there were no vegetations or other findings compatible with IE identified.

As her medical history (IDU) and clinical presentation (fever, subconjunctival hemorrhages) maintained a suspicion of IE (three minor modified Duke criteria, 2015), transesophageal echocardiography (TEE) was ordered, two sets of blood (aerobic and anaerobic) were taken for culture 12 hours apart, prior to the initiation of antibiotic therapy (ABT).

Oxacillin 2 g 4 times per day iv was given having in mind a high probability of right-sided IE caused by *Staphylococcus aureus (S. aureus)* in iv drug abusers along with the standard treatment of her liver cirrhosis and heart failure (albumin, furosemide, spironolactone, lactulose, etc.). The IE team decided to withhold from gentamicin use due to the presence of acute kidney injury (AKI) of unknown origin.

The TEE performed on the 3rd day revealed a hyperechogenic mobile structure of 10×9 mm in size located along the free edge of the noncoronary leaflet of the aortic valve (Figure 1).

On the 4th day of the presentation, the patient remained febrile and there was no improvement in inflammatory markers seen – Figure 2 and Table 1. A preliminary report indicated a positive blood culture with the growth of *P. multocida* in 4/4 samples. The isolate was sent to a reference laboratory for reidentification and susceptibility testing.

The patient was reexamined by the IE team. With additional detailed questioning, it turned out that 5 cats live in the patient's house, one of which had recently scratched her and bit her finger on her left hand. As such episodes had happened before, the patient did not pay special attention to this. Presumably the cat had bitten her about 3 weeks earlier.

Oxacillin was switched to meropenem 1 g 3 times per day iv. Three days later, tigecycline 100 mg loading dose, then 50 mg 2 times per day iv was added. Surgery was not offered due to the high perioperative risk associated with comorbidities. After changing the ABT, the patient's condition improved: her temperature and WBC returned to normal, CRP level decreased to 28.5 mg/L, peripheral edema, hydrothorax and ascites resolved – Table 1. The repeated blood culture performed 10 days later was negative.

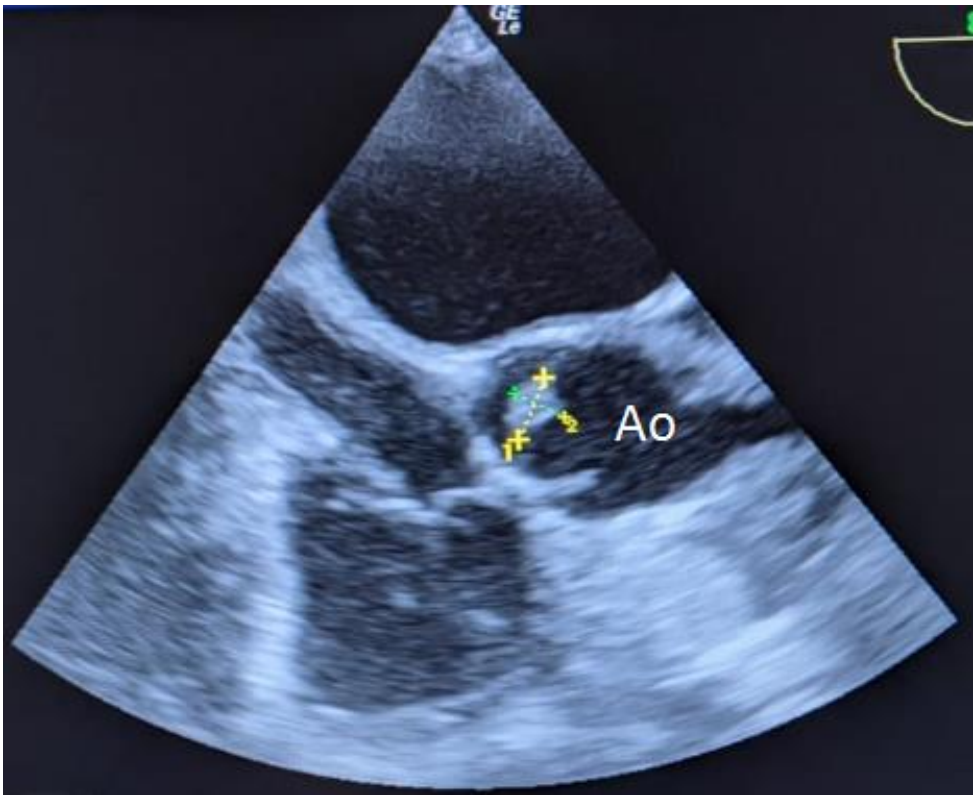
The result of reidentification in a reference laboratory confirmed the presence of *P. multocida* in blood samples, the isolate was susceptible to benzylpenicillin, amoxicillin + clavulanic acid, cefotaxime, ciprofloxacin, levofloxacin; meropenem minimal inhibitory concentration was 0.25 μg/mL (Table 2). The determination of susceptibility to antibiotics was carried out by the disk diffusion method and the gradient diffusion method using cation-balanced Mueller-Hintnon agar (BD, USA) with the addition of lysed horse blood, final concentration of 5 (E&O Laboratories Ltd, Scotland) and beta-nicotinamide adenine dinucleotide 20 mg/L (Fluka, BioChemika, Sweden) and interpreted in accordance with EUCAST (v 11.0) guidelines.[4] A control strain of *Haemophilus influenzae* ATCC 49766 was used to evaluate the quality of susceptibility testing.

Three weeks later the patient was discharged from the hospital for outpatient treatment with recommendations to continue oral ABT with amoxicillin 1 g TID for up to 4 weeks. Repeated TTE revealed no vegetations or regurgitation on aortic valve. TEE was not done due to the positive clinical response and a high risk of bleeding from varicose veins of the esophagus.

After 3 and 6 months, follow-up telephone contacts revealed the patient's condition remaining stable, she denied any complaints and reported completion of the recommended course of ABT. There were no readmissions or requests for medical help recorded, except the supervision of her GP, who conducted the treatment of liver cirrhosis and referred her to a drug addiction clinic, to assist in withdrawing from alcohol and drug abuse.

## Discussion

We aimed to present a clinical case of left-sided native valve IE caused by




A hyperechogenic mobile structure located along the free edge of the noncoronary leaflet of the aortic valve is indicated.

**Figure 1. Transesophageal echocardiography of the patient, 37 years old, on the 3rd day after admission**

| **Past history** |
|---|
| • Heroin addiction<br>• Alcohol abuse<br>• Smoking (20 pack-years)<br>• Hepatitis C complicated by liver cirrhosis<br>• Close home contact with cats |
| **Complaints and physical exam findings** |
| Body temperature, °C 37.7 38.1 38.5 36.0 |
| Chills |
| Subconjunctival hemorrhages |
| Scratches on hands |
| Ascites |
| Edema of feet |

**Figure 2. Medical history, complaints and physical exam findings**

**Table 1. Clinical course of infective endocarditis in a 37 years old female**

| | | Day of hospitalization | | |
|---|---|---|---|---|
| | | 1 | 4 | 21 |
| **Lab tests** | | | | |
| | Reference range | | | |
| WBC | 4-9 $10^9$/L | 17.0 | 20.0 | 9.0 |
| HBG | 120-140 g/L | 73 | 75 | 95 |
| PLT | 180-400 $10^9$/L | 63 | 33 | 78 |
| CRP | 0-5 mg/L | 155 | 95 | 25.8 |
| PCT | <0.05 ng/mL | >2 | >2 | <0.05 |
| Urea | 2.8-7.2 mmol/L | 17.2 | 15.2 | 6.8 |
| Creatinine | 59-104 mqmol/L | 182.1 | 156.4 | 98.3 |
| Albumin | 35-53 g/L | 13 | 15 | 20 |
| Total/direct bilirubin | 3-17/0-5 mqmol/L | 65.2/43.8 | 42.0/34.2 | 32.3/20.5 |
| PT | 15-17 sec | 23 | 22 | 20 |
| **Instrumental investigations** | | | | |
| Chest CT | | Bilateral mild hydrothorax | ND | Normal |
| Abdominal ultrasound and CT | | Ascites, hepatomegaly, splenomegaly, portal vein expansion | ND | Hepatomegaly, splenomegaly, portal vein expansion |
| TTE | | Mild mitral and tricuspid valve regurgitation | ND | Normal |
| TEE | | ND | Aortic valve vegetation 10×9 mm | ND |
| Blood culture, two sets 12 h apart | | NA | *P. multocida* | Negative |
| **Antibacterial therapy** | | | | |
| | | Oxacillin 2 g QID iv | Meropenem 1 g TID iv + tigecyc-line[1] 50 mg BID iv | Amoxicillin 1 g TID PO |

[1]Added to meropenem in 3 days, loading dose was 100 mg.

BID – two times per day; CRP – C-reactive protein; CT – computer tomography; HBG – hemoglobin; NA – not applicable; ND – not done; PCT – procalcitonin; PLT – platelets; PT – prothrombin time; QID – four times per day; **TEE** – transesophageal echocardiography; **TID** – three times per day; **TTE** – transthoracic echocardiography; **WBC** – white blood cells

**Table 2. Susceptibility testing of *P. multocida***

| Antibiotic | Amount of drug | IZD/MIC | Category |
|---|---|---|---|
| Benzylpenicillin | 1 IU | 23 mm/0.016 µg/mL | S |
| Amoxicillin + clavulanic acid | 2+1 µg | 21 mm | S |
| Cefotaxime | 5 µg | 32 mm/0.008 µg/mL | S |
| Ciprofloxacin | 5 µg | 32 mm | S |
| Levofloxacin | 5 µg | 34 mm/0.0016 µg/mL | S |
| Meropenem | | 0.25 µg/mL | -* |

**IZD** – inhibition zone diameter; **MIC** – minimal inhibitory concentration; **S** – susceptible.

*Susceptibility criteria are not available.

*P. multocida* in a young female with multiple risk factors and comorbidities (iv drug abuse, chronic HCV infection, alcohol addiction and decompensated liver cirrhosis).

*P. multocida* is widespread in the animal population considered to be a part of the normal microbiota of their oral cavity, nasopharynx, and upper respiratory tract. Zoonotic transmission to humans usually occurs through animal bites or contact with nasal secretions, with *P. multocida* being the most common isolate seen in human infections.[5] The majority of cases with the development of IE have been associated with bites and/or scratches of cats and dogs.[3]

The diagnosis of IE caused by *P. multocida* in clinical practice can be challenging, as the pathogen is rarely expected. Thus, it leads to an inadequate or untimely ABT. It is well known that IDU is an independent risk factor for IE; it affects mostly the tricuspid valve, characterized by a high prevalence of *S. aureus* in etiology and frequent relapses.[6] In the described case the initial assumption of right-sided staphylococcal IE turned out to be wrong, since the patient's epidemiological anamnesis (a close contact with pets, scratches on the skin and cat bites) was not taken into account.

Liver cirrhosis diagnosed in our patient as a complication of untreated HCV infection and long-term alcohol abuse could be considered an additional risk factor of severe *Pasteurella* infection. A recent literature review indicated a link between chronic liver diseases and *P. multocida*-associated septicemia.[7] Porter RS et al. also noted a significant increase in mortality among patients with *Pasteurella* spp. IE and concomitant liver diseases (62.5% versus 10.7% in a control group).[3] It distinguishes this group of patients from others as clinically more complex and requiring special attention and early treatment.

The overall mortality rate in patients with IE associated with *Pasteurella* spp. is reported to be 19%, which generally corresponds to this indicator in the general population.[1-3,6] Noteworthy, a particularly high mortality rate (35%) was recorded among patients in the absence of surgical treatment of the affected valve.[3] At the same time, the potential long-term benefits of valvular surgery in drug dependent individuals with uncomplicated IE remain unclear due to the high risk of recurrence of the disease and the requirement for reoperation.

In our case, the patient's treatment was complicated by severe concomitant diseases, primarily liver cirrhosis and thrombocytopenia, which significantly increases the perioperative risk. In addition, we observed a fairly rapid positive response to ABT; a 6-month follow-up was completed and there were no complications/relapse of IE revealed.

The choice of ABT for the treatment of *P. multocida* infections does not cause difficulties as the isolates usually remain susceptible to most antibiotics.[8] Nevertheless, rare cases of detection of *P. multocida* strains resistant to penicillins have been described.[9,10] In the previously cited review, the majority of patients received penicillins once the culture and susceptibility results became available.[3] By the time we started the therapy, we had no data on the sensitivity of *P. multocida* to antibiotics and, as a result, the ABT was not optimal. It is worth mentioning that in our case the choice of ABT was complicated by the presence of AKI.

## Conclusions

In conclusion, it should be emphasized that *P. multocida*, being a rare causative agent of IE, is currently poorly studied, and therefore it is relevant to accumulate clinical experience and develop recommendations for future patients' management. This case also highlights the importance of epidemiological anamnesis, such as cats exposure, as it can alter the expected etiology of IE and further treatment.

**Consent:** Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

**Authors' contributions statement:** OEU, SMN and NAC conducted the clinical examination and treatment intervention. ENB and NVI performed microbiological investigations, the identification of blood culture isolate and susceptibility testing. NVM and ISK drafted the manuscript. SAR supervised all decisions on behalf of the IE team and reviewed the manuscript. All authors read and approved the final version of the manuscript.

**Conflicts of interest:** All authors – none to declare.

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