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MEDICINE

# Endocarditis of Native Valve due to *Proteus mirabilis*: Case Report and Literature Review

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## Abstract

Endocarditis due to *Proteus mirabilis* is very uncommon and the optimal surgical and/or antibiotic treatment is not well defined. Guidelines from the AHA and ESC recommend prolonged courses of combined antibiotic therapy but information regarding the clinical presentation, the choice of treatment, the surgical management, and the duration of therapy can only be taken from clinical cases reported in literature. We describe a case of native valve endocarditis due to *Proteus mirabilis*, successfully treated with antibiotic therapy alone with a review of the relevant literature on this topic.

**Keywords** Infective endocarditis · *Proteus mirabilis* · Antibiotic therapy

## Introduction

Infective endocarditis (IE) is a life-threatening condition. If left untreated, it can have adverse consequences including elevated mortality. The usual treatment involves a prolonged course of antibiotics with up to 40–50% of patients needing valve replacement during initial hospital admission [1]. The most common organisms implicated are *Staphylococci*, *Streptococci*, and *Enterococci*; Gram-negative agents are rarely implicated [2]. *Proteus mirabilis* is one such pathogen that frequently appears in the bloodstream during urinary tract infection but rarely results in endocarditis. The best antibiotic treatment for these patients is currently unknown; guidelines from the AHA and ESC recommend prolonged courses of combined antibiotic therapy [1, 3] but information regarding the clinical presentation, the choice of treatment, the surgical management, and the duration of therapy can only be taken from clinical cases reported in literature. Although a systematic review was recently published [4], our aim was to compare data, investigate clinical characteristics of patients and risk factors, type of treatment, duration of therapy with a focus on native valve endocarditis. We describe a case of native valve endocarditis due to *Proteus mirabilis*, successfully treated with antibiotic therapy alone and a literature review on this topic (through 1 November 2020).

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## Case Report

A 86-year-old female with a history of aorta arch replacement in 2015 and atrial fibrillation in medical treatment was admitted to our Hospital with fever, urinary burning, and altered mental status. At the time of admission, the patient's temperature was 39 °C, the blood pressure was 90/60 mmHg, and the heart rate was 94 beats per minute. No focal neurological signs were present. Cardiac examination was negative and the lungs were clear to auscultation. Laboratory investigation revealed the following measurements: white blood cell count 14.2 × $10^3$ cells/μL with 90% neutrophils, creatinine 2.57 mg/dL (0.40–1.10 mg/dL), and C-reactive protein (CRP) 13.22 mg/

dL (0.00–0.75 mg/dL). Sequential Organ Failure Assessment (SOFA) Score was 3 points. The urine sediment showed 500 white blood cells and bacteria on microscopy examination.

Renal ultrasound showed bilateral non-obstructive kidney stones with no urologic indication to extraction or dissolution. Two blood culture sets and urine sample were drawn, and an empiric therapy with ciprofloxacin iv 400 bid was started.

ESBL-negative *Proteus mirabilis*, resistant to ciprofloxacin and trimethoprim/sulfamethoxazole, was cultured both from blood (Table 2) and urinary culture samples. After a questionable transthoracic cardiac ultrasound, the suspicion of endocarditis persisted and the patient underwent transesophageal echocardiogram (TEE) which revealed a mobile mass measuring 12 mm attached to the anterior leaflet of the mitral valve and a moderate regurgitation.

The patient fulfilled the Duke clinical criteria for definite endocarditis based on the trans-esophageal echocardiographic findings and positive blood culture (two major criteria). The surgeon did not pose a clear indication for valvular replacement but a "wait and see" indication and a revaluation by TEE after 2 weeks of antibiotic therapy.

The patient was treated with intravenous ceftazidime 2 g × 2/day and gentamicin 160 mg/day according to renal function. During the first week of hospitalization, the patient reported a sudden visus reduction. The fundoscopic examination and formal ophthalmology evaluation showed a posterior pole ischemic edema of the retina to be reported to a supratemporal branch retinal artery occlusion due to embolic event. After 1 week of antibiotic therapy, surveillance blood cultured was negative and after 2 weeks, TEE showed a reduction of the vegetation. Gentamicin was stopped and ceftazidime was continued. After 4 weeks of antibiotic treatment, the patient was discharged with a home therapy ertapenem for 4 weeks. After 8 weeks, at the end of antibiotic treatment, the TEE showed an absence of vegetation. The serum creatinine value was 1.66 mg/dL and the CRP was 1.26 mg/dL.

## Results

We searched the literature using the Pubmed database (http://www.ncbi.nlm.nih.gov/pubmed). Query terms were "*Proteus*" and "Endocarditis." To date, only 13 cases about IE due to *Proteus* spp. were published that include sufficient clinical details reported in Table 1. Including our clinical case, the mean age of the patients was 54.1 years (range: 25–86 years). Eight (57.1%) were female, and 6 (42.9%) were male. Considering the cases that reported the presence of urinary tract infection (9/14), in 8/9 (88.8%) cases, the patients had a concomitant urinary tract infection due to *Proteus* spp. Nephrolithiasis was not reported in 8/14 (57.1%). In the remaining 6/14, nephrolithiasis was present in 5/6 (83.3%), in 1 case (16.7%) was absent. In 10/14 case, the vegetation was attached to a native valve (71.4%), mitral valve in 8/10 cases, and aortic valve in 2/10 cases. Instead, in 4/14 cases (28.6%), the vegetation was attached to a prosthetic valve; in 2/4 cases, it concerned the tricuspid valve in intravenous drug users. Embolic events were present in 4/14 cases (28.6%), whereas in 5/14 cases (35.7%) were not mentioned.

With respect to antimicrobial treatment, in 2/14 cases, it was not reported. In 7/12 (58.3%) patients, a combination regimen based on a beta-lactam agent was started, in 5/7 cases plus aminoglycoside, in 2/7 cases plus fluoroquinolone. In the others cases, a monotherapy with a beta-lactam agent (4/12) and chloramphenicol (1/12) was prescribed.

In 3/14 case, the duration of antibiotic therapy was not reported. In 7/11 (63.6%) cases, it was equal or longer to 6 weeks while in 4/11(36.4%) cases, it was inferior or equal to 4 weeks. Six out of 14 patients (42.8%) underwent surgical intervention of valve replacement: in one case treated with monotherapy and only for 3 weeks, in 3 cases in combination therapy for 6 weeks, in 2 cases, no therapy data was available. All cases were cured, and one patient died. Eight of the 14 cases that did not undergo surgery (57.1%), 6/8 were cured (75%) and 2/8 died (25%).

In 3/8 (37.5%) patients who did not undergo surgical intervention and were cured, a combination therapy was administrated and its duration was equal or longer to 6 weeks.

Of all cases reported, 11/14 patients were cured (78.6%) and 3/14 died (21.4%) (Table 2).

## Discussion

Non-HACEK (species other than *Haemophilus* species, *Aggregatibacter actinomycetemcomitans* (previously known as *Actinobacillus actinomycetemcomitans*), *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species) Gram-negative bacteria (GNB) are uncommon causes of infective endocarditis. The International Collaboration on Endocarditis (ICE) study, a multinational IE registry, reported an incidence of endocarditis due to non-HACEK GNB of approximately 2% [2].

According to the AHA, in approximately half of the cases, the responsible pathogens are *Escherichia coli* and *Pseudomonas aeruginosa*. The IE due to Gram-negative non-HACEK involves a prosthetic valve in the 59% of cases. Although management included cardiac surgery in 51% of cases, the in-hospital mortality rate is 24% [3]. We did an updated review of the cases described in the literature including the review of Kalra [5–11]. After 2011, we found 6 more cases [12–17].

The mean age of study population was 54.1 years (range: 25–86 years).

As in almost all cases (71.4%), including ours, the involved valve was the native mitral valve.

**Table 1** Clinical cases of *Proteus* spp. endocarditis reported in the PubMed database

| Previously reported cases of valve *Proteus mirabilis* endocarditis/reference | Age | UTI/ nephrolithiasis | Embolic event | Valve | Antibiotic therapy | Duration of therapy | Surgical intervention | Outcome |
|---|---|---|---|---|---|---|---|---|
| Kalra A., 2011 | 62/F | Pos/no | No | Native MV | Ampicillin + gentamicin | 6 weeks | None | Cure |
| Claasen D., 2007 | 58/F | Pos/yes | Yes | Native MV | Ceftriaxone | 4 weeks | None | Cure |
| Lloyd M., 2005 | 64/M | Pos/yes | No | Native MV | Ceftriaxone | 3 weeks | MV replacement | Cure |
| Vandenbos F., 2000 | 25/F | NR/yes | Yes | Native MV | Cefotaxime + ofloxacin | 6 weeks | MV replacement | Cure |
| Carruthers MM., 1977 | 45/M | Pos/NR | NR | Native MV | Ampicillin + gentamicin followed by carbenicillin + kanamycin | 12 days and 3 days | None | Death |
| Rosen P., 1973 | 52/F | NR/NR | NR | Native MV | Chloramphenicol | NR | None | Death |
| Albuquerque I., 2019 | 62/M | NR/NR | No | Prosthetic AV | Cefepime + levofloxacin | 6 weeks | AV replacement | Cure |
| Liu C.H., 2015 | 71/M | Neg/NR | NR | Native AV | Augmentin + gentamicin followed by ceftazidim + amikacin followed by ceftriaxone + fosfomycin | 20 days in total | None | Cure |
| Ananthasubramaniam K., 2000 | 50/F | Pos/NR | No | Prosthetic AV | NR | NR | AV replacement | Death |
| Salsano A., 2016 | 43/F | Pos/NR | NR | Prosthetic TV | NR | NR | TV replacement | Cure |
| Rimoldi S. G, 2016 | 39/F | NR/NR | Yes | Native AV | Piperacillin/tazobactam followed by tigecycline followed by daptomycin + ertapenem | 6 weeks | AV replacement | Cure |
| Goel R, 2015 | 42/M | NR/NR | | Prosthetic TV | Amoxicillin | 6 weeks | None | Cure |
| Brotzki CR., 2016 | 59/M | Pos/yes | NR | Native AV | Ceftriaxone + gentamicin | 6 weeks | None | Cure |
| Our case report | 86/F | Pos/yes | Yes | Native MV | Ceftazidime + gentamicin followed by ertapenem | 4 weeks and 4 weeks | None | Cure |

*MV*, mitral valve; *AV*, aortic valve; *TV*, tricuspid valve; *UTI*, urinary tract infection; *NR*, not reported; *Pos*, positive

**Table 2** Blood culture and sensitivity panel

| *Proteus mirabilis* | MIC | Interpretation |
|---|---|---|
| Amoxicillin/clavulanate | ≤ 2 | S |
| Amikacin | ≤ 2 | S |
| Ertapenem | ≤ 0.5 | S |
| Ciprofloxacin | 1 | R |
| Colistin | > 8 | R |
| Cefepime | ≤ 1 | S |
| Fosfomycin | ≤ 16 | S |
| Gentamicin | ≤ 1 | S |
| Imipenem | 8 | I |
| Meropenem | 1 | S |
| Trimethoprim-sulfamethoxazole | 160 | R |
| Cefotaxime | ≤ 1 | S |
| Ceftazidime | ≤ 1 | S |
| Piperacillin/tazobactam | ≤ 4 | S |

*MIC*, minimum inhibitory concentration; *S*, sensitive; *R*, resistant; *I*, intermediate

In 88.8% cases, the patients had a concomitant urinary tract infection (UTI). Therefore, we can assert that the IE by *Proteus* is sustained by urinary tract infections and this could also explain the higher prevalence reported in the female population. In 83.3% cases, the patients presented nephrolithiasis which could be explained by the ability of *Proteus* to produce urease that convert urea to ammonia, determining an increase in pH value which favors the precipitation of the magnesium ammonium phosphate and calcium phosphate crystals, resulting in the formation of the renal stones [6]. In 4 cases (8.6%), an embolic event was reported: two cases on retinal artery (6, our case), one case on the spleen [7], one case on the liver [14].

The optimal antimicrobial regimen to treat *Proteus* endocarditis is unknown. The scientific statement on IE from the American Heart Association (AHA) published in 2015 recommends a combination of antibiotic therapy with a beta-lactam (penicillins, cephalosporins, or carbapenem), and either a third- or fourth-generation cephalosporin or ampicillin and ciprofloxacin in patients unable to tolerate cephalosporin and ampicillin [3]. The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC) recommended treatment is early surgery plus long-term (at least 6 weeks) therapy with bactericidal combinations of betalactams and aminoglycosides, sometimes with additional quinolones or cotrimoxazole [1].

Our clinical case is the sixth case among those reported in literature who was successfully treated with antimicrobial therapy alone. In our literature review, we found that in 58.3%, a combination regimen was administrated according to the recommendations, while in 41.7%, a monotherapy regimen was administered.

The AHA scientific statement says that cardiac surgery in combination with prolonged courses of combined antibiotic therapy (6 weeks) is reasonable [1]. In our review, we did not have sufficient sample sizes to assess for an association between the type of antimicrobial treatment regimen administered or whether surgery was performed and outcome.

However, we can say that all the patients who underwent surgical intervention, excluding a case in which the patient had congenital aortic insufficiency, survived and a shorter antimicrobial treatment was administered. Therefore, the 75% of patients who did not undergo surgical intervention were cured and the duration of administration was in 4/6 cases equal or longer than 6 weeks. Two patients recovered with a therapy of less than 4 weeks. The 2 other cases that died were reported on 1973 and in 1977 when the antibiotic choices were limited [9, 10].

An important limitation of the study is that only Pubmed was searched.

## Conclusion

Native endocarditis due to *Proteus* is rare. The major risk factor appears to be urinary tract infections with the concomitant presence of nephrolithiasis. The embolic events are not rare. The optimal antimicrobial treatment, the duration of treatment, and the association with surgery are unknown. The patients who underwent surgery have done a shorter antibiotic therapy. However, most patients were treated only with medical therapy with a good cure rate and the only two cases that died were reported in literature on 1973 and 1977. The clinical cases reported in literature are the only guide for the clinicians, but are a few sample size to assess for an association between the type of antimicrobial treatment regimen administered or whether surgery was performed and outcome; so it is more important to report the clinical case in order to provide an increase in sample size.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethic Approval** Not applicable.

**Consent to Participate** Not applicable.

**Consent for Publication** Not applicable.

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