Journal of Advances in Medicine and Medical Research

Volume 35, Issue 24, Page 100-127, 2023; Article no.JAMMR.110815
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Microbiological and Epidemiological Aspects of Endocarditis Caused by *Rothia* spp.: A Systematic Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2023/v35i245328

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/110815

Systematic Review Article

Received: 15/10/2023
Accepted: 19/12/2023
Published: 20/12/2023

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ABSTRACT

Background and Aim: *Rothia*, a genus comprising pleomorphic Gram-positive bacteria found in the human oral, intestinal, and skin microbiota, is recognized as an opportunistic pathogen. Case reports of *Rothia* spp. endocarditis in the scientific literature are scarce, with limited knowledge of relevant data on *Rothia* endocarditis and clinical aspects of its treatment. The objective of this literature review is to compile clinical aspects of endocarditis caused by *Rothia* species, analyzing results and clinical practices to elucidate the most important risk factors, comorbidities, prognostic factors, and appropriate antibiotic treatment options.

Methods: Employing the PRISMA model, a systematic review was conducted utilizing PubMed, SciELO, and Google Scholar databases, encompassing articles published from 1978 to November 2023. Pertinent aspects were systematically recorded and summarized for subsequent analysis.

Results: *Rothia dentocariosa* (48.69%), *Rothia mucilaginosa* (22.37%), *Rothia aeria* (14.47%), and *Rothia kristinae* (14.47%) were recognized as the agents of endocarditis cases. Patients exhibited an average age of 48.5 years, with a notable male preponderance (71.6%). Clinical manifestations of *Rothia* spp. endocarditis presented similar features compared to other Gram-positive bacterial endocarditis cases. The mortality rate was notably lower than observed in other infectious endocarditis instances (11.84%). Predominant risk factors included preexisting cardiovascular diseases (50%), followed by odontological procedures, caries, and precarious oral hygiene (17.1%), immunocompromised status (14.47%), injectable illicit drug use (11.84%), and diabetes (9.21%). Embolic events were documented in 35.53% of patients, predominantly in Central Nervous System (28.95%). Mycotic aneurysms were identified in 6.58% of cases. Resistance to antibiotics was identified in only 13.16% of strains causing endocarditis, although certain strains displayed characteristics indicative of multidrug resistance.

Conclusion: Despite its rarity, *Rothia* spp. endocarditis exhibits clinical parallels with endocarditis caused by other Gram-positive bacteria, but with a comparatively lower mortality rate. Challenges in identifying *Rothia* spp. species based on cultural and microscopic characteristics, associated to early resolution in antibiotic therapy, seems to contribute to the underreporting of endocarditis caused by these bacteria.

Keywords: Rothia spp; endocarditis; opportunistic infection; rare endocarditis agents.

1. INTRODUCTION

Rothia is a genus of Gram-positive bacteria. Species within this genus exhibit pleomorphism, manifesting in coccoid, spherical, rod-shaped, or filamentous forms. They typically have a diameter of approximately 1.0 µm, with occasional irregular dilations and rounded ends reaching up to 5.0 µm in diameter. The coexistence of various forms within a single colony is commonly observed. Non-motile and lacking endospore formation, *Rothia* ferment carbohydrates, primarily producing lactic acid, and are generally catalase-positive [1,2].

The taxonomy of the *Rothia* genus was initially proposed based on biological and metabolic characteristics attributed primarily to *Rothia dentocariosa*, previously classified as a member of the *Nocardia* genus within the Actinomycetaceae family. Unlike *Nocardia*, *Rothia* bacteria are not acid-alcohol-resistant [3]. *Rothia mucilaginosa*, initially classified as *Stomatococcus mucilaginosus*, was included as a second species after genetic and molecular analyses [1]. Recent genetic studies led to the reclassification of three *Kocuria* species (*K. kristinae*, *K. halotolerans*, and *K. koreensis*) into the *Rothia* genus [2]. Currently, *Rothia* is classified within the Micrococcaceae family, comprising fourteen recognized species [4], with ongoing research indicating potential undiscovered species [5].

Rothia bacteria are part of the normal human microbiota in the skin [6,7,8], intestine [9,10,11], and oral cavity [12,13,14,15,16]. Considered opportunistic pathogens with low virulence [17], *Rothia* spp. infections are associated with invasive medical procedures [17,18] and conditions leading to immunocompromise [18,19]. Comparative studies on microbiome composition revealed alterations due to COVID-19, with a notable increase in *Rothia* spp. relative abundance [20,21,22].

Infections by *Rothia* spp. are considered rare. The relative abundance of *Rothia* spp. in the oral microbiota is often associated with better periodontal health [23,24,25]. However, an increased relative abundance of *Rothia* spp. in the oral microbiota is also observed in underlying diseases, especially in individuals with cancer and acute neutropenia [26,27,28]. Dysbiosis, with an imbalance favoring the abundance of a particular opportunistic pathogen, poses a risk to the host. Regarding the oral microbiota, this imbalance may increase the risk of dental caries, periodontal disease, and even traverse local immune barriers, leading to infections in other parts of the body or systemic infections [29]. *Rothia* spp. have been implicated in opportunistic infections affecting the respiratory tract, meningitis, cerebral empyema, infectious arthritis, endophthalmitis, keratitis, skin infections, pyelonephritis, infectious ascites, peritoneal dialysis-related peritonitis, catheter-associated infections, bacteremia, sepsis, and endocarditis [30-33].

Infective endocarditis is a systemic and potentially life-threatening condition characterized by bacterial infection affecting native or prosthetic heart valves, the endocardial surface, or cardiac devices. This clinical entity is associated with prolonged hospitalizations, significant morbidity, and elevated mortality rates [34,35]. Currently, approximately 130 pathogens, predominantly *bacteria* and fungi, are recognized as causative agents of infective endocarditis [36]. The majority of cases, ranging from 80% to 90%, are attributed to Gram-positive cocci, mainly from the *Staphylococcus*, *Streptococcus*, and *Enterococcus* genera [35,37-42].

The pathogenesis of infective endocarditis involves the adherence of microorganisms, particularly on cardiac valves or prosthetic valves, leading to the formation of bacterial vegetations. These vegetations can induce lesions on heart valves and facilitate the dissemination of infection to other organs. The intricate infectious dynamics of endocarditis pose substantial health risks, often culminating in fatal outcomes. Endocardial infection typically arises from direct colonization or, more commonly, during episodes of bacteremia. Asymptomatic bacteremia, frequently associated with oral flora followed dental procedures, is prevalent in humans. Nosocomial infections commonly arise following surgical prosthetic valve implantation, vascular catheterization, hemodialysis, or other invasive medical interventions. Community-acquired infections are often linked to immunosuppression, intravenous drug usage, poor oral hygiene, degenerative valve disease, or rheumatic fever resulting from infections with Lancefield Group A *Streptococcus pyogenes* [41]. On a global scale, the incidence and mortality rates of infective endocarditis have experienced a substantial increase over the past three decades. Chen et al. [37] estimated a case count of 478,000 and 28,750 deaths in 1990, escalating to 1,090,530 cases and 66,320 deaths in 2019. During the period from the 1970s to 2000, the annual incidence of infective endocarditis worldwide was estimated at 5 to 7 cases per 100,000 person-years [43]. In the last two decades, incidence rates have averaged 10 to 15 cases per 100,000 people per year, indicating a notable surge in cases globally [37,44].

According to Graevenitz [45], reports of infective endocarditis caused by *Rothia* spp. in the scientific literature are very scarce, and relevant data on *Rothia* endocarditis and clinical aspects of its treatment are not well-known. The objective of this literature review is to gather clinical aspects of endocarditis caused by *Rothia* species, analyzing results and clinical practices that help elucidate the most important risk factors and comorbidities, prognostics, and suitable antibiotic treatment options.

2. METHODS

A systematic review was conducted following the methodological guidelines proposed by Moher et al. [46], as updated by Page et al. [47], utilizing the PRISMA model. The objective of the review was to investigate the etiology of Infective Endocarditis caused by *Rothia* species, including associated comorbidities or baseline conditions, prognosis, and antibiotic treatment. The review utilized sources from databases including PubMed, SciELO, and Google Scholar. The search employed descriptors such as “*Rothia*”, “*Stomatococcus mucilaginosus*”, “*Micrococcus mucilaginosus*”, "*Actinomyces dentocariosus*", "*Nocardia salivae*", "*Nocardia dentocariosa*", "*Kocuria halotolerans*", "*Kocuria koreensis*", “*Kocuria kritinae*”; “Endocaditis”; “valve”, “Prothetic valve”, and “Cardiac” The reviewed manuscripts spanned publications in English, Portuguese, and Spanish, covering the period from 1978 to 2023.

Studies and case reports of Infective Endocarditis caused by *Rothia* species were evaluated, and cases were included in the review if they met the Updated Modified Duke Criteria [48]. In this context, the incorporated investigations needed to satisfy a minimum of two criteria: either a culture derived from hemoculture or culture from cardiac biopsy samples, identified through biochemical methods, mass spectrometry, genetic sequencing analysis, or an alternative method tailored for the precise determination of *Rothia* genus species. Confirmation through diagnostic methodologies affirming the existence of vegetation in cardiac tissue, explanted prosthetic valve or sewing ring, ascending aortic graft, endovascular intracardiac implantable electronic device, or originating from an arterial embolus was also required. Although the inclusion filter adheres to the Updated Modified Duke Criteria, some clinical aspects and the diagnostic trajectory of endocarditis will not be examined, as well as the clinical assessment of the cardiological evaluation within the article's scope. This constrained focus allows for a more detailed exploration of the epidemiology, identification, and secondary complications associated with *Rothia* species implicated in endocarditis cases, along with an evaluation of the efficacy of antibiotic therapy employed in this pathogenic context.

After reading the full text of each article and case report, relevant information was selected and evaluated. The most crucial aspects were recorded and summarized for analysis. Review articles, opinion articles, and articles with incomplete data or controversial diagnostic interpretations were excluded. A flowchart (Fig. 1) was provided to illustrate the rationale for selecting the reference material for this review. Summarized results are categorized by species (Tables 1,2,3, and 4) and antibiotic resistance profile of the strains (Table 5), subsequently analyzed in the discussion section.

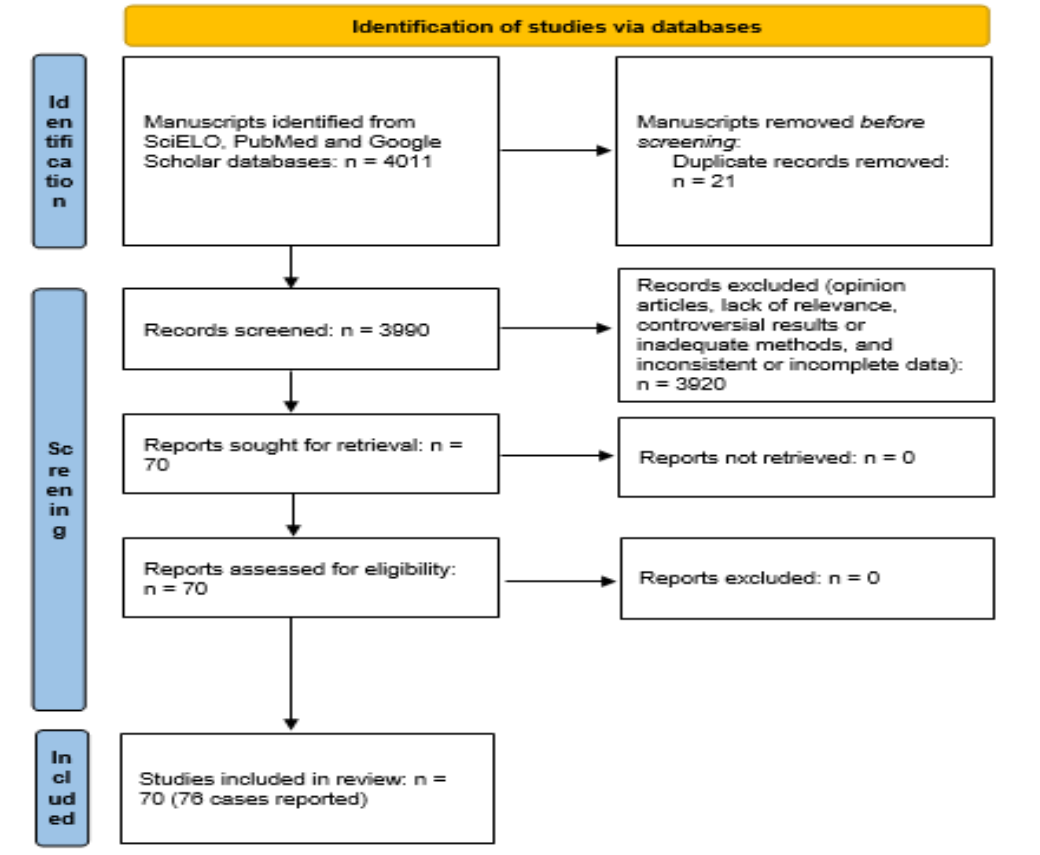

Fig. 1. Flowchart of the screening process of publications according to the PRISMA model
**Source: the authors*

Table 1. Key clinical aspects of endocarditis cases attributed to *Rothia aeria*

Reference	Gender	Age	Comorbidities or underlying conditions	Suspected infection sources	Other infection sites	Antibiotic treatment	Outcome
Tarumoto et al. [49]	Male	40	Allergic conjunctivitis. smoking	Not reported	Stroke	Ceftriaxone, Gentamicin and Imipenem	Deceased (stroke)
Holleran and Kasiah [50]	Not reported	58	-	Not reported	Multiple infective intracranial aneurysms. Subarachnoid haemorrhage	Not reported	Death (subarachnoid haemorrhage)
Thiyagarajan et al. [51]	Male	61	Hypertension and renal calculi	Not reported	Cerebral septic emboli	Benzylpenicillin, Rifampicin and Gentamicin	Discharged after 4 weeks
Crowe et al. [52]	Male	48	Hypertension, ex-smoker, IgM positive for *Mycoplasma pneumoniae*	Not reported	Multiple infective intracranial aneurysms; Cerebral septic embolization.	Benzylpenicillin, Gentamicin, Ceftriaxone, Rifampicin, and Ciprofloxacin	Discharged
Hiraiwa and Izumi [53]	Male	63	Renal transplantation. Immunosuppressive therapy. Dental caries with gingival pain	Not reported	Cerebral septic emboli	Levofloxacin, Vancomycin, Ceftriaxone, Trimethoprim/ sulfamethoxazole, and Penicillin G	Discharged after 8 weeks
Nicodemo et al. [54]	Male	25	-	Not reported	-	Levofloxacin, Ampicillin and Vancomycin	Discharged after 5 weeks
Kim et al. ([55]	Male	53	History of ankylosing spondylitis, aortic valvuloplasty, tricuspid valvuloplasty, and a Maze operation owing to severe aortic valve regurgitation with atrial fibrillation. Four dental implant placements. Immunosuppressive therapy	Not reported	-	Ceftriaxone and Doxycycline	Discharged after 4 weeks with sequels (complete atrioventricular block occurred after surgery; permanent pacemaker implanted 10 days after the surgery)
Collarino et al. [56]	Male	57	History of of right sub-thalamic ischaemic stroke and severe mitral insufficiency without ventricular dysfunction for dystrophic mitral valve	Not reported	Subarachnoid haemorrhage. Femoral mycotic aneurysms	Amoxicillin and Gentamicin	Discharged after 4 weeks
Aoiyagi et al. [57]	Male	53	Smoking	Cut on his left	Multiple systemic	Cefmetazole, Penicillin G	Discharged

Reference	Gender	Age	Comorbidities or underlying conditions	Suspected infection sources	Other infection sites	Antibiotic treatment	Outcome
				thumb and wound licking	embolisms. Subarachnoid hemorrhage. Mycotic aneurysms of the peripheral and visceral arteries		
Greve et al. [58]	Female	18	Phenylketonuria. Interstitial viral pneumonia.	Viral pneumonia	Skin rashes.	Gentamycin (resistant), Ampicillin and Ceftriaxone	Discharged
Zeng et al. [59]	Not reported	-	Not reported	Not reported	-	Imipenem, Cilastatin sodium and Vancomycin	Discharged after 36 days

**Source: the authors*

Table 2. Key clinical aspects of endocarditis cases attributed to *Rothia dentocariosa*

Reference	Gender	Age	Comorbidities or underlying conditions	Suspected infection sources	Other infection sites / clinical signs	Antibiotic treatment	Outcome
Pape et al. [60]	Male	61	-	Not reported	-	Gentamicin and Penicilin	Discharged
Schafer et al. [61]	Male	57	Refitting of dental bridges one month before	Oral infection	-	Fenoximetilpenicilina, Streptomycin and Penicilin G	Discharged after 4 months
Broeren and Peel [62]	Male	53	Impaired function of the mitral valve as a consequence of previous attacks of rheumatic fever. Dental carie.	Nor reported	-	Rifampicin, Penicillin and Gentamycin	Discharged after 8 weeks
Shands [63]	Male	41	Previous mitral valve pro-lapse, myxomatous degeneration, and regurgitant flow	Not reported	-	Penicilin and Vancomycin	Discharged
Isaacson and Grenko [64]	Male	27	Migraine headaches	Not reported	Brain abscess	Penicilin G	Discharged
Ruben [65]	Male	71	Previous valve prosthesis implant	Previous invasive cardiac interventions (14 years late)	-	Vancomycin, Gentamicin, Penicilin and Ceftriaxone	Discharged
Sudduth and Farrar [66]	Male	35	"Heart murmur" diagnosed fourteen years before. Alcohol abuse	Not reported	Perivalvular Abscess	Nafcillin, Gentamicin and Vancomycin	Discharged
Weersink et al. [67]	Male	17	Rheumatic with consequent cardiac valve disease	Not reported	Abdominal aneurysm	Ceftriaxone, Amoxicillin/Clavulanate, Gentamicin and Penicilin	Discharged
Binder et al. [68]	Female	70	Dental carie and Alcohol abuse	Oral infection	-	Penicilin, Netilmycin and	Deceased

Reference	Gender	Age	Comorbidities or underlying conditions	Suspected infection sources	Other infection sites / clinical signs	Antibiotic treatment	Outcome
						Vancomycin	(mitral valve reconstruction surgery complications)
Binder et al. [68]	Male	67	Periodontal disease and residual root of a lost molar. Aortic valve replacement with a bioprosthesis 30 years before	Oral infection	Bacteremia with maculopapular rash	Rifampicin and Ciprofloxacin	Discharged after nine weeks
Binder et al. [68]	Male	50	Extensive periodontitis	Oral infection	Abscess between aortic wall and composite graft. Skin rashes	Rifampicin and Ceftriaxone	Discharged after six weeks
Kong et al. ([69]	Male	37	Alcohol abuse. Several dental caries. Hepatic carcinoma diagnosed two months after endocarditis	Oral infection	-	Netilmicin, Metronidazole and Amoxicillin	Discharged
Ferraz et al. [70]	Male	54	valvular heart disease diagnosed 20 years late.	Not reported	Aortic root abscess	Penicilin, Gentamycin and Cloxacillin	Deceased (cardiac failure)
Braden et al. [71]	Female	7	Perimembranous ventricular septal defect with congestive heart failure	Not reported	-	Cefaclor, Amoxicilin, Imipenem-Cilastatin and Ceftriaxone	Discharged after 9 days
Llopis and Carratalà [72]	Male	62	Alcohol abuse. Several dental caries.	Oral infection	Vertebral osteomyelitis	Penicilin, Gencamycin and Ceftriaxone	Discharged
Nguyen et al. [73]	Male	15	Poor dental hygiene	Oral infection	-	Penicilin and Gentamicin	Discharged
Ricaurte et al. [74]	Male	49	“Heart murmur” since his childhood. Odontologic intervention (root canal) six months before. Cocaine and marijuana abuse.	Oral infectiion	Ischaemic stroke	Cefotaxime, Gentamycin and Penicilin G	Discharged
Larkin et al. [75]	Female	61	Iiliac embolectomy. Chronic atrial fibrillation and long-standing mitral stenosis	Not reported	-	Penicilin G	Discharged
Salamon and Prag [76]	Female	72	Inoperable rectal cancer and extensive abdominal metastasis.	Not reported	-	Antibiotic therapy not performed	Deceased (Deteriorated health status. No septic shock signals)
Salamon and Prag [76]	Male	51	Arterial hypertension. Dental abscesses.	Not reported	-	Penicillin G and Dicloxacillin	Discharged
Salamon and	Male	78	Acute myocardial	Not reported	-	Penicillin G	Discharged

Reference	Gender	Age	Comorbidities or underlying conditions	Suspected infection sources	Other infection sites / clinical signs	Antibiotic treatment	Outcome
Prag [76]			Infarction. Admitted with angina pectoris. multiple diverticulosis and bleeding in the sigmoid colon.				
Boudewijns et al. [77]	Female	17	Impaired function of the aortic valve as a consequence of a congenital bicuspid valve. Valvotomy at the age of 4 and percutaneous dilatation at the age of 13. Orthodontic treatment.	Previous invasive cardiac interventions or orthodontic treatment.	Subarachnoid hemorrhage. infective intracranial aneurysms. Skin rashes.	Penicillin and Amikacin	Discharged after 20 days
Almuzara et al. [78]	Female	22	-	Not reported	Subarachnoid hemorrhage. Multiple septic embolisms in the SNC	Ceftriaxone, Vancomycin, Gentamicin, Penicilin	Discharged
Morris et al. [79]	Female	41	Bilateral nephrectomy and failed renal transplant. Peritoneal dialysis peritonitis eleven years before presentation.	Catheter contamination	-	Vancomycin, Gentamicin and Trimethoprim-sulfamethoxazole	Discharged
Sadhu et al. [80]	Male	55	Type 2 diabetes mellitus, essential hypertension, and liver cirrhosis due to hepatitis C. Several dental extractions without antibiotic prophylaxis.	Oral infection	Multiple cerebellar hemorrhages	Penicillin G and Gentamicin	Discharged
Shakoor et al. [81]	Male	37	Cholecystectomy after an episode of acute cholecystitis two months prior to presentation. Smoking.	Not reported	Osteomyelitis	Vancomycin, Penicillin-G and Ceftriaxone	Discharged
Chowdhary et al. [82]	Male	34	Methamphetamine abuse	Not reported	Ischaemic stroke	Vancomycin, Ceftriaxone and Doxycycline	Discharged after 2 weeks
Fridman et al. [83]	Male	58	-	Nor reported	Endophthalmitis. Cerebral infarct, with intracranial hemorrhaging	Amoxicillin, Clavulanate and Penicilin G	Discharged after 2 weeks
Willner et al. [84]	Female	62	Not reported	Not reported	Brain embolic infarction	Vancomycin, Ceftriaxone and Penicilin G	Discharged after 6 weeks
Doddapaneni et al. [85]	Male	65	Aortic valve stenosis, hypertension, and migraines	Not reported	Ischaemic stroke	Penicillin G and Ceftriaxone	Discharged
Myadam et al. [86]	Male	37	Three previous episodes of pneumonia with antibiotic treatment.	Oral infection	-	Rifampim	Discharged

Reference	Gender	Age	Comorbidities or underlying conditions	Suspected infection sources	Other infection sites / clinical signs	Antibiotic treatment	Outcome
			Congenital bicuspid aortic valve stenosis with bioprosthetics. Dental abscesses				
Kisilevsky et al. [87]	Male	62	hypertension, type 2 diabetes mellitus and dyslipidaemia. Poor dental hygiene and inconsistent dental care. Dental caries.	Oral infection	Multiple infective intracranial aneurysms and ischaemic stroke	Ceftriaxone	Discharged after three months
Elkattawy et al. [88]	Male	69	Diabetes mellitus, hypertension, hepatitis-C, and end-stage renal disease on hemodialysis	Not reported	Multiple embolic hemorrhagic strokes	Ceftriaxone and Penicillin	Discharged
Greve et al. [58]	Male	46	Previous valve prosthesis implant	Valve prosthesis implant	-	Vancomycin, Rifampicin, Gentamicin and Fenoximetilpenicilina	Discharged (no follow-up)
Franconieri et al. [32]	Female	21	Coarctation of the aorta repaired 18 days after birth and a persistent but asymptomatic ventricular septal defect	Not reported	-	Amoxicillin and Gentamicin	Discharged
Obi et al. [89]	Male	33	Implanted cardioverter defibrillator five years before	Cardioverter defibrillator implant surgery	-	Vancomycin, Gentamycin, Rifampin,	Discharged after 6 weeks
Jianjian et al. [90]	Male	40	Not reported	Not reported	Subarachnoid hemorrhage. Brain abscess. Thrombo-cytopenic purpura	Piperacillin Tazobactam, Tigecycline, Penicillin, Amikacin, and Meropenem	Discharged

**Source: the authors*

Table 3. Key clinical aspects of endocarditis cases attributed to *Rothia kristinae*

Reference	Gender	Age	Comorbidities or underlying conditions	Suspected infection sources	Other infection sites	Antibiotic treatment	Outcome
Lai et al. [91]	Female	89	Ischaemic bowel disease, , short bowel syndrome, Total parenteral nutrition, Port-A Catheter	Not reported	-	Vancomycin, Teicoplanin and Oxacillin	Discharged
Bastidas et al. [92]	Male	42	-	Accidental left hand incision	-	Gentamicin and Oxacillin	Discharged
Seyman et al. [93]	Male	65	Diabetes mellitus	Not reported	-	Ampicillin and Sulbactam	Discharged after 6 weeks

Reference	Gender	Age	Comorbidities or underlying conditions	Suspected infection sources	Other infection sites	Antibiotic treatment	Outcome
Citro et al. [94]	Male	74	Systemic hypertension. Diabetes mellitus. Diabetic foot.	Not reported	Pneumonia	Ceftriaxone, Metromidazole, Sulbactam/Ampicillin, Gentamicin and Rifampicin	Deceased (multiple organ failure due to sepsis)
Hollanda et al. [95]	Female	27	Systemic Lupus Erythematosus	Not reported	-	Not described	Discharged
Aleksic et al. [96]	Female	35	Chronic hepatitis C. Intravenous Illicit drug user.	Not reported	Stroke	Vancomycin, Gentamicin and Ceftriaxone	Discharged
Robles-Marhuenda et al. [97]	Male	56	Aortic-bifemoral bypass surgery secondary to Leriche's syndrome	Not reported	-	Cloxacillin and Amoxicillin	Discharged
Horino et al. [98]	Male	61	Hemodialysis patient. Diabetes mellitus	Not reported	Septic arthritis	Piperacillin, Ampicillin/Sulbactam and Gentamicin	Discharged
Rojas-Molina et al. [99]	Female	44	-	Not reported	Endophtalmitis	Vancomycin, Ampicillin	Discharged
Ali et al. [100]	Female	-	Ventricular septal defect. Poor dental hygiene and carious teeth.	Oral infection	-	Ampicillin, Tetracycline, Azithromycin, Ciprofloxacin, Linezolid, Vancomycin, Amikacin, Moxifloxacin, Gentamicin and Daptomycin	Discharged after 2 weeks
Dewi et al. [101]	Female	25	-	Not reported	-	Cefotaxime, Gentamicin	Deceased (Cardiac arrest. Endocarditis by coinfection of *Rothia kristinae* and *Streptococcus alactolyticus*)

**Source: the authors*

Table 4. Key clinical aspects of endocarditis cases attributed to *Rothia mucilaginosa*

Reference	Gender	Age	Comorbidities or underlying conditions	Suspected infection sources	Other infection sites / clinical signs	Antibiotic treatment	Outcome
Rubin et al. [102]	Male	63	-	Not reported	-	Cephalosporin, Penicillin	Discharged after 5 weeks
Prag et al. [103]	Male	46	"heart murmur" diagnosed two years before	Not reported	-	Ampicillin, Penicilin G, Methicilin	Discharged
Coudron et al. [104]	Male	29	Intravenous drug abuse. Aortic valve endocarditis caused by *Aspergillus fumigatus*. Aortic valve replacement with a porcine bioprosthesis four months before.	Not reported	-	Rifampin	Deceased (cardio-respiratory arrest)
Relman et al. [105]	Female	34	Illicit intravenous drug abuse.	Not reported	-	Nafcillin,Piperacillin, Gentamicin and Penicillin G	Discharged after 6 weeks
Pinsky et al. [106]	Male	35	Intravenous drug abuse. *Streptococcus mitis* Endocarditis 5 months before; Aortic and mitral insuficciency	Not reported	-	Vancomycin and Gentamicin	Not reported
Castaño et al. [107]	Male	79	Chronic heart failure; Chronic obstructive pulmonary disease. Cor pulmonale. Arterial hypertension.Right adrenal myolipoma diagnosed 4 years before. Immunossupressive treatment.	Nor reported	-	Rifampicin, Vancomycin and Tetraciclin	Deceased (Severe cardiac insufficiency)
Pérez-Vega et al. [108]	Male	44	Mitral valve prolapse diagnosed 10 years before	Not reported	-	Ampicillin, Gentamicin, Penicillin G	Discharge
Rolland and Wallet [109]	Male	73	Hypercholesterolemia. Arterial hypertension. Pulmonary embolism 4 years before.	Not reported	nodular liver lesions compatible with secondary abscesses.	Ceftriaxone, Gentamicin and Rifampin	Not reported
Faiad et al. [110]	Female	52	Intravenous drug user. Mitral and aortic infective endocarditis resulting in bioprosthe- tic replacement of both valves	Not reported	Brain multiple small subcortical and pontine embolic infarct. Periaortic abscess	Vancomycin , Gentamicin, Rifampin, Ampicillin and Penicillin G	Deceased

Reference	Gender	Age	Comorbidities or underlying conditions	Suspected infection sources	Other infection sites / clinical signs	Antibiotic treatment	Outcome
			seven years before.				
Faiad et al. [110]	Male	21	Pre-B acute lymphocytic leukemia diagnosed two years before. Immunossupressive therapy.	Not reported	-	Vancomycin, Ceftriaxone, Rifampin,	Discharged
Bruminhent et al. [111]	Male	36	Previous *Streptococcus mitis* mitral valve endocarditis and prosthetic valve replacement five years before.	Not reported	Left popliteal artery thrombosis	Vancomycin, Piperacillin-tazobactam	Discharged
Ramanan et al. [17]	Female	28	Intravenous drug user. Prosthetic aortic valve. native tricuspid and aortic valve. Previous endocarditis by *Staphylococcus aureus*	Not reported	-	Ceftriaxone, Vncomicyn and Rifampin	Discharged
Sugunesegran et al. [112]	Female	-	Two previous sternotomies.	Not reported	-	Antibiotic therapy not described	Discharged
Song et al. [113]	Male	65	Aortic valvoplasty two decades before. Three episodes of prosthetic valve endocarditis in the last 11 years by *Enterococcus avium*, *Enterococcus faecalis*, and *Streptococcus gallolyticus*. Diabetes mellitus, hypertension, dyslipidemia, and alcoholic liver.	Not reported	Multiple brain hemorrhages suggesting septic emboli on both hemisphere, corticomedullary junction area and cerebellum	Vancomycin, Rifampin, Ampicillin and Ceftriaxone	Discharged (Right side motor weakness remained as a sequela to the patient)
Haddad et al. [114]	Male	80	Coronary artery disease, mild intermittent asthma and moderate aortic stenosis	Not reported	-	Ceftriaxone, Vancomycin	Discharged
Abdelmaseih et al. [115]	Male	46	Chronic hepatitis C. Intravenous Illicit drug user.	Not reported	-	Vancomycin	Discharged after 6 weeks
López et al. [116]	Female	68	Extraction of a third molar	Oral infection	Embolic splenic infarction due to septic embolism	Antibiotic therapy not described	Discharged

**Source: the authors*

Table 5. Antibiotic sensitivity profile of *Rothia* spp. strains isolated from patients with endocarditis showing some degree of antimicrobial resistance

Reference	Species	Antibiogram results		
		Resistant	**Intermediary resistance**	**Sensible**
Greve et al. [58]	*R. aeria*	Gentamycin		Penicilin, Ampicillin, Amoxacillin-clavulanic acid, Piperacillin+Tazobactam, Meropenem, Moxifloxacin, Clindamycin, Vancomycin, Rifampicin, Linezolid, Tigecycline
Ruben [65]	*R. dentocariosa*	Amikacin, Ciprofloxacin, Kanamycin, Sulfamethoxa zole -trimethoprim	Erythromycin, Gentamycin, Rifampin, Tetracycline.	Ceftizoxime, Ceftriaxone, Cephalothin, Chloramphenicol, Imipenem, Penicillin, Vancomycin,
Kong et al. [69]	*R. dentocariosa*	Tobramycin, Gentamicin, Doxycycline, Pristinamycin, Sulfonamide, Pefloxacin		Penicillin, Amoxicillin, Imipenem, Erythromycin, Spiramycin,Rifampin.
Greve et al. [58]	*R. dentocariosa*	Gentamycin		Penicillin, Cefotaxime, Vancomycin, Rifampicin
Ali et al. [100]	*R. kristinae*	Erythromycin, Clindamycin, Tobramycin, Vancomycin, Teicoplanin, Tetracycline, Rifampicin, Cefoxitin, Penicillins and Cephalosporins	Levofloxacin, Gentamycin	Moxifloxacin, Sulphamethoxazole -Trimethoprim
Prag et al. [103]	*R. mucilaginosa*	Nalidixic acid	Mecillinam	Cephalothin, Cefoxitine, Cefotaxime, Carbenicillin, Sulphosomidine, Trimethoprim, Tobramycin, Erythromycin, Tetracycline, Chloramphenicol, Clindamycin, Nitrofurantoin, Piperacillin
Relman et al. [105]	*R. mucilaginosa*		Tetracycline	Penicillin, Methicillin, Cephalothin, Vancomycin, Chloramphenicol, Clindamycin, Erythromycin
Castaño et al. [107]	*R. mucilaginosa*	Ciprofloxacin, Cotrimoxazol, Gentamycin, Penicilin		Rifampicin, Vancomycin, Nitrofurantoin, Tetraciclin, Teicoplamin, Cloranfenicol
Song et al. [113]	*R. mucilaginosa*	Clindamycin, Sulfamethoxazole-Trimethoprim, Tobramycin		Penicilin, Ampicillin-sulbactam, Erythromycin, Rifampin, Tetracycline, Levofloxacin, Vancomycin
Haddad et a. [114]	*R. mucilaginosa*	Sulfamethoxazole-Trimethoprim	Clindamycin, erythromycin	Penicilin, Vancomycin, Levofloxacin

3. RESULTS

The systematic review of the currently available scientific literature revealed a total of 70 articles describing 76 cases of endocarditis caused by *Rothia* spp. The most frequently attributed species was *Rothia dentocariosa*, accounting for 37 cases, followed by *Rothia mucilaginosa* with 17 cases, *Rothia kristinae* with 11 cases, and *Rothia aeria*, also with 11 cases. Antibiotic resistance profiles were assessed in only 10 cases, where strains were identified as resistant to some antibacterial agents. Clinical manifestations were recorded as described by the manuscripts authors.

4. DISCUSSION

The scientific literature on endocarditis caused by *Rothia* spp. is scarce, and currently, there are no systematic studies addressing this clinical condition. Systematic review studies may not necessarily provide a reliable overview, particularly for pathogenies considered rarer, as case studies are often outlined based on peculiarities, circumstances, or specificities of medical practice [117,118,119]. However, the investigative approach of systematic literature review has the potential to identify particular situations, formulate hypotheses, compare situations to consolidated knowledge, and highlight trends, associations, or clinical reasoning that can guide future systematic research [117].

The incidence of endocarditis caused by *Rothia* spp. is likely underreported. The species of this genus are challenging to identify and are often confused with *Staphylococcus* spp. [108,120,121,122], *Streptococcus* spp. [108,120,121,122], *Micrococcus* spp. [55,120], or *Nocardia* spp. [31,55] due to the pleomorphism of the genus. The disposition of *Rothia* spp. cocci may manifest in patterns akin to those observed in other Gram-positive species commonly associated with endocarditis. Advanced methodologies, such as polymerase chain reaction (PCR) and targeted gene sequencing, are not commonly employed for the confirmation of diagnoses through microscopy, leading to a misdiagnose and underreport of endocarditis cases caused by *Rothia* spp. The high sensitivity of most *Rothia* spp. strains causing endocarditis to antibiotics may contribute to the lack of specific diagnosis and registration as an infectious agent. The resolution of the infectious clinical condition with empirical antibiotic therapy does not stimulate greater interest on the part of the medical team in the effort to precisely identify the pathogenic agent.

The taxonomic resemblance among species within the *Rothia* genus adds complexity to the analysis of pathogenesis caused by this group of microorganisms. *Rothia dentocariosa* and *Rothia aeria* exhibit similar biochemical profiles, both manifesting positivity for nitrate reduction, α-glucosidase, alanine-phenylalanine-proline arylamidase, and esculin hydrolysis, while demonstrating negativity for urease [55,123]. Some strains exhibit even more closely aligned biochemical profiles, testing positive for alanine-phenylalanine-proline arylamidase, α-glucosidase, and esculin hydrolysis, and negative for urease. Notably, certain strains of *Rothia dentocariosa* display biochemical profiles akin to those of *Rothia mucilaginosa* [55]. The differentiation among various *Rothia* species through biochemical reactions poses challenges due to their similar profiles [52,124]. Sequencing comparison of 16S rRNA between *Rothia dentocariosa* and *Rothia mucilaginosa* reveals homology at 98.0% and 96.4%, respectively, to the genetic material of *Rothia aeria* [123]. These attributes substantially contribute to the inherent lack of precision in laboratory identification tests. Michon et al. [125] reveal a unique microorganism was identified as *Rothia dentocariosa* or *Rothia kristinae* by the Api CORYNE and ID 32 STAPH strips method from BioMérieux with 99.9% similarity; as *Rothia kristinae* by the VITEK 2 system from BioMérieux with 99.9% similarity; until genetic analysis of 16S rRNA sequencing identified it as *Rothia aeria*. The 16S rRNA sequencing of this strain also showed little divergence from *Rothia mucilaginosa* [125]. Fatahi-Bagfi [31] reports that a strain of *Rothia dentocariosa* was distributed by the Swiss External Quality Assessment Scheme in Bacteriology and Mycology for analysis in 50 laboratories, and only 36 (72%) were able to provide an accurate result for species identification. In this context, the reliability of species identification in various previous studies cannot be guaranteed, especially in those where 16S rRNA sequencing was not performed. It is still likely that many cases of endocarditis identified as caused by *Rothia dentocariosa* may have actually been caused by *Rothia aeria*, described more recently. Therefore, the

retrospective analysis of infectious endocarditis cases by *Rothia* species should be conducted without considering species distinction as a baseline for comparison.

Among the *Rothia* species attributed as agents of endocarditis, *Rothia dentocariosa* was the most prevalent. Considering the year 2012, when *Rothia aeria* was first identified as a causative agent of endocarditis, the number of reported cases of endocarditis caused by *Rothia dentocariosa* and *Rothia aeria* are equivalent, with 11 cases reported for each species, This parity suggests that up to 50% of cases previously categorized as *Rothia dentocariosa* may have been misclassified. Disregarding alternative possibilities of misidentification, the combined *Rothia dentocariosa* (48.69%) and *Rothia aeria* (14.47%) accounted for 63.16% of cases, followed by *Rothia mucilaginosa* with 22.37% and *Rothia kristinae* with 14.47%. The comprehensive examination of endocarditis cases involving *Rothia* species reveals an average patient age of 48.5 years, with male predominance at 71.6%.

Within the set of reported cases of *Rothia* spp. endocarditis, 11.84% (9/76) progressed to mortality. This observed mortality rate is notably lower when compared to documented rates in studies investigating infectious endocarditis caused by other pathogens, where mortality rates typically fall within the range of 18% to 32% for individuals affected by this clinical condition [126,127]. The diminished mortality rate may be attributed to the heightened susceptibility of a substantial proportion of *Rothia* spp. strains to a broad spectrum of antibiotics, a lower inherent pathogenicity intrinsic to the genus, or a potential bias arising from suboptimal sampling. Notably, all patients in fatal cases exhibited multiple comorbidities, immunosuppression, or succumbed to mortality due to complications arising from surgical procedures.

Only 27.6% of the scrutinized case reports provided insights into the putative primary focus of infection or contamination. Within this specific subset, an overwhelming 61.9% implicated dental procedures or substandard oral hygiene practices, conceivably linked to periodontal disease, as the primary focus. It is noteworthy that two cases within this subset explicitly mentioned a history of dental caries.

Despite assertions by numerous researchers that infections caused by *Rothia* spp. are strongly linked to individuals with compromised immune systems[17,56,85,89,108,111,113,114,115,122,125], only seven patients diagnosed with endocarditis were explicitly characterized as immunocompromised. Additionally, four individuals could be presumed immunocompromised due to a combination of comorbidities, constituting 14.47% of the total cases. Endocarditis patients attributed to *Rothia* spp. presented a diverse range of comorbidities and underlying conditions, with a higher association with pre-existing cardiac issues, dental caries, inadequate oral hygiene, and dental procedures.

A study conducted by Tsuzukibashi et al. [128] reported *Rothia mucilaginosa* as the most prevalent species in human saliva (74%), followed by *Rothia dentocariosa* (16%) and *Rothia aeria* (10%). Conversely, AlEraky et al. [129] investigated bacterial species associated with the progression of dental caries, revealing that *Rothia mucilaginosa* and *Rothia aeria* predominate in individuals with a low incidence of caries, while *Rothia dentocariosa* is more prevalent in individuals with a high incidence of caries. Moreover, the absence of *Rothia mucilaginosa* and Streptococcus salivarius was noted in individuals with a high incidence of caries, in contrast to their coexistence in individuals with a low incidence of caries. Concerning *Rothia* spp. endocarditis, 29.7% (11/37) of cases were ascribed to *Rothia dentocariosa* in patients with a clinical history of dental caries, periodontal disease, and poor oral hygiene. In contrast, only one case (1/17) was attributed to *Rothia mucilaginosa* following the extraction of a molar tooth. These findings suggest that inadequate oral hygiene, periodontitis, and dental caries may play a significant role in the prevalence of *Rothia dentocariosa* as an etiological agent of endocarditis through direct invasive processes. In the context of cariogenic processes and subsequent dysbiosis of the oral microbiota, bacteria with invasive potential, such as Streptococcus spp., may access blood vessels in periodontal tissues and dental pulp, ultimately colonizing the endocardium after bacteremia [130,131]. Considering the parallels between the pathogenic processes leading to endocarditis caused by *Streptococcus* spp. and *Rothia* spp., it is noteworthy that species from both genera

possess the ability to produce adhesins. These adhesins play a pivotal role in biofilm formation in both the oral cavity and cardiac valves [10,40,41]. In this context, it is plausible that *Rothia dentocariosa*, prevalent in the oral cavity of patients with a high incidence of caries and periodontal diseases, may exhibit a more prominent invasive potential compared to other species within the genus, following an infectious dynamic akin to that observed in *Streptococcus* spp. for the entry of bacteria into the bloodstream and subsequent colonization of the endocardium. This hypothesis highlights the predominance of endocarditis linked to deteriorating oral health and subsequent invasive infection by *Rothia dentocariosa*, as observed in our literature analysis. The subset of endocarditis cases in patients with a history of dental procedures, dental caries, and poor oral hygiene constituted 17.1%.

Recent research outlines new trends in the factors of contamination by infectious agents triggering endocarditis, highlighting a significant increase in the incidence of this cardiac condition in individuals who use intravenous illicit drugs [132-138], a considerable proportion of whom are carriers of the hepatitis C virus [132-136]. The investigation of case reports pertaining to endocarditis caused by *Rothia* spp. substantiates this inclination, wherein nine patients (11.84%) acknowledged intravenous illicit drug use. This incidence aligns with findings by Marques et al. [127], who reported that 13.4% of patients exhibiting infectious endocarditis caused by other pathogens were users of intravenously administered illicit drugs. In the examination of cases involving endocarditis due to *Rothia* spp., four patients (5.26%) were diagnosed with chronic hepatitis C, indicative of potential syringe and needle sharing. The likelihood of underestimating the incidence of endocarditis resulting from needle contamination during illicit drug use exists, given that drug users may not consistently disclose such substance use during the anamnesis process [139].

The prevalence of pre-existing cardiovascular diseases is prominent among patients who develop endocarditis caused by *Rothia* spp., occurring in 50% (38/76) of the reported cases. Within this subset of patients with cardiovascular diseases, 28.9% (11/38) were identified as hypertensive, 31.5% (12/38) had undergone prosthetic valve implantation, and 18.4% (7/38) exhibited valvular insufficiency. Six cases (15.79%) involved individuals with a history of previous episodes of endocarditis, encompassing one instance of fungal endocarditis (*Aspergillus fumigatus*) and five instances of bacterial endocarditis caused by Gram-positive cocci (*Streptococcus mitis*, *Streptococcus gallolyticus*, *Staphylococcus aureus*, *Enterococcus avium*, and *Enterococcus faecalis*). Bussani et al. [140] emphasize that the persistence of risk factors contributes to the recurrence of infectious endocarditis. In the study conducted by Marques et al. [127], the majority of cases were associated with native valves (71.6%), while the remainder were linked to prosthetic heart valves (25.4%), a distribution analogous to that observed in *Rothia* spp. endocarditis cases (71.1% in patients with natural heart valves and 28.9% in patients with prosthetic heart valves). The incidence of diabetes was reported in 9.21% (7/76) of patients. Overall, the prevalence of cardiovascular diseases, arterial hypertension, prosthetic valve implants, valvular insufficiency, prior episodes of endocarditis, and diabetes mirrors findings in other studies on infectious endocarditis [127,140,141], suggesting that risk factors for *Rothia* spp. endocarditis align closely with those associated with endocarditis caused by other pathogens.

Embolisms are commonly recognized as complications in the context of infectious endocarditis. The incidence of embolic events, occurring in roughly 40% of cases, is a notable feature. Events related to embolism in the Central Nervous System are identified in approximately 25% of patients [126,142]. Among individuals with *Rothia* spp. endocarditis, embolic events were documented in 35.53% (27/76) of cases, with 28.95% (22/76) specifically involving Central Nervous System embolisms—incidences consistent with those observed across endocarditis cases in general. Mycotic aneurysms were discerned in 6.58% (5/76) of patients. Although constituting a small proportion of all intracranial aneurysms, these aneurysms carry a heightened mortality risk upon rupture [143,144,145]. One fatal case of *Rothia aeria* endocarditis was linked to subarachnoid hemorrhage resulting from such an aneurysm. Despite the noted association between strokes and intravenous illicit drug use in infectious endocarditis cases reported by Ridha et al. [146] for the period between 2005 and 2015, this

specific type of embolism was documented in only two case reports of *Rothia* spp. endocarditis.

The presence of abscesses in *Rothia* spp. endocarditis indicates that bacteria of this genus have the potential to disseminate hematogenously, leading to the establishment of focal infections in diverse anatomical sites. In the compilation of case reports, three aortic abscesses, one perivalvular abscess, one cerebral abscess, and one hepatic abscess were described. The presence of aortic abscesses in patients with endocarditis is considered a high-risk factor [147,148,149], and it was diagnosed in two cases of *Rothia* spp. endocarditis (one aortic root abscess and one peri-aortic abscess). Remarkably, these cases accounted for 22.22% of the total fatalities documented in the study. Additionally, two cases of osteomyelitis induced by *Rothia dentocariosa* were observed, presumably as a secondary consequence of endocardial infection. Additionally, two cases of osteomyelitis induced by *Rothia dentocariosa* were observed, presumably as a secondary consequence of endocardial infection.

In a comprehensive literature review, Franconieri et al. [32] emphasized a robust association between *Rothia mucilaginosa* and endocarditis, attributing 70% of *Rothia* genus-induced endocarditis cases to this particular species. In contrast, our systematic analysis of the current scientific literature reveals a higher proportion of endocarditis cases associated with *Rothia dentocariosa*. With an examination of an extended case report sample (76 cases) compared to the study conducted by Franconieri et al. [32] (50 cases), each species presenting distinct incidence rates. It emphasizes the need for systematic studies, including control groups, comprehensive patient histories, and standardized genetic sequencing methodology to determine the genuine epidemiological landscape of *Rothia* spp. endocarditis.

Despite the absence of systematic investigations concerning endocarditis caused by *Rothia* spp, studies on bacteremias caused by species within this genus reveal notable disparities in epidemiological patterns. In a retrospective 12-year analysis of *Rothia* spp. bacteremias at a Hungarian teaching hospital, Gajdács et al. [122] documented 37 cases, being *Rothia dentocariosa* responsible for 28 instances (75.67%) and *Rothia mucilaginosa* for the remaining 9 cases (24.33%). A slight female predominance (56.76%) was discerned, and the average age of affected patients stood at 57 years. Conversely, Odeberg et al. [150], in a retrospective study spanning from 2012 to 2021 at a Swedish clinic, identified 108 cases of *Rothia* spp. bacteremia, classifying 24 as infections and the rest as contamination. *Rothia mucilaginosa* accounted for 53 cases, with 16 deemed genuine infections. *Rothia dentocariosa* was detected in 26 cases, of which two were considered authentic infections. *Rothia kristinae* featured in two cases classified as contamination, while *Rothia aeria* was identified in a lone case, also categorized as contamination. Unidentified *Rothia* species were associated with 27 cases, of which six were classified as true infections. Distinctively, half of the cases considered genuine infections occurred in immunocompromised individuals. The substantial epidemiological variances between the findings of Gajdács et al. [122] and Odeberg et al. [150] highlight the imperative for timely and systematic research to elucidate such disparities.

The majority of *Rothia* spp. strains responsible for endocarditis displayed susceptibility to most or nearly all antibiotics (86.84%). However, a subset of strains (13.16%) manifested resistance to antibiotics across various classes, encompassing Aminoglycosides (Gentamicin, Amikacin, Kanamycin, and Tobramycin), Quinolones (Ciprofloxacin, Pefloxacin, and Nalidixic acid), Sulfonamides (Sulfamethoxazole-trimethoprim), Tetracyclines (Doxycycline and Tetracycline), Macrolides (Erythromycin), Lincosamides (Clindamycin), Glycopeptides (Vancomycin and Teicoplanin), Streptogramins (Pristinamycin), Rifamycins (Rifampicin), Cephamycins (Cefoxitin), Penicillins, and First and Second-generation Cephalosporins. The *Rothia kristinae* strain, as isolated by Ali et al. (2020), is an illustrative example of a multidrug-resistant strain, lacking sensitivity to antibiotics from diverse classes (Macrolides, Lincosamides, Aminoglycosides, Glycopeptides, Tetracyclines, Rifamycins, Penicillins, and First and Second-generation Cephalosporins).

The acquisition of antimicrobial resistance by pathogens is widely acknowledged as one of the foremost contemporary threats to human health. Antibiotic utilization exerts selective pressure not only on the target pathogens but also on the

entire microbiome, wherein resilient microorganisms persist as commensals post-treatment. Resistance in commensal bacteria entails risks, as these microorganisms function as reservoirs of resistance genes that may be horizontally transferred to pathogens or precipitate opportunistic infections in subsequent instances. This predicament assumes even greater gravity when antibiotic therapy is administered incompletely or inadequately [151,152,153]. In instances of opportunistic infections by *Rothia* spp., apart from the selection of resistant strains, antibiotic therapy can induce dysbiosis, diminishing organisms that modulate the abundance of normal microbiota species. This, in turn, fosters the proliferation of *Rothia* spp., heightening the probability of this bacterias's involvement in inflammatory, lytic, and cariogenic processes that precede invasive infection [154,155,156,157,158,159].

While the primary focus and empirical antibiotic therapy planning for infectious endocarditis target bacteria more prevalent in these infections, such as *Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp., the effectiveness of currently recommended regimens can be extrapolated to the analysis of *Rothia* spp. endocarditis. Recent research suggests that the use of aminoglycosides, once considered part of standard treatment, should be restricted due to the high incidence of strains resistant to these antibiotic compounds [160,161,162,163]. This recommendation aligns with the resistance patterns exhibited by *Rothia* spp., wherein 7 out of the 10 strains resistant to antibiotics were not sensitive to at least one aminoglycoside, notably gentamicin, with four resistant strains and two moderately sensitive. It is worth mentioning that gentamicin was part of the antibiotic therapy regimens in 38.16% (29/76) of *Rothia* spp. endocarditis cases.

In a consensus article authored by 51 researchers from ten different countries and published in the Journal of the American Medical Association, the recommended antibiotic therapy regimen for managing cases of infectious endocarditis involves a combination of Vancomycin or Daptomycin and beta-lactams, specifically Ceftriaxone or Cefazolin. The authors advocate reserving aminoglycosides and Rifampin for deployment in definitive antibiotic therapy, contingent upon the identification of the etiological agent [164]. By aligning the proposed antibiotic therapy regimen by McDonald et al. [164,165,166,167] with the antibiotic susceptibility profiles of *Rothia* spp. strains responsible for endocarditis, it becomes evident that this regimen holds efficacy in curbing the disease's progression caused by this particular pathogen. The latest recommendations from the European Society of Cardiology propose an empirical treatment approach for infectious endocarditis, encompassing Ampicillin in conjunction with Ceftriaxone or Flucloxacillin, and Gentamicin, all administered prior to ascertaining the causative agent [163]. When considering the antibiotic susceptibility patterns in *Rothia* spp. strains triggering endocarditis, this antibiotic therapy regimen proves effective, encompassing substances to which these strains exhibited susceptibility, with the sole exception being Gentamicin.

5. CONCLUSION

Species belonging to the *Rothia* genus pose challenges in identification due to pleomorphism and genetic proximity. Regarding species implicated as causative agents in endocarditis cases, prevalent strains include *Rothia dentocariosa* (48.69%), *Rothia mucilaginosa* (22.37%), *Rothia aeria* (14.47%), and *Rothia kristinae* (14.47%). The average age of affected patients was 48.5 years, with a male predominance of 71.6%.

Endocarditis induced by *Rothia* spp. lacks distinctive clinical features specifying its uniqueness in comparison to Gram-positive bacterial endocarditis cases. The observed lower mortality rate (11.84%) compared to endocarditis caused by other pathogens may be attributed to heightened susceptibility of most strains to a diverse range of antibiotics, facilitating resolution during empirical antibiotic therapy. This characteristic, combined with the challenge of *Rothia* spp. species identification based on cultural and microscopic characteristics, contributes to significant underreporting of endocarditis involving these bacteria.

The predominant risk factor in *Rothia* spp. endocarditis is the preexistence of cardiovascular diseases (50%). Other relevant factors included dental procedures, caries, and poor oral hygiene (17.1%), immunocompromise (14.47%), intravenous drug use (11.84%), and diabetes (9.21%). Among extra-cardiac consequences,

embolic events were documented in 35.53% of patients, mainly manifesting as Central Nervous System embolisms, observed in 28.95% of total cases. Mycotic aneurysms were identified in 6.58%.

Merely 13.16% of strains causing endocarditis exhibited resistance to antibiotics, although some strains presented multidrug resistance. We caution that projections about the efficacy of antibiotic therapy regimens in *Rothia* spp. endocarditis cases based on the percentage of resistant strains in this review study should be considered in conjunction with current recommendations from systematic studies and patient histories. Given the limited number of reported cases, antibiotic resistance testing, regional and individual patient microbiota variations, the results provide a static overview spanning almost four decades, and antibiotic susceptibility patterns have decreased for almost all pathogenic species, especially those constituting the normal human microbiota. We suggest that empirical antibiotic therapy be based on the recommendations of the European Society of Cardiology, offering a broader antibiotic spectrum, also considering the patients' history of antibiotics used in previous infections to establish a personalized regimen with a better likelihood of success.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Austin B. Rothia. In: Whitman WB, editor. Bergey's Manual of Systematics of Archaea and Bacteria [Internet]. 1st ed. Wiley. 2015;[cited 2023 Nov 3]:1–13.
2. Nouioui I, Carro L, García-López M, Meier-Kolthoff JP, Woyke T, Kyrpides NC, et al. Genome-Based Taxonomic Classification of the Phylum Actinobacteria. Front Microbiol. 2018;9:2007.
3. Georg LK, Brown JM. Rothia, gen. nov. an aerobic genus of the family Actinomycetaceae. International Journal of Systematic Bacteriology. 1967;17(1):79–88.
4. Oliveira IMFD, Ng DYK, Van Baarlen P, Stegger M, Andersen PS, Wells JM. Comparative genomics of Rothia species reveals diversity in novel biosynthetic gene clusters and ecological adaptation to different eukaryotic hosts and host niches. Microbial Genomics [Internet]. 2022; [cited 2023 Nov 3];8(9).
5. Tuikhar N, Kirdat K, Nair G, Padma S, Thorat V, Swetha P, et al. Rothia santali sp. nov., endophytic bacteria isolated from sandalwood (Santalum album L.) seedling. Arch Microbiol. 2022;204(10):609.
6. Hu X, Tang M, Dong K, Zhou J, Wang D, Song L. Changes in the skin microbiome during male maturation from 0 to 25 years of age. Skin Research and Technology. 2023;29(9):e13432.
7. Murphy B, Hoptroff M, Arnold D, Cawley A, Smith E, Adams SE, et al. Compositional Variations between Adult and Infant Skin Microbiome: An Update. Microorganisms. 2023;11(6):1484.
8. Shen Z, Robert L, Stolpman M, Che Y, Walsh A, Saffery R, et al. A genome catalog of the early-life human skin microbiome [Internet]. Genomics; 2023 May [cited 2023 Nov 6].
9. Sasso JM, Ammar RM, Tenchov R, Lemmel S, Kelber O, Grieswelle M, et al. Gut Microbiome–Brain Alliance: A Landscape View into Mental and Gastrointestinal Health and Disorders. ACS Chem Neurosci. 2023;14(10):1717–63.
10. Jeong J, Ahn K, Mun S, Yun K, Kim YT, Jung W, et al. Understanding the bacterial compositional network associations between oral and gut microbiome within healthy Koreans. Journal of Oral Microbiology. 2023;15(1):2186591.
11. Gacesa R, Kurilshikov A, Vich Vila A, Sinha T, Klaassen MAY, Bolte LA, et al. Environmental factors shaping the gut microbiome in a Dutch population. Nature. 2022;604(7907):732–9.

12. Wilbert SA, Mark Welch JL, Borisy GG. Spatial Ecology of the Human Tongue Dorsum Microbiome. Cell Reports. 2020;30(12):4003-4015.e3.
13. Araújo V, Fehn AM, Phiri A, Wills J, Rocha J, Gayà-Vidal M. Oral microbiome homogeneity across diverse human groups from southern Africa: first results from southwestern Angola and Zimbabwe. BMC Microbiol. 2023;23(1):226.
14. Ruan JW, Liao YC, Chen PC, Chen YJ, Tsai YH, Tsai PJ, et al. The composition of the maternal breastmilk microbiota influences the microbiota network structure during early infancy. Journal of Microbiology, Immunology and Infection. 2023;56(5):1084–97.
15. Aso Y, Matsuo N, Miyamoto A, Tsuji N, Maeda H. Intermembrane rhomboid protease activity of Rothia mucilaginosa. World J Adv Res Rev. 2023;17(1):974–83.
16. Gomes BPFA, Berber VB, Chiarelli-Neto VM, Aveiro E, Chapola RC, Passini MRZ, et al. Microbiota present in combined endodontic-periodontal diseases and its risks for endocarditis. Clin Oral Invest. 2023;27(8):4757–71.
17. Ramanan P, Barreto JN, Osmon DR, Tosh PK. Rothia Bacteremia: a 10-Year Experience at Mayo Clinic, Rochester, Minnesota. Diekema DJ, editor. J Clin Microbiol. 2014;52(9):3184–9.
18. Bissell BD, Kreimer A, Burgess DS. Epidemiology of Infections With Rothia Species in an Academic Medical Center. Ann Pharmacother. 2022;56(3):363–5.
19. Poyer F, Friesenbichler W, Hutter C, Pichler H, Dworzak M, Peters C, et al. Rothia mucilaginosa bacteremia: A 10-year experience of a pediatric tertiary care cancer center. Pediatric Blood & Cancer. 2019;66(7):e27691.
20. Maddah R, Goodarzi V, Asadi-Yousefabad SL, Abbasluo M, Shariati P, Shafiei Kafraj A. Evaluation of the gut microbiome associated with COVID-19. Informatics in Medicine Unlocked. 2023;38:101239.
21. Jiang Z, Yang L, Qian X, Su K, Huang Y, Qu Y, et al. Tongue coating microbiome composition reflects disease severity in patients with COVID-19 in Nanjing, China. Journal of Oral Microbiology. 2023;15(1): 2236429.
22. Giannos P, Prokopidis K. Gut dysbiosis and long COVID-19: Feeling gutted. Journal of Medical Virology. 2022;94(7):2917–8.
23. Ikeda E, Shiba T, Ikeda Y, Suda W, Nakasato A, Takeuchi Y, et al. Japanese subgingival microbiota in health vs disease and their roles in predicted functions associated with periodontitis. Odontology. 2020;108(2):280–91.
24. Nibali L, Sousa V, Davrandi M, Spratt D, Alyahya Q, Dopico J, et al. Differences in the periodontal microbiome of successfully treated and persistent aggressive periodontitis. J Clinic Periodontology. 2020;47(8):980–90.
25. Mazurel D, Carda-Diéguez M, Langenburg T, Žiemytė M, Johnston W, Martínez CP, et al. Nitrate and a nitrate-reducing Rothia aeria strain as potential prebiotic or synbiotic treatments for periodontitis. npj Biofilms Microbiomes. 2023;9(1):40.
26. Amer A, Galvin S, Healy CM, Moran GP. The Microbiome of Potentially Malignant Oral Leukoplakia Exhibits Enrichment for Fusobacterium, Leptotrichia, Campylobacter, and Rothia Species. Front Microbiol. 2017;8:2391.
27. Shaeer KM, Addisu A, Nanjappa S, Greene JN. Epidemiologic Evaluation of Rothia Bacteremias: A Cancer Center's 4-Year Experience. Infect Dis Clin Pract. 2018;26(5):270–4.
28. Wright RJ, Pewarchuk ME, Marshall EA, Murrary B, Rosin MP, Laronde DM, et al. Exploring the microbiome of oral epithelial dysplasia as a predictor of malignant progression. BMC Oral Health. 2023;23(1):206.
29. Radaic A, Kapila YL. The oralome and its dysbiosis: New insights into oral microbiome-host interactions. Computational and Structural Biotechnology Journal. 2021;19:1335–60.
30. Satoshi T, Hiroshi M, Norimasa T, Hideaki I, Masataka Y. Distribution of Rothia species in root canals in a Japanese population. World J Adv Res Rev. 2019;4(2):020–6.
31. Fatahi-Bafghi M. Characterization of the Rothia spp. and their role in human clinical infections. Infection, Genetics and Evolution. 2021;93:104877.

32. Franconieri F, Join-Lambert O, Creveuil C, Auzou M, Labombarda F, Aouba A, et al. Rothia spp. infective endocarditis: A systematic literature review. Infectious Diseases Now. 2021;51(3):228–35.
33. Miernikiewicz P, Barylski J, Wilczak A, Dragoš A, Rybicka I, Bałdysz S, et al. New Phage-Derived Antibacterial Enzyme PolaR Targeting Rothia spp. Cells. 2023;12(15):1997.
34. Mostaghim AS, Lo HYA, Khardori N. A retrospective epidemiologic study to define risk factors, microbiology, and clinical outcomes of infective endocarditis in a large tertiary-care teaching hospital. SAGE Open Medicine. 2017;5:205031211774177.
35. Liaqat W, Palaiodimos L, Li W, Karamanis D, Tahir A, Tzoumas A, et al. Epidemiologic and clinical characteristics of infective endocarditis: a single-center retrospective study in the Bronx, New York. Infection. 2022;50(5):1349–61.
36. Demin AA, Kobalava ZhD, Skopin II, Tyurin PV, Boytsov SA, Golukhova EZ, et al. Infectious endocarditis and infection of intracardiac devices in adults. Clinical guidelines 2021. Russ J Cardiol. 2022;27(10):5233.
37. Chen H, Zhan Y, Zhang K, Gao Y, Chen L, Zhan J, et al. The Global, Regional, and National Burden and Trends of Infective Endocarditis From 1990 to 2019: Results From the Global Burden of Disease Study 2019. Front Med. 2022;9:774224.
38. Resende P, Fortes CQ, Do Nascimento EM, Sousa C, Querido Fortes NR, Thomaz DC, et al. In-hospital Outcomes of Infective Endocarditis from 1978 to 2015: Analysis Through Machine-Learning Techniques. CJC Open. 2022;4(2):164–72.
39. Paul G, Ochs L, Hohmann C, Baldus S, Michels G, Meyer-Schwickerath C, et al. Surgical Procedure Time and Mortality in Patients with Infective Endocarditis Caused by Staphylococcus aureus or Streptococcus Species. JCM. 2022;11(9):2538.
40. Nappi F, Martuscelli G, Bellomo F, Avtaar Singh SS, Moon MR. Infective Endocarditis in High-Income Countries. Metabolites. 2022;12(8):682.
41. Yallowitz AW, Decker LC. Infectious Endocarditis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available :http://www.ncbi.nlm.nih.gov/books/NBK557641/
42. Liu J, Xu H. Infective Endocarditis. In: Li H, Liu J, Li L, editors. Radiology of Infectious and Inflammatory Diseases - Volume 3 [Internet]. Singapore: Springer Nature Singapore. 2023; [cited 2023 Dec 1]:357–63.
43. Tleyjeh IM, Steckelberg JM, Murad HS, Anavekar NS, Ghomrawi HMK, Mirzoyev Z, et al. Temporal Trends in Infective Endocarditis: A Population-Based Study in Olmsted County, Minnesota. JAMA. 2005;293(24):3022.
44. Pant S, Patel NJ, Deshmukh A, Golwala H, Patel N, Badheka A, et al. Trends in Infective Endocarditis Incidence, Microbiology, and Valve Replacement in the United States From 2000 to 2011. Journal of the American College of Cardiology. 2015;65(19):2070–6.
45. Graevenitz A. Importance of Coryneform Bacteria in Infective Endocarditis. Infectious Disease Reports. 2015;7(3):6103.
46. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 ;6(7):e1000097.
47. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;n71.
48. Fowler VG, Durack DT, Selton-Suty C, Athan E, Bayer AS, Chamis AL, et al. The 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis: Updating the Modified Duke Criteria. Clinical Infectious Diseases. 2023;77(4):518–26.
49. Tarumoto N, Sujino K, Yamaguchi T, Umeyama T, Ohno H, Miyazaki Y, et al. A First Report of Rothia aeria Endocarditis Complicated by Cerebral Hemorrhage. Intern Med. 2012;51(23):3295–9.
50. Holleran K, Rasiah S. Atypical thunderclap headache. 2nd international congress on neurology and epidemiology. Neuroepidemiology. 2012;39:177–283.

51. Thiyagarajan A, Balendra A, Hillier D, Hatcher J. The first report of survival post Rothia aeria endocarditis. Case Reports. 2013 Oct 9;2013(oct09 1):bcr2013200534–bcr2013200534.
52. Crowe A, Ding NS, Yong E, Sheorey H, Waters MJ, Daffy J. Rothia aeria mitral valve endocarditis complicated by multiple mycotic aneurysms: laboratory identification expedited using MALDI-TOF MS. Infection. 2014;42(2):419–23.
53. Hiraiwa T, Izumi M. Successful management of Rothia aeria endocarditis with renal transplantation patient: A case report. European Journal of Internal Medicine. 2013;24:e204.
54. Nicodemo AC, Gonçalves LG, Odongo FCA, Martino MDV, Sampaio JLM. Rothia aeria endocarditis in a patient with a bicuspid aortic valve: case report. The Brazilian Journal of Infectious Diseases. 2014;18(5):561–4.
55. Kim UJ, Won EJ, Kim JE, Jang MO, Kang SJ, Jang HC, et al. Rothia aeria Infective Endocarditis: a First Case in Korea and Literature Review. Ann Lab Med. 2014;34(4):317–20.
56. Collarino R, Vergeylen U, Emeraud C, Latournèrie G, Grall N, Mammeri H, et al. Mitral endocarditis due to Rothia aeria with cerebral haemorrhage and femoral mycotic aneurysms, first French description. New Microbes and New Infections. 2016;13:40–2.
57. Aoyagi S, Tobinaga S, Wada K, Nata SI, Yasunaga H. Rothia aeria Endocarditis Complicated with Multiple Systemic Embolisms. Kurume Med J. 2021;68(3.4):259–63.
58. Greve D, Moter A, Kleinschmidt MC, Pfäfflin F, Stegemann MS, Kursawe L, et al. Rothia aeria and Rothia dentocariosa as biofilm builders in infective endocarditis. International Journal of Medical Microbiology. 2021;311(2):151478.
59. Zeng X, Wu J, Li X, Xiong W, Tang L, Li X, et al. Application of Metagenomic Next-Generation Sequencing in the Etiological Diagnosis of Infective Endocarditis During the Perioperative Period of Cardiac Surgery: A Prospective Cohort Study. Front Cardiovasc Med. 2022 ;9:811492. 164.
60. Pape J. Infective Endocarditis Caused by Rothia dentocariosa. Ann Intern Med. 19791;91(5):746.
61. Schafer FJ. Infectious Endocarditis Caused by Rothia dentocariosa. Ann Intern Med. 1979 ;91(5):747.
62. Broeren SA, Peel MM. Endocarditis caused by Rothia dentocariosa. Journal of Clinical Pathology. 1984;37(11):1298–300.
63. Shands JW. Rothia dentocariosa endocarditis. The American Journal of Medicine. 1988 ;85(2):280–1.
64. Isaacson JH, Grenko RT. Rothia dentocariosa endocarditis complicated by brain abscess. The American Journal of Medicine. 1988;84(2):352–4.
65. Ruben SJ. Rothia dentocariosa endocarditis. West J Med. 1993 Dec;159(6):690–1.
66. Sudduth EJ, Rozich JD, Farrar WE. Rothia dentocariosa Endocarditis Complicated by Perivalvular Abscess. Clinical Infectious Diseases. 1993;17(4):772–5.
67. Weersink AJL, Rozenberg-Arska M, Westerhof PW, Verhoef J. Rothia dentocariosa Endocarditis Complicated by an Abdominal Aneurysm. Clinical Infectious Diseases. 1994 ;18(3):489–90.
68. Binder D, Widmer U, Opravil M, Krause M, Zbinden R. Native and prosthetic valve endocarditis caused byRothia dentocariosa: Diagnostic and therapeutic considerations. Infection. 1997 ;25(1):22–6.
69. Kong R, Mebazaa A, Heitz B, De Briel DA, Kiredjian M, Raskine L, et al. Case of Triple Endocarditis Caused by Rothia dentocariosa and Results of a Survey in France. J Clin Microbiol. 1998;36(1):309–10.
70. Ferraz V, McCarthy K, Smith D, Koornhof HJ. Rothia dentocariosa endocarditis and aortic root abscess. Journal of Infection. 1998;37(3):292–5.
71. Braden DS, Feldman S, Palmer AL. Rothia Endocarditis in a Child: Southern Medical Journal. 1999;92(8):815–6.
72. Llopis F, Carratalà J. Vertebral Osteomyelitis Complicating Rothia dentocariosa Endocarditis. European Journal of Clinical Microbiology & Infectious Diseases. 2000 Aug 3;19(7):562–3.

73. Nguyen QV, Kavey RE, Colella C, Weiner LB. Infectious endocarditis caused by Rothia dentocariosa. Infectious Medicine. 2000;17:428.
74. Ricaurte JC, Klein O, LaBombardi V, Martinez V, Serpe A, Joy M. Rothia dentocariosa endocarditis complicated by multiple intracranial hemorrhages. South Med J. 2001;94(4):438–40.
75. Larkin J, Montero J, Targino M, Powers A, Accurso C, Campbell M. Rothia dentocariosa Endocarditis. Clinical Microbiology Newsletter. 2001;23(2):13–5.
76. Salamon SA, Prag J. Three Cases of Rothia dentocariosa Bacteraemia: Frequency in Denmark and a Review. Scandinavian Journal of Infectious Diseases. 2002;34(2):153–7.
77. Boudewijns M, Magerman K, Verhaegen J, Debrock G, Peetermans WE, Donkersloot P, et al. Rothia dentocariosa, endocarditis and mycotic aneurysms: case report and review of the literature. Clinical Microbiology and Infection. 2003;9(3):222–9.
78. Almuzara MN, Mariñansky AL, Valenzuela VC, Vay CA. Endocarditis por Rothia dentocariosa complicada por embolias sépticas cerebrales. Enfermedades Infecciosas y Microbiología Clínica. 2004;22(4):255–6.
79. Morris SK, Nag S, Suh KN, Evans GA. Recurrent Chronic Ambulatory Peritoneal Dialysis-Associated Infection due to Rothia dentocariosa. Canadian Journal of Infectious Diseases and Medical Microbiology. 2004;15(3):171–3.
80. Sadhu A, Loewenstein R, Klotz SA. Rothia dentocariosa endocarditis complicated by multiple cerebellar hemorrhages. Diagnostic Microbiology and Infectious Disease. 2005;53(3):239–40.
81. Shakoor S, Fasih N, Jabeen K, Jamil B. Rothia dentocariosa endocarditis with mitral valve prolapse: case report and brief review. Infection. 2011;39(2):177–9.
82. Chowdhary M, Farooqi B, Ponce-Terashima R. Rothia dentocariosa: A Rare Cause of Left-Sided Endocarditis in an Intravenous Drug User. The American Journal of the Medical Sciences. 2015;350(3):239–40.
83. Fridman D, Chaudhry A, Makaryus J, Black K, Makaryus AN. Rothia dentocariosa Endocarditis: An Especially Rare Case in a Previously Healthy Man. Texas Heart Institute Journal. 2016 ;43(3):255–7.
84. Willner S, Imam Z, Hader I. Rothia dentocariosa Endocarditis in an Unsuspecting Host: A Case Report and Literature Review. Case Reports in Cardiology. 2019;2019:1–3.
85. Doddapaneni D, Reddy V, Rayapudi M. Cerebrovascular accident in a 65-year-old patient with Rothia dentocariosa-associated endocarditis. J Global Infect Dis. 2020;12(3):156.
86. Myadam R, DeZorzi C, Schmidt L, Lin P, McGhie AI. Melody Valve Endocarditis Due to Rothia dentocariosa: A Diagnostic Challenge. Cureus [Internet]. 2020 Jun 26; Available:https://www.cureus.com/articles/30668-melody-valve-endocarditis-due-to-Rothia-dentocariosa-a-diagnostic-challenge
87. Kisilevsky E, Pesin N, Mandell D, Margolin EA. Rothia dentocariosa causing intracranial mycotic aneurysm and ischaemic stroke. BMJ Case Rep. 2021;14(3):e240349.
88. Elkattawy S, Alyacoub R, Younes I, Mowafy A, Noori M, Mirza M. A rare report of Rothia dentocariosa endocarditis. Journal of Community Hospital Internal Medicine Perspectives. 2021 ;11(3):413–5.
89. Obi CA, Egbuche O, Nwokike SI, Mezue K, Abe T, Bulsara K, et al. Implantable Cardiac Defibrillator Lead Infective Endocarditis Due to Rothia Specie: A Rare Case in An Immunocompetent Man. Rev Cardiovasc Med. 2022;23(5):149.
90. Jianjian S, Heping J, Feifei L, Kang G, Yinghao G. Thrombocytopenic Purpura in a 40-year-old Patient with Rothia dentocariosa-associated Endocarditis. Journal of Global Infectious Diseases. 2023;15(4):166-168.
91. Lai CC, Wang JY, Lin SH, Tan CK, Wang CY, Liao CH, et al. Catheter-related bacteraemia and infective endocarditis caused by Kocuria species. Clinical Microbiology and Infection. 2011 ;17(2):190–2.
92. Bastidas AR, Vélez CA, Gutiérrez M. CV, Bahamón NJ. Endocarditis bacteriana por Kocuria kristinae en paciente inmunocompetente. Reporte de un caso.

Revista Colombiana de Cardiología. 2013;20(5):316–9.

93. Seyman D, Kizilates F, Oztoprak N, Ayoglu RU, Arslan S. Kocuria kristinae: A Rare Cause of Infective Endocarditis Involving 2 Native Valves. Infectious Diseases in Clinical Practice. 2013 ;21(6):407–9.
94. Citro R, Prota C, Greco L, Mirra M, Masullo A, Silverio A, et al. Kocuria kristinae endocarditis related to diabetic foot infection. Journal of Medical Microbiology. 2013;62(6):932–4.
95. Hollanda BC, Cortez AF, Silva EBS, Tolentino JC, Maia LFH. Endocardite infecciosa por Kocuria kristinae em paciente com Lúpus Eritematoso Sistêmico. 13º Congresso Brasileiro de Clinica Médica; 2015. Available:https://clinicamedica2015.iweventos.com.br/evento/clinicamedica/trabalhosaprovados/naintegra/893
96. Aleksic D, Miletic-Drakulic S, Boskovic-Matic T, Simovic S, Toncev G. Unusual case of stroke related to Kocuria kristinae endocarditis treated with surgical procedure. Hippokratia. 2016;20(3):231–4.
97. Robles-Marhuenda A, Romero-Gómez MP, García-Rodríguez J, Arnalich-Fernández F. Native valve endocarditis caused by Kocuria kristinae. Enfermedades Infecciosas y Microbiología Clínica. 2016;34(7):464–5.
98. Horino T, Shimamura Y, Ogata K, Inoue K, Terada Y. Kocuria kristinae septic arthritis associated with infectious endocarditis in a hemodialysis patient with diabetes mellitus: a case report and literature review. Ren Replace Ther. 2016;2(1):32.
99. Rojas-Molina SM, Rivera-Marín JD, Leiva-Panqueba LM. Endocarditis bacteriana por Kocuria kristinae en un paciente inmunocompetente. Reporte de caso. Infect. 2019;23(4):399.
100. Ali AM, Waseem GR, Arif S. Rare case report of infective endocarditis due to Kocuria kristinae in a patient with ventricular septal defect. Access Microbiology. 2019;2(1):acmi000076.
101. Dewi IP, Damanik I, Dewi KP, Yogiarto M, Andrianto. Infective Endocarditis Caused by Streptococcus alactolyticus and Kocuria kristinae Complicated with Severe Thrombocytopenia: A Rare Case. Cardiologia Croatica. 2021;16(7–8):246–51.
102. Rubin SJ, Lyons RW, Murcia AJ. Endocarditis associated with cardiac catheterization due to a Gram-positive coccus designated Micrococcus mucilaginosus incertae sedis. J Clin Microbiol. 1978;7(6):546–9.
103. Prag J, Kjøller E, Espersen F. Stomatococcus mucilaginosus endocarditis. Eur J, Clin Microbiol. 1985;4(4):422–4.
104. Coudron PE, Markowitz SM, Mohanty LB, Schatzki PF, Payne JM. Isolation of Stomatococcus mucilaginosus from drug user with endocarditis. J Clin Microbiol. 1987;25(8):1359–63.
105. Relman DA, Ruoff K, Ferraro MJ. Stomatococcus mucilaginosus Endocarditis in an Intravenous Drug Abuser. Journal of Infectious Diseases. 1987;155(5):1080–2.
106. Pinsky RL, Piscitelli V, Patterson JE. Endocarditis caused by relatively penicillin-resistant Stomatococcus mucilaginosus. J Clin Microbiol. 1989;27(1):215–6.
107. Castaño MA, Gascón F, Sánchez E, Bermudo P, Valle M, Morales R, et al. Bacteriemia por Stomatococcus mucilaginosus en un paciente de riesgo. Revista de Diagnóstico Biológico. 2001;50:147–8.
108. Pérez-Vega C, Narváez J, Calvo G, Castro-Bohorquez FJ, Falgueras MT, Vilaseca-Momplet J. Cerebral Mycotic Aneurysm Complicating Stomatococcus mucilaginosus Infective Endocarditis. Scandinavian Journal of Infectious Diseases. 2002;34(11):863–6.
109. Rolland C, Wallet F. Endocarditis caused by Stomatococcus mucilaginosus in an immunocompetent patient. Clinical Microbiology Newsletter. 2004;26(5):37–9.
110. Faiad G, Singh M, Narasimhan A, Mendez M, Sharma S, Nassar N. Rothia mucilaginosa life threatening infections in non-neutropenic hosts. OJIM. 2011;01(03):68–71.
111. Bruminhent J, Tokarczyk MJ, Jungkind D, DeSimone JA. Rothia mucilaginosa Prosthetic Device Infections: a Case of Prosthetic Valve Endocarditis. J Clin Microbiol. 2013;51(5):1629–32.

112. Sugunesegran R, Mohyieldin O, Tam A, Davis P, Bhagwat K. P64 Rothia mucilaginosa: A Rare Cause of Prosthetic Valve Endocarditis. Heart, Lung and Circulation. 2021;30:S54.
113. Song YJ, Bongyoung K, Kim YE, Lee Y, Pai H. A Case of Prosthetic Valve Endocarditis with Cerebral Hemorrhage Caused by Rothia mucilaginosa. Ann Clin Microbiol, 2020;23(4):271-276.
114. Haddad S, Saade Y, Ramlawi B, Kreidieh B, Gilbert B, Rao S. Native valve endocarditis complicated by abscess formation caused by Rothia mucilaginosa. IDCases. 2021;26:e01348.
115. Abdelmaseih R, Abdelmasih R, Faluk M, Hasan M. Uncommon Pathogen in an Unexpected Host: A Rare Case of Rothia mucilaginosa Infective Endocarditis in an Immunocompetent Patient Without an Underlying Valvular Disease. Cureus 13(6):e15458
116. López LAR, Moreno ER, Passang EA, Hoyos CMP. Infectious Endocarditis due to Stomatococcus mucilaginosus complicated by Splenic Infarction due to Septic Embolism. Journal of MAR Cardiology. 2021;3(4):1-8.
117. Nissen T, Wynn R. The clinical case report: a review of its merits and limitations. BMC Res Notes. 2014;7(1):264.
118. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ EBM. 2018;23(2):60–3.
119. Roukis TS. Case reports/series & bias considerations. Foot & Ankle Surgery: Techniques, Reports & Cases. 2021;1(3):100057.
120. Maraki S, Papadakis IS. Rothia mucilaginosa pneumonia: a literature review. Infectious Diseases. 2015;47(3):125–9.
121. Song YY, Ahn M, Cho NC, You IC. A Case of Rothia mucilaginosa Keratitis in South Korea. Korean J Ophthalmol. 2017;31(5):460.
122. Gajdács M, Ábrók M, Lázár A, Burián K. Rothia Bacteremia: A 12-Year Experience at a Tertiary-Care Teaching Hospital in Szeged, Hungary. Infect Dis Clin Pract. 2020;28(6):361–5.
123. Li Y, Kawamura Y, Fujiwara N, Naka T, Liu H, Huang X, et al. Rothia aeria sp. nov., Rhodococcus baikonurensis sp. nov. and Arthrobacter russicus sp. nov., isolated from air in the Russian space laboratory Mir. International Journal of Systematic and Evolutionary Microbiology. 2004;54(3):827–35
124. Swierzbinski MJ, Pandya S, Zelazny AM, Keiser J, Siegel MO. Diagnostic Challenges in the Identification of Rothia aeria Bacteremia in a Patient With Relapsing Acute Myeloid Leukemia. Infectious Diseases in Clinical Practice. 2015;23(6):336–8.
125. Michon J, Jeulin D, Lang JM, Cattoir V. Rothia aeria acute bronchitis: the first reported case. Infection. 2010;38(4):335–7.
126. Habib G, Erba PA, Iung B, Donal E, Cosyns B, Laroche C, et al. Clinical presentation, aetiology and outcome of infective endocarditis. Results of the ESC-EORP EURO-ENDO (European infective endocarditis) registry: a prospective cohort study. European Heart Journal. 2019 ;40(39):3222–32.
127. Marques A, Cruz I, Caldeira D, Alegria S, Gomes AC, Broa AL, et al.. Risk Factors for In-Hospital Mortality in Infective Endocarditis. Arq Bras Cardiol [Internet]. 2020Jan;114(1):1–8.
128. Tsuzukibashi O, Uchibori S, Kobayashi T, Umezawa K, Mashimo C, Nambu T, et al. Isolation and identification methods of Rothia species in oral cavities. Journal of Microbiological Methods. 2017;134:21–6.
129. AlEraky DM, Madi M, El Tantawi M, AlHumaid J, Fita S, AbdulAzeez S, et al. Predominance of non-Streptococcus mutans bacteria in dental biofilm and its relation to caries progression. Saudi Journal of Biological Sciences. 2021;28(12):7390–5.
130. Yumoto H, Hirota K, Hirao K, Ninomiya M, Murakami K, Fujii H, et al. The Pathogenic Factors from Oral Streptococci for Systemic Diseases. IJMS. 2019;20(18):4571.
131. Del-Giudice C, Vaia E, Liccardo D, Marzano F, Valletta A, Spagnuolo G, et al. Infective Endocarditis: A Focus on Oral Microbiota. Microorganisms. 2021;9(6): 1218.

132. Weir MA, Slater J, Jandoc R, Koivu S, Garg AX, Silverman M. The risk of infective endocarditis among people who inject drugs: a retrospective, population-based time series analysis. CMAJ. 2019;191(4):E93–9.
133. Schranz AJ, Fleischauer A, Chu VH, Wu LT, Rosen DL. Trends in Drug Use–Associated Infective Endocarditis and Heart Valve Surgery, 2007 to 2017: A Study of Statewide Discharge Data. Ann Intern Med. 2019;170(1):31.
134. Kadri AN, Wilner B, Hernandez AV, Nakhoul G, Chahine J, Griffin B, et al. Geographic Trends, Patient Characteristics, and Outcomes of Infective Endocarditis Associated With Drug Abuse in the United States From 2002 to 2016. JAHA. 2019;8(19):e012969.
135. Bates MC, Annie F, Jha A, Kerns F. Increasing incidence of IV-drug use associated endocarditis in southern West Virginia and potential economic impact. Clinical Cardiology. 2019 ;42(4):432–7.
136. See I, Gokhale RH, Geller A, Lovegrove M, Schranz A, Fleischauer A, et al. National Public Health Burden Estimates of Endocarditis and Skin and Soft-Tissue Infections Related to Injection Drug Use: A Review. The Journal of Infectious Diseases. 2020 ;222(Supplement_5):S429–36.
137. Marji M, Christian J, Browning S, Leung SW, Charnigo R, Kucharska-Newton A. Spatial and Temporal Trends of Infective Endocarditis Hospitalizations in Kentucky, 2008-2018. Circulation [Internet]. 2023 Feb 28 [cited 2023 Nov 29];147(Suppl_1). Available:https://www.ahajournals.org/doi/10.1161/circ.147.suppl_1.P272
138. Selitsky L, Racha S, Rastegar D, Olsen Y. Infective endocarditis in people who inject drugs: A scoping review of clinical guidelines. Journal of Hospital Medicine. 2023;18(2):169–76.
139. Hunt DE, Kling R, Almozlino Y, Jalbert S, Chapman MT, Rhodes W. Telling the Truth About Drug Use: How Much Does It Matter? Journal of Drug Issues. 2015;45(3):314–29.
140. Bussani R, De-Giorgio F, Pesel G, Zandonà L, Sinagra G, Grassi S, et al. Overview and Comparison of Infectious Endocarditis and Non-infectious Endocarditis: A Review of 814 Autoptic Cases. In Vivo. 2019;33(5):1565–72.
141. Çakır H, Uysal S, Karagöz A, Toprak C, Öcal L, Emiroğlu MY, et al. The Clinical Course of Infective Endocarditis and Independent Predictors of In-Hospital Mortality. Koşuyolu Heart J. 2022;25(2):115–21.
142. Kildahl HA, Brenne EL, Dalen H, Wahba A. Systemic embolization in infective endocarditis. Indian J Thorac Cardiovasc Surg [Internet]. 2023 Nov 6 [cited 2023 Dec 1]; Available:https://link.springer.com/10.1007/s12055-023-01616-2
143. Ram A, Deslouches J, Punnapuzha S. Mycotic Aneurysm: A Rare Etiology of a Common Presentation. Cureus [Internet]. 2022 Jul 21 [cited 2023 Dec 3]; Available:https://www.cureus.com/articles/95123-mycotic-aneurysm-a-rare-etiology-of-a-common-presentation
144. Islam S, Harnarayan P, Naraynsingh V. Mycotic Arterial Aneurysm. In: Anand DrA, editor. Issues and Developments in Medicine and Medical Research Vol 10 [Internet]. Book Publisher International (a part of SCIENCEDOMAIN International); 2022; [cited 2023 Dec 3]:95–112. Available:https://stm.bookpi.org/IDMMR-V10/article/view/5827
145. Majeed H, Ahmad F. Mycotic Aneurysm. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Dec 3]. Available: http://www.ncbi.nlm.nih.gov/books/NBK560736/
146. Ridha M, Flaherty ML, Aziz Y, Ades L, Alwell K, Khoury JC, et al. Changing Trends in Demographics, Risk Factors, and Clinical Features of Patients With Infective Endocarditis–Related Stroke, 2005–2015. Neurology. 2023;100(15):e1555–64.
147. Harris WM, Sinha S, Caputo M, Angelini GD, Vohra HA. Surgical outcomes and optimal approach to treatment of aortic valve endocarditis with aortic root abscess – systematic review and meta-analysis. Perfusion. 2022;026765912211374.
148. Rasslan R, Alves V, Damous SHB, De Santis A, Tarasoutchi F, Menegozzo CAM, et al. Splenic Abscesses in Endocarditis: A

Rare Disease with High Mortality. The Experience of a Heart Institute in Brazil. Journal of Investigative Surgery. 2022;35(11–12):1836–40.

149. Boukobza M, Ilic-Habensus E, Mourvillier B, Duval X, Laissy JP. Brain abscesses in infective endocarditis: contemporary profile and neuroradiological findings. Infection. 2023;51(5):1431–44.
150. Odeberg G, Bläckberg A, Sunnerhagen T. Infection or Contamination with Rothia, Kocuria, Arthrobacter and Pseudoglutamicibacter— a Retrospective Observational Study of Non-Micrococcus Micrococcaceae in the Clinic. Burnham CAD, editor. J Clin Microbiol. 2023 ;61(4):e01484-22.
151. Lamberte LE, Van Schaik W. Antibiotic resistance in the commensal human gut microbiota. Current Opinion in Microbiology. 2022;68:102150.
152. Waldetoft KW, Sundius S, Kuske R, Brown SP. Defining the Benefits of Antibiotic Resistance in Commensals and the Scope for Resistance Optimization. Levin BR, editor. mBio. 2023 ;14(1):e01349-22.
153. Lee K, Raguideau S, Sirén K, Asnicar F, Cumbo F, Hildebrand F, et al. Population-level impacts of antibiotic usage on the human gut microbiome. Nat Commun. 2023;14(1):1191.
154. Lê S, Cecchin-Albertoni C, Thomas C, Kemoun P, Minty M, Blasco-Baque V. The Role of Dysbiotic Oral Microbiota in Cardiometabolic Diseases: A Narrative Review. Diagnostics. 2023;13(20): 3184.
155. Zdziarski P, Paściak M, Gamian A. Microbiome Analysis and Pharmacovigilance After Inhaled Glucocorticoid: Oral Dysbiosis With the Isolation of Three Rothia Species and Subsequent Sjögren's Syndrome. Front Pharmacol. 2022;13:636180.
156. Akomoneh EA, Gestels Z, Abdellati S, Vereecken K, Bartholomeeusen K, Van Den Bossche D, et al. Genome Mining Uncovers NRPS and PKS Clusters in Rothia dentocariosa with Inhibitory Activity against Neisseria Species. Antibiotics. 2023;12(11):1592.
157. Dissanayake E, Stubbendieck RM, Wisdorf SS, Brockman-Schneider RA, Currie CR, Gern JE. Rothia Species Inhibit Rhinovirus-induced Moraxella Catarrhalis Cell Association in Airway Epithelium. In: C68 Topics in Airway and Alveolar Epithelial Cell Biology. American Thoracic Society. 2023;A5677–A5677.
158. Goeteyn E, Grassi L, Van Den Bossche S, Rigauts C, Vande Weygaerde Y, Van Braeckel E, et al. Commensal bacteria of the lung microbiota synergistically inhibit inflammation in a three-dimensional epithelial cell model. Front Immunol. 2023;14:1176044.
159. Taglialegna A. Competition in the nasal microbiome. Nat Rev Microbiol. 2023;21(6):345–345.
160. Lebeaux D, Fernández-Hidalgo N, Pilmis B, Tattevin P, Mainardi JL. Aminoglycosides for infective endocarditis: time to say goodbye? Clinical Microbiology and Infection. 2020 ;26(6):723–8.
161. Mirna M, Topf A, Schmutzler L, Hoppe UC, Lichtenauer M. Time to abandon ampicillin plus gentamicin in favour of ampicillin plus ceftriaxone in Enterococcus faecalis infective endocarditis? A meta-analysis of comparative trials. Clin Res Cardiol. 2022;111(10):1077–86.
162. Ryder JH, Tong SYC, Gallagher JC, McDonald EG, Thevarajan I, Lee TC, et al. Deconstructing the Dogma: Systematic Literature Review and Meta-analysis of Adjunctive Gentamicin and Rifampin in Staphylococcal Prosthetic Valve Endocarditis. Open Forum Infectious Diseases. 2022;9(11):ofac583.
163. Delgado V, Ajmone Marsan N, De Waha S, Bonaros N, Brida M, Burri H, et al. 2023 ESC Guidelines for the management of endocarditis. European Heart Journal. 2023;44(39):3948–4042.
164. McDonald EG, Aggrey G, Tarık Aslan A, Casias M, Cortes-Penfield N, Dong MQ (Denise), et al. Guidelines for Diagnosis and Management of Infective Endocarditis in Adults: A WikiGuidelines Group Consensus Statement. JAMA Netw Open. 2023;6(7):e2326366.
165. Silva NA, Taxa SKF, Silva Junior CLD, Barcelos RM, Pires EF, Garcia WF, et al. Endocardite infecciosa e atualizações nos Critérios de Duke. Acervo Médico. 2023;23(11):e14631.
166. Lam JC, Bourassa-Blanchette S. Ten common misconceptions about antibiotic

use in the hospital. Journal of Hospital Medicine. 2023;18(12):1123–9.

167. Ortwine JK, Wei W, Mang NS, Hall BC, Ding H. One Small Step (Down) for Antibiotics, One Giant Leap for Outpatient Therapy: The Role of Oral Antibiotics in Serious Bacterial Infections. Curr Infect Dis Rep. 2023;25(12):293–304.

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