Infective endocarditis by *Proteus* species: a systematic review

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Abstract

Proteus spp. are members of the Enterobacteriaceae family and are Gram-negative, rod-shaped bacteria known to mainly cause urinary tract infections (UTIs) in humans. However, even though scarce evidence exists suggesting their potential to cause infective endocarditis (IE), a study summarizing the existing evidence is lacking. The purpose of this study was to systemically review all published cases of IE by *Proteus* species in the literature. A systematic review of PubMed, Scopus and Cochrane Library (through 5th May 2020) for studies providing epidemiological, clinical and microbiological data as well as data on treatment and outcomes of IE by *Proteus* species was performed. A total of 16 studies, containing data of 16 patients, were included. A prosthetic valve was present in 25%, while the most common causative pathogen was *P. mirabilis*. Aortic valve was the most common infected site in 33.3%, followed by mitral valve in 26.7%. Diagnosis was set with transesophageal echocardiography in 37.5%, and transthoracic echocardiography in 25%, while the diagnosis was set at autopsy in 25%. Fever and sepsis were present in 100% and 84.6%, respectively. Aminoglycosides and cephalosporins were the most common antimicrobials used for treatment. Clinical cure was noted in 62.5%, while overall mortality was 43.8%. This systematic review describes IE by *Proteus* species in detail and provides information on epidemiology, clinical presentation, treatment and outcomes.

Keywords Endocarditis, systematic review, *Proteus*, *P. mirabilis*.

Introduction

Proteus spp. are members of the Enterobacteriaceae family and are motile, lactose-negative, urease-producing, Gram-negative, rod-shaped bacteria that are able to differentiate from typical enterobacterial bacilli into highly elongated rods covered with thousands of flagella, thus producing swarming colonies.^{1,3} Even though there are several species of the *Proteus* genus, the vast majority of the isolated clinical

isolates are *P. mirabilis* and *P. vulgaris*.¹ *Proteus* spp. are most commonly associated with urinary tract infections (UTIs), both in regular hosts, as well as in patients with indwelling catheters and anatomic or functional abnormalities of the urinary tract.^{1,3}

P. mirabilis, due to its flagella and the production of adhesins, can form biofilms quite quickly and easily, leading to fouling of foreign materials, such as urinary tract catheters.⁴ This ability to form biofilms is associated with its ability to cause UTIs.³ Furthermore, *Proteus* spp. are commonly isolated from the blood of patients, more commonly in the context of a UTI.⁵ Importantly, *Proteus* spp. have been associated with several other infections beyond UTIs, such as primary bacteremias and more rarely with other types of infections, such as respiratory tract, or wound infections.⁵

The ability of *Proteus* to form biofilms, in combination with its ability to cause bacteremia, could denote the potential to cause complicated bloodstream infections, such as infective endocarditis (IE), which is of particular importance, due to the notable morbidity and mortality that IE carries.^{6,7} Due to its rarity, IE by

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Gram-negative bacteria poses therapeutic dilemmas due to the lack of adequate experience and clear guidelines on how to treat these infections.⁷ Interestingly, even though there are some case reports with short literature reviews summarizing the characteristics of IE by *Proteus* species, a review adequately summarizing all available evidence in the literature is lacking.⁸

The aim of this paper was to systemically review all published cases of IE by *Proteus* species in the literature and describe the epidemiology, microbiology, clinical characteristics, treatment and outcomes of these infections.

Methods

Data search

For this study, we adopted the Meta-analysis of observational studies in epidemiology (MOOSE) guidelines.⁹ Eligible studies were identified through search of PubMed, Scopus and Cochrane Library with the following terms: *Proteus* AND endocarditis. Day of last search was 5th May 2020.

Study selection

Studies meeting the following criteria were included in analysis: 1) published in English; 2) reporting data on patients' clinical characteristics, microbiology, treatment and outcomes. Studies with the following criteria were excluded from the analysis: 1) secondary research papers (e.g., reviews), editorials and papers not reporting results on primary research; 2) studies not in humans; 3) studies not in English. Two investigators (PI, GV) using Abstrackr¹⁰ independently reviewed the titles and abstracts of the resulting references and then they retrieved and rescreened the full text publications of potentially relevant articles. Study selection was based on consensus. Reference lists of included studies were searched for relevant articles.

Outcomes of interest

The primary outcomes of the study were to record data on: a) epidemiology of patients with IE by *Proteus* species and b) patients' outcomes. Secondary outcomes were to record data on: a) the exact site of infection, b) the clinical

characteristics of the patients, c) antimicrobial susceptibility and d) their treatment. Finally, another endpoint was the identification of independent risk factors for mortality by these infections.

Data extraction and definitions

Data from each eligible study were extracted by two investigators (PI, GV). The extracted data included study type, year of publication and country; patient demographic data (age and gender); patient's relevant medical history (previous cardiac surgery or cardiac valve replacement, time after cardiac valve replacement); infection data and microbiology (infection site, isolated strains, presence of complications, presence of embolic phenomena); treatment administered for IE; and outcomes (i.e., cure or death). Data on microbiology and relation of death to the index infection was reported according to the study authors. Diagnosis of IE was confirmed by the investigators based on the information provided by the authors and the modified Dukes' criteria if the diagnosis was at least possible (at least 1 major and 1 minor criterion or at least 3 minor criteria) or if pathological data established a diagnosis of IE.¹¹ The complications recorded included any organ dysfunction or clinical deterioration that was considered by the authors to be related to the IE. The quality of evidence of the outcomes of included studies was assessed using the Grading of recommendations assessment, development and evaluation (GRADE).¹²

Statistical analysis

Data are presented as number (%) for categorical variables and median (interquartile range, IQR) or mean ($\pm$ standard deviation, SD) for continuous variables. A univariate linear regression analysis was conducted to identify factors associated with all-cause mortality and IE-specific mortality of patients with IE by *Proteus* species. The above-mentioned statistics were calculated with GraphPad Prism 6.0 (GraphPad Software, Inc., San Diego, CA).

Results

Literature search

A total of 294 articles from PubMed, Scopus and Cochrane Library were screened. After reviewing the titles and abstracts, 23 articles were selected for full-text review.¹³⁻³⁵ From these studies, 8 were excluded from the review: 3 had non-extractable data,²⁸⁻³⁰ 2 did not describe IE by *Proteus*,^{31,32} 1 full text could not be found,³³ 1 did not include any outcomes of interest³⁴ and 1 study was a secondary research article (review).³⁵ One additional study was found during the hand-screening of the included articles' references. Finally, 16 met the present study's inclusion criteria.^{8,13-27} The review process is graphically presented in Figure 1.

Included studies' characteristics

The 16 studies that were finally included in the present analysis involved 16 patients in total. Table 1 (appendix) summarizes the characteristics of included studies. Among those studies, 10 were conducted in North and South America, 5 in Europe and 1 in Asia. There were 13 case reports and 3 case series, thus, the overall quality of the evidence that contributed to this systematic review was rated as low to very low, implying that further research is very likely to have an important impact on our confidence in the data presented in this systematic review.¹²

Epidemiology of IE by *Proteus* species

Age of patients ranged from 1 to 71 years, mean age was 52.4 years, and 56.3% (9 out of 16 patients) were male. A prosthetic cardiac valve was present in 25% (4 out of 16 patients) and was metallic in 1 patient and bioprosthetic in 3 patients. Furthermore, 18.8% (3 patients) had a history of intravenous drug use (IVDU), 12.5% (2 patients) had a history of a previous IE, 6.3% (1 patient) had a central venous catheter and 6.3% (1 patient) had a foreign material in the heart (bristle) due to unintended ingestion. The characteristics of patients with IE by *Proteus* species can be seen in Table 2 (Appendix).

Microbiology of IE and antimicrobial resistance of *Proteus* species

The most commonly identified species was *P. mirabilis* in 87.5% (14 out of 16 patients), *P. vulgaris* in 6.3% (1 patient), while in 6.3% (1 patient), the species were not specified. *S. aureus* and *E. coli* were isolated in 6.3% (1 patient) of IE each. Resistance to trimethoprim-sulfamethoxazole was noted in 33.3% (1 out of 3 patients), to quinolones in 25% (1 out of 4 patients), to aminopenicillins in 16.7% (1 out of 6 patients), while no resistance was noted to cephalosporins, piperacillin/tazobactam, carbapenems, and aminoglycosides.

Diagnosis of IE by *Proteus* species

The most common site of infection was the aortic valve in 33.3% (5 out of 15 patients with available data), the mitral valve in 26.7% (4 patients), the tricuspid valve in 20% (3 patients), the mural endocardium in 12.5% (2 patients) and the eustachian valve in 6.3% (1 patient). Diagnosis was set with transesophageal echocardiography in 37.5% (6 out of 16 patients), with transthoracic echocardiography in 25% (4 patients), at autopsy in 25% (4 patients), through valve culture in 6.3% (1 patient) while diagnosis was set empirically due to non-diagnostic echocardiography in 6.3% (1 patient). In the last case, the patient presented with signs and symptoms of IE and was treated as such, while according to the Duke criteria, diagnosis of IE was possible (one major and one minor criterion), thus, this study was included in this analysis.

Clinical characteristics of IE by *Proteus* species

Fever was present in 100% (15 out of 15 patients with available data); sepsis in 84.6% (11 out of 13 patients with available data), a concurrent UTI in 43.8% (7 out of 16 patients), while embolic phenomena occurred in 42.9% (6 out of 14 patients with available data) and immunologic phenomena and heart failure in 14.3% (2 out of 14 patients) each. Furthermore, 13.3% (2 out of 15 patients with available data) developed a paravalvular abscess, and a skin and

Figure 1. Flow diagram of study inclusion

soft tissue infection (SSTI) was present in 6.3% (1 out of 16 patients).

Treatment and outcomes of IE by *Proteus* species

Treatment administered for IE by *Proteus* species can be seen in detail in Table 1 and in summary in Table 2. Duration of treatment among survivors ranged from 4 to 6 weeks, with a median duration of 6 weeks. Surgical intervention was performed in 31.3% (5 out of 16 patients). Clinical cure was achieved in 62.3% (10 out of 16 patients), overall mortality was 43.8% (7 patients) and the mortality attributed directly to IE was 31.3% (5 patients).

Statistical analysis of IE by *Proteus* species

We performed a univariate linear regression analysis in order to identify any association between gender, age, being an IVUD, having a prosthetic cardiac valve, concurrent UTI, having IE at the aortic, the mitral or the tricuspid valve, presenting with sepsis or embolic phenomena, treatment with aminoglycosides or

cephalosporins, and having a surgery, with overall mortality and IE-specific mortality. The analysis did not identify any statistically significant association with mortality.

Discussion

IE is an uncommon disease that carries a significant mortality and is mostly caused by Gram-positive microorganisms. However, Gram-negative microorganisms may be involved in some cases of IE.^{28,36} More specifically, IE by *Proteus* species is a very rare disease. Thus, even though there are some case reports in the literature, there is no study summarizing its characteristics. To our knowledge, this is the first study that systematically reviews IE by *Proteus* species, and provides thorough information on its clinical and microbiological characteristics, as well as data on treatment and outcomes.

Mean age at diagnosis of patients with *Proteus* IE herein was 52.4 years, while a slight male predominance was noted; findings that share similarity with IE caused by non-HACEK Gram-

negative bacteria (NHGNB) according to literature.^{28,29,37} Among all patients with IE by *Proteus* species, 25% had a prosthetic cardiac valve, which is similar to the rate in other studies that ranged from 19% to 67%.^{28,37,39} Furthermore, 12.5% of patients with IE by *Proteus* species had a previous episode of IE, while, in other studies, that rate ranged from 3.8% to 67%.^{28,37,39} Finally, 18.8% of patients with IE by *Proteus* species were IVDU, while the rate of IVDU patients with IE by NHGNB in the literature varied widely from 0% to 93%.^{28,37,39}

The most commonly infected intracardiac sites were the aortic valve in 33.3% and the mitral valve in 26.7%. In other studies, with IE by NHGNB, the infected sites differed, with the aortic valve being most commonly infected in 42%, followed by the tricuspid valve in 33% in one study³⁷ and the mitral valve being the commonest infected valve in 31%, followed by the aortic valve in 24% in another study.²⁸

Regarding clinical presentation, fever was the most common symptom, and it occurred in all patients with available data, while 84.6% of patients were septic. In studies with IE caused by NHGNB, presence of fever ranged from 77% to 92%.^{37,38} Among patients with *Proteus* IE, 14.3% developed heart failure, which is similar to the rate in other studies that ranged from 8% to 38%.^{28,29,37,38} Embolic and immunologic phenomena in *Proteus* IE were present in 42.9% and 14.3% respectively, which are similar to the rates in IE caused by NHGNB that ranged from 14% to 65% and from 8% to 40% respectively.^{28,37,39} A paravalvular abscess occurred in 13.3% of patients with IE by *Proteus* species, which approximates the rate of abscess development in IE by NHGNB, that ranged from 5.2% to 42%.^{28,37,39}

Among the studies included in this systematic review, the most common species causing IE was *P. mirabilis*, while in one case *P. vulgaris* was identified and in one remaining case the species was not noted. This is, however, in line with the literature that shows that, in general, *P. mirabilis* is the most clinically relevant species causing human infection.¹ Interestingly, a close association of IE with concomitant UTI was

noted, since 43.8% of patients with IE had a diagnosis of UTI at the same time, which confirms the predilection of this pathogen to causing UTIs.^{1,3} In terms of pathophysiology, the most reasonable scenario would be that a UTI led to bacteremia and that led to IE. However, based on the data provided from the included studies, one cannot exclude the possibility of a bacteremia due to IE leading to bacterial seeding of the kidneys and secondary UTI.

Proteus spp. are not globally considered to pose a significant problem in terms of antimicrobial resistance until now. This systematic review identified resistance of *Proteus* strains to co-trimoxazole and quinolones in up to 33%, while the resistance to other antimicrobials was minimal. However, many of the studies were old, and may not represent the current trends of antimicrobial resistance. Additionally, few studies provided data on antimicrobial resistance and thus, this information should be read with caution. These data come to confirm the literature, where increased resistance of *Proteus* strains to co-trimoxazole and quinolones has been noted, even though those resistance rates were higher than in this systematic review.⁴⁰

Given the above, it is no surprise that for the treatment of IE by *Proteus* species, aminoglycosides, cephalosporins and aminopenicillins were the most common antimicrobials used, while quinolones and carbapenems were used in fewer cases. Mortality was, however, high, with two out of five patients dying and the vast majority of them dying specifically due to the IE by *Proteus* which was higher than the rate in studies of IE by NHGNB, where mortality ranged from 5% to 24%.^{28,29,38,39} However, it should be noted that even though the in-hospital mortality was relatively low in those studies, two studies showed data on one-year mortality that reached up to 30%, thus, implying that IE by NHGNB is a lethal disease.^{37,39}

The present systematic review has some limitations. First of all, it consists of case reports and case series, rendering the quality of evidence contributed low to very low. Furthermore, the possibility of publication bias also exists.

However, since there is no study in the literature giving specifically data on IE by *Proteus* species with an adequate number of patients, we could not have used another methodology than the one we used.

Conclusions

To conclude, this study describes the epidemiology, clinical characteristics, microbiology, treatment and outcomes of IE by *Proteus* species. *P. mirabilis* was the most common cause, while mortality was high. Antimicrobial resistance does not seem to be a problem until now, with most of the cases being treated with aminoglycosides, cephalosporins and aminopenicillins.

Authors' contributions statement: PI conceived the study; PI and GV collected and analyzed the data and led the writing. All authors read and approved the final version of the manuscript.

Conflicts of interest: All authors – none to declare.

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Appendix

Table 1. Characteristics of the included studies

Study, year published	Age (years)	Gender	Site of infection	Microbiology of infection	Site of microorganism isolation	Treatment administered, duration	Infection outcomes, n
Taniguchi et al., 1950 ¹³	55	Female	Mural	<i>Proteus</i> spp.	Blood Vegetation Splenic abscesses	Penicillin, NR and aminoglycoside, NR	Clinical cure 0 ^a Overall mortality 1 IE-specific mortality 1
Hiller et al., 1968 ¹⁴	1	Male	TrV	<i>Proteus mirabilis</i> <i>Escherichia coli</i>	Blood	Chloramphenicol, NR	Clinical cure 0 Overall mortality 1 IE-specific mortality 1
Rosen et al., 1973 ¹⁵	52	Female	NR	<i>Proteus mirabilis</i>	Blood Valve Urine	Chloramphenicol, NR	Clinical cure 0 Overall mortality 1 IE-specific mortality 1
Carruthers et al., 1977 ¹⁶	45	Male	MV	<i>Proteus mirabilis</i>	Blood Urine	Aminopenicillin, 12 days and aminoglycoside, 12 days then carbenicillin, 3 days and aminoglycoside, 3 days	Clinical cure 0 Overall mortality 1 IE-specific mortality 0
Venezio et al., 1984 ¹⁷	67	Male	Mural	<i>Proteus mirabilis</i>	Blood	Cephalosporin, 42 days post-surgery and aminoglycoside, 42 days post-surgery Surgery	Clinical cure 1 Overall mortality 0
Ananthasubramaniam et al., 2000 ¹⁸	50	Female	AoV	<i>Proteus mirabilis</i>	Blood Urine	NR Surgery	Clinical cure 0 Overall mortality 1 IE-specific mortality 1
Sawhney et al., 2001 ¹⁹	68	Male	Eustachian valve	<i>Proteus vulgaris</i>	Blood	NR	Clinical cure 0 Overall mortality 1 IE-specific mortality 1
Lloyd et al., 2005 ²⁰	64	Male	MV	<i>Proteus mirabilis</i>	Blood	Cephalosporin, NR Surgery	Clinical cure 1 Overall mortality 0
Claassen et al., 2007 ²¹	58	Female	MV	<i>Proteus mirabilis</i>	Blood Urine	Cephalosporin, 28 days	Clinical cure 1 Overall mortality 0
Kalra et al., 2011 ⁸	62	Female	MV	<i>Proteus mirabilis</i>	Blood Urine	Aminopenicillin, 42 days and aminoglycoside, 42 days	Clinical cure 1 Overall mortality 0

Study, year published	Age (years)	Gender	Site of infection	Microbiology of infection	Site of microorganism isolation	Treatment administered, duration	Infection outcomes, n
Liu et al., 2015 ²²	71	Male	AoV	<i>Proteus mirabilis</i>	Blood Wound	Aminopenicillin, NR and aminoglycoside, NR then cephalosporin, NR and fosfomycin, NR and aminoglycoside, NR	Clinical cure 1 Overall mortality 1 IE-specific mortality 0
Goel et al., 2015 ²³	42	Male	TrV	<i>Proteus mirabilis</i>	Blood	Aminopenicillin, 42 days	Clinical cure 1 Overall mortality 0
Rimoldi et al., 2016 ²⁴	39	Female	AoV	<i>Proteus mirabilis</i> <i>Staphylococcus aureus</i> (MSSA)	Blood Valve	Carbapenem, 42 days and daptomycin, 42 days	Clinical cure 1 Overall mortality 0
Brotzki et al., 2016 ²⁵	59	Male	AoV	<i>Proteus mirabilis</i>	Blood Urine	Carbapenem, NR then cephalosporin, 42 days and aminoglycoside, 42 days ^b	Clinical cure 1 Overall mortality 0
Salsano et al., 2016 ²⁶	43	Female	TrV	<i>Proteus mirabilis</i>	Blood Urine BAL	NR Surgery	Clinical cure 1 Overall mortality 0
Albuquerque et al., 2019 ²⁷	62	Male	AoV	<i>Proteus mirabilis</i>	Prosthetic valve BAL	Cephalosporin, 42 days and quinolone, 42 days Surgery	Clinical cure 1 Overall mortality 0

^aDefined as clinical resolution of the infection as a result of treatment.

^bMonotherapy with carbapenem led to clinical failure. Time-kill assays revealed that the combination of ceftriaxone and gentamicin were associated with the most efficient bacterial killing.

Each study included one patient.

AoV – aortic valve; **BAL** – bronchoalveolar lavage; **MV** – mitral valve; **NR** – not reported; **TrV** – tricuspid valve.

Table 2. Characteristics of 16 patients with infective endocarditis by *Proteus* species. Values show cases among patients with available data.

Characteristic	Value
Male, n (%)	9 out of 16 (56.3%)
Age, mean ($\pm$ SD) in years	52.4 ($\pm$ 16.9)
Predisposing factors	
Prosthetic valve, n (%)	4 out of 16 (25%)
IVDU, n (%)	3 out of 16 (18.8%)
Previous IE, n (%)	2 out of 16 (12.5%)
CVC, n (%)	1 out of 16 (6.3%)
Foreign material in heart (traumatic), n (%)	1 out of 16 (6.3%)
Site of infection inside heart	
Aortic valve, n (%)	5 out of 15 (33.3%)
Mitral valve, n (%)	4 out of 15 (26.7%)
Tricuspid valve, n (%)	3 out of 15 (20%)
Mural endocardium, n (%)	2 out of 15 (13.3%)
Eustachian valve, n (%)	1 out of 15 (6.7%)
Microbiology	
<i>Proteus mirabilis</i> , n (%)	14 out of 16 (87.5%)
<i>Proteus vulgaris</i> , n (%)	1 out of 16 (6.3%)
<i>Proteus</i> spp., n (%)	1 out of 16 (6.3%)
Polymicrobial, n (%)	2 out of 16 (12.5%)
<i>Staphylococcus aureus</i> , n (%)	1 out of 16 (6.3%)
<i>Escherichia coli</i> , n (%)	1 out of 15 (6.7%)
Antimicrobial resistance	
Trimethoprim-sulfamethoxazole, n (%)	1 out of 3 (33.3%)
Quinolones, n (%)	1 out of 4 (25%)
Aminopenicillins, n (%)	1 out of 6 (16.7%)
Cephalosporins, n (%)	0 out of 8 (0%)
Piperacillin/tazobactam, n (%)	0 out of 3 (0%)
Carbapenems, n (%)	0 out of 4 (0%)
Aminoglycosides, n (%)	0 out of 9 (0%)
Method of diagnosis	
Transesophageal echocardiography, n (%)	6 out of 16 (37.5%)
Transthoracic echocardiography, n (%)	4 out of 16 (25%)
Echocardiography non-diagnostic*, n (%)	1 out of 16 (6.3%)
Autopsy, n (%)	4 out of 16 (25%)
Clinical characteristics	
Feverish, n (%)	15 out of 15 (100%)
Septic, n (%)	11 out of 13 (84.6%)
Concurrent UTI, n (%)	7 out of 15 (43.8%)
Embolic phenomena, n (%)	6 out of 14 (42.9%)
Heart failure, n (%)	2 out of 14 (14.3%)
Immunologic phenomena, n (%)	2 out of 14 (14.3%)
Paravalvular abscess, n (%)	2 out of 15 (13.3%)
Concurrent SSTI, n (%)	1 out of 16 (6.3%)
Treatment	
Duration of treatment in weeks, median (IQR)	6 (6, 6)
Aminoglycosides, n (%)	6 out of 13 (46.2%)
Cephalosporin, n (%)	6 out of 13 (46.2%)
Aminopenicillin, n (%)	3 out of 13 (23.1%)
Chloramphenicol, n (%)	2 out of 13 (15.4%)
Carbapenem, n (%)	1 out of 13 (7.7%)
Quinolone, n (%)	1 out of 13 (7.7%)
Fosfomycin, n (%)	1 out of 13 (7.7%)
Carbenicillin, n (%)	1 out of 13 (7.7%)

Characteristic	Value
Penicillin, n (%)	1 out of 13 (7.7%)
Daptomycin, n (%)	1 out of 13 (7.7%)
Surgical intervention, n (%)	5 out of 16 (31.3%)
Outcomes	
Clinical cure, n (%)	10 out of 16 (62.5%)
Deaths due to infection, n (%)	5 out of 16 (31.3%)
Deaths overall, n (%)	7 out of 16 (43.8%)

*Diagnosis of IE met current (Duke's) diagnostic criteria.

CVC – central venous catheter; **IE** – infective endocarditis; **IVDU** – intravenous drug use; **IQR** – interquartile range; **SD** – standard deviation; **SSTI** – skin and soft tissue infection; **UTI** – urinary tract infection.