Risk Factors and Patient Profile of Infective Endocarditis due to *Gemella* spp.

Pramod Theetha Kariyanna¹,²,³, Bayu Sutarjono³,⁴, Naga Pranavi Ellanti¹, Apoorva Jayarangaiah⁵, Amog Jayarangaiah⁶, Harshith Priyan Chandrakumar², Ashkan Tadayoni², Moro O. Salifu², Isabel M. McFarlane²

¹Division of Interventional Cardiology Fellow, Mount Sinai Heart, Icahn School of Medicine at Mount Sinai Morningside/Beth Israel, New York City, New York-10025
²Division of Cardiovascular Disease and Department of Internal Medicine, State University of New York, Downstate Medical Center, Brooklyn, NY 11203, USA
³Saba University School of Medicine, 27 Jackson Road, Devens, MA 01434, USA
⁴Department of Family Medicine, Mount Sinai Hospital, Chicago, IL 60608, USA
⁵Department of Internal Medicine, NYC Health and Hospitals/Jacobi Medical Center, Bronx, NY 10461, USA
⁶Trinity School of Medicine, 925 Woodstock Road, Roswell, GA 30075, USA

#These authors contributed equally to this work.

*Corresponding author: isabel.mcfarlane@downstate.edu

Received November 05, 2020; Revised December 06, 2020; Accepted December 13, 2020

Abstract Background. The diagnosis of infective endocarditis is difficult, especially when it involves atypical organisms. Therefore, our study identified risk factors of infective endocarditis caused by rare pathogen, *Gemella* spp. Methods. A systematic review was conducted to investigate characteristics of endocarditis patients infected with *Gemella* spp. using the search term “*Gemella*” and “endocarditis.” Case reports were gathered by searching Medline/Pubmed, Google Scholar, CINAHL, Cochrane CENTRAL, and Web of Science databases. 83 articles were selected for review. Results. Five species of *Gemella* were identified. Typical patients were males between 31 and 45 years of age. On admission, patients had fever, tachycardia, and normal blood pressure. Common clinical manifestation other than fever included fatigue and weakness, chills and sweating, and nausea, vomiting, diarrhea, and weight changes. One in four reported a history of congenital heart disease, and a recent oral cavity infection. Laboratory tests reveal anemia, leukocytosis, and elevated erythrocyte sedimentation in all age groups, elevated C-reactive protein is observed among adult and geriatric populations only. Mitral and aortic valves were most commonly infected by *Gemella* spp.. The most common *Gemella* spp.-susceptible antibiotics were penicillin, vancomycin, cephalosporin, macrolide, and aminoglycosides. However, antibiotic resistance was observed against penicillin, aminoglycoside, and fluoroquinolone. Antibiotic course of at least six weeks resulted in superior clinical improvements than durations under six weeks. Finally, one in two patients underwent valve replacement or repair, with common complications affecting the cardiovascular, neurological, and renal systems. Finally, death occurred in 1 in 8 patients, half of which occurred post-surgical procedure, and the majority occurring equal to or greater than 1 week from admission. Conclusion. Our systematic review highlights the importance of considering rare pathogens, particularly in the presence of predisposing risk factors.

Keywords: Gemella, endocarditis

Cite This Article: Pramod Theetha Kariyanna, Bayu Sutarjono, Naga Pranavi Ellanti, Apoorva Jayarangaiah, Amog Jayarangaiah, Harshith Priyan Chandrakumar, Ashkan Tadayoni, Moro O. Salifu, and Isabel M. McFarlane, “Risk Factors and Patient Profile of Infective Endocarditis due to *Gemella* spp.” *American Journal of Medical Case Reports*, vol. 9, no. 2 (2021): 103-115. doi: 10.12691/ajmcr-9-2-4.

1. Introduction

Infective endocarditis is a rare disease with an incidence of approximately 3-10 per 100,000 people per year in industrialized countries. [1,2,3,4] Recognizing infective endocarditis is difficult due to the non-specific symptoms, such as sepsis of unknown origin or fevers without recognizing the risk factors. [5] Currently, the accepted criteria for diagnosis are the modified Duke criteria. Furthermore, targeted antibiotic therapy for infective endocarditis should be guided by the results of two to three sets of blood cultures obtained from separate venipuncture sites. Any delay in treatment will have negative effects on clinical outcomes in acute bacterial infectious diseases [6] and raises the risk of developing complications including infectious recurrences, cardiac surgery because of the valvular sequelae of the disease, and death [7].
A number of factors predispose to the development of infective endocarditis, such as age, sex, injection drug use, and dental infection, as well as the presence of co-morbid conditions such as structural heart disease, valvular disease, or intravascular device. Presently, there is ample information available regarding the common causes of infective endocarditis: staphylococci, streptococci, and enterococci. [8,9,10] However, there is limited knowledge for lesser known pathogens. One prominent microorganism is Gemella spp.

Gemella spp. are facultatively anaerobic non-motile and non-spore forming Gram-positive cocci. Due to its misidentification as viridans group group streptococci, [11] it is very likely that Gemella is a more important cause of clinical disease than is presently recognized. These are organisms are present in the mouth, gastrointestinal tract, and genitourinary tract of humans and other warm-blood organisms are present in the mouth, gastrointestinal tract, of clinical disease than is presently recognized. These are it is very likely that Gemella is  more important cause of clinical disease than is presently recognized. These are organisms are present in the mouth, gastrointestinal tract, and genitourinary tract of humans and other warm-blood animals, although serious systemic infections such as endocarditis usually lead to the clinical presentations. [12] Although Gemella spp. are associated with previous valvular injury or prosthetic valves, dental surgery, and colorectal surgery, [13] the true mode of infection leading to infective endocarditis still remains unclear.

To understand the pathogenicity of the microorganism, identify risk factors and susceptible patient populations, a systematic review was conducted to elucidate the characteristics of endocarditis patients infected with Gemella spp. based on existing case reports and case series.

2. Methods

2.1. Protocol and Registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was adhered to for this systematic review. The protocol was not registered.

2.2. Eligibility Criteria

2.2.1. Inclusion Criteria

Only articles that reported the association of the genus of the gram-positive bacteria Gemella spp. and endocarditis were included.

2.2.2. Exclusion Criteria

Studies were excluded if: (1) they were not case reports or case series, (2) they were not peer-reviewed, and (3) they were not in English.

2.3. Information Sources and Search Strategies

A comprehensive literature search using Medline/Pubmed, Google Scholar, CINAHL, Cochrane CENTRAL, and Web of Science databases up to and including 1 January 2020 using the terms “Gemella” and “endocarditis.”

| Reference, publication year | Country | Patient profile (age in years, sex) | Species of Gemella | Diagnosis and association |
|-----------------------------|---------|------------------------------------|--------------------|--------------------------|
| Agrawal N et al, 2014 [14]  | India   | 40, female                         | Gemella morbillorum| Endocarditis              |
| Agrawal T et al, 2019 [15]  | USA     | 38, male                           | Gemella haemolytica| Endocarditis              |
| Akyama K et al, 2001 [16]  | Japan   | 55, male                           | Gemella morbillorum| Endocarditis              |
| Al Chekakie MO et al, 2009 [17] | USA    | 44, male                           | Gemella morbillorum| Endocarditis and prosthetic valve |
| Al Souh H et al, 2003 [18] | Sri Lanka | 41, female                       | Gemella morbillorum| Endocarditis              |
| Al-Hujailan G et al, 2007 [19] | Canada | 37, male                           | Gemella morbillorum| Endocarditis and prosthetic valve |
| Almaghrabi R et al, 2009 [20] | Saudi Arabia | 23, male                 | Gemella sanguinis   | Endocarditis              |
| Ando A et al, 2016 [21]    | USA     | 24, male                           | Gemella haemolytica| Endocarditis, aneurysm and stroke |
| Avgoustidis N et al, 2011 [22] | Greece | 56, female                       | Gemella haemolytica| Endocarditis and systemic lupus erythematosus |
| Bell E et al, 1992 [23]    | UK      | 19, male                           | Gemella morbillorum| Endocarditis, intravenous drug users and body piercing |
| Benes J et al, 2002 [24]   | Czech   | 31, male                           | Gemella morbillorum| Endocarditis              |
| Brack MJ et al, 1991 [25]  | UK      | 74, male                           | Gemella haemolytica| Endocarditis              |
| Breathnach AS et al, 1997 [26] | UK   | 6, male                            | Gemella haemolytica| Endocarditis and anti-Streptolysin-O |
| Calopa M et al, 1990 [27]  | Spain   | 45, male                           | Gemella morbillorum| Endocarditis, aneurysm and stroke |
| Carano N et al, 2010 [28]  | Italy   | 18, female                         | Gemella morbillorum| Endocarditis, intravenous drug users and body piercing |
| Chadha S et al, 2013 [29]  | USA     | 73, male                           | Gemella sanguinis   | Endocarditis              |
| Constantinou M et al, 2015 [30] | Cyprus | 80, female                       | Gemella morbillorum| Endocarditis and tricuspid valve |
| Czamecki A et al, 2007 [31] | Canada | 75, male                           | Gemella morbillorum| Endocarditis and septic arthritis |
| Devuyst O et al, 1993 [32] | Belgium | 53, female                       | Gemella haemolytica| Endocarditis              |
| Elsayed S et al, 2004 [33] | Canada | 32, male                           | Gemella bergeriae   | Endocarditis              |
| Emmanouilidis G et al, 2019 [34] | Greece | 85, female                       | Gemella sanguinis   | Endocarditis              |
| Farmaki E et al, 2000 [35] | Greece | 9, female                         | Gemella morbillorum| Endocarditis and children |
| Fresard A et al, 1993 [36] | France  | 42, male                           | Gemella haemolytica| Endocarditis              |
| Gimigliano F et al, 2005 [37] | Italy  | 10, female                         | Gemella morbillorum| Endocarditis and children |
| Godinho AR et al, 2013 [38] | Portugal | 72, male                         | Gemella morbillorum| Endocarditis              |
| Gandre PR et al, 2011 [39] | USA     | 28, female                         | Gemella sanguinis   | Endocarditis              |
| Helft G et al, 1993 [40]   | France  | 71, male                           | Gemella haemolytica| Endocarditis and colorectal cancer |
| Reference, publication year | Country | Patient profile (age in years, sex) | Species of Gemella | Diagnosis and association |
|----------------------------|---------|------------------------------------|--------------------|--------------------------|
| Hikone M et al, 2017 [41]  | Japan   | 52, female                         | Gemella taiwanensis | Endocarditis              |
| Holland J et al, 1996 [42] | Australia | 84, female                        | Gemella morbillorum | Endocarditis and prosthetic valve |
| Hull JE, 2010 [43]         | USA     | 87, male                           | Gemella morbillorum | Endocarditis              |
| Hussain K et al, 2014 [44] | Philippines | 24, male                        | Gemella bergeriae   | Endocarditis, aneurysm and stroke |
| Jayananda S et al, 2017 [45] | USA     | 82, male                           | Gemella spp.        | Endocarditis and bacteremia |
| Kaufhold A et al, 1989 [46] | Germany | 62, female                         | Gemella haemolysans | Endocarditis              |
| Kerr JR et al, 1994 [47]   | Northern Ireland | 29, female                  | Gemella morbillorum | Endocarditis and hypertrophic obstructive cardiomyopathy |
| Khan R et al, 2004 [48]    | USA     | 80, male                           | Gemella haemolysans | Endocarditis              |
| Kofteridis DP et al, 2006 [49] | Greece | 46, male                          | Gemella morbillorum | Endocarditis and anti-microbial resistance |
| Kofteridis DP et al, 2006 [49] | Greece | 53, male                          | Gemella morbillorum | Endocarditis and anti-microbial resistance |
| Kolkari VB et al, 2014 [50] | India   | 34, female                         | Gemella morbillorum | Endocarditis and hypertrophic obstructive cardiomyopathy |
| Kumar G et al, 2017 [51]   | UAE     | 12, female                         | Gemella morbillorum | Endocarditis and children |
| La Scola B et al, 1998 [52] | France  | 63, male                           | Gemella haemolysans | Endocarditis              |
| La Scola B et al, 1998 [52] | France  | 74, male                           | Gemella morbillorum | Endocarditis              |
| La Scola B et al, 1998 [52] | France  | Age unknown, male                  | Gemella morbillorum | Endocarditis              |
| Li D et al, 2017 [53]      | China   | 28, male                           | Gemella morbillorum | Endocarditis              |
| Liu D et al, 2016 [54]     | USA     | 87, female                         | Gemella haemolysans | Endocarditis and multiple myeloma |
| Logan LK et al, 2008 [55]  | USA     | 15, male                           | Gemella bergeriae   | Endocarditis and children |
| Lopez-Dupla M et al, 1996 [56] | Spain | 73, female                          | Gemella morbillorum | Endocarditis and colonic cancer |
| Maraki S et al, 2019 [57]  | Greece  | 21, male                           | Gemella sanguinis   | Endocarditis and bicuspid aortic valve |
| Martin MJ et al, 1995 [58] | UK      | 75, male                           | Gemella morbillorum | Endocarditis              |
| Matsis PP et al, 1994 [59] | New Zealand | 20, male                        | Gemella haemolysans | Endocarditis              |
| Morea P et al, 1991 [60]   | Italy   | 47, male                           | Gemella haemolysans | Endocarditis and prosthetic valve |
| Mosquera JD et al, 2008 [61] | Spain  | 77, male                           | Gemella haemolysans | Endocarditis and hemochromatosis |
| Mugunthan M et al, 2016 [62] | India  | 4, male                            | Gemella sanguinis   | Endocarditis and children |
| Murai M et al, 2006 [63]   | Japan   | 53, male                           | Gemella morbillorum | Endocarditis, aneurysm and stroke |
| Nandakumar R et al, 1997 [64] | USA    | 71, male                           | Gemella morbillorum | Endocarditis and tricuspid valve |
| Pachirat O et al, 2015 [65] | Thailand | 37, male                           | Gemella bergeriae   | Endocarditis and tricuspid valve |
| Palma G et al, 2011 [66]   | Italy   | 13, male                           | Gemella spp.        | Endocarditis and prosthetic valve |
| Purecell LK et al, 2001 [67] | Canada | 12, female                          | Gemella spp.        | Endocarditis and children |
| Raja NS et al, 2009 [68]   | UK      | 72, male                           | Gemella haemolysans | Endocarditis              |
| Raja NS et al, 2009 [68]   | UK      | 69, male                           | Gemella haemolysans | Endocarditis              |
| Ramchandani MS et al, 2014 [69] | USA   | 40, female                         | Gemella haemolysans | Endocarditis and prosthetic valve |
| Rosa RG et al, 2015 [70]   | Brazil  | 72, male                           | Gemella morbillorum | Endocarditis, cardiogenic shock and STEMI |
| Rousseau-Gagnon M et al, 2013 [71] | Canada | 67, male                           | Gemella sanguinis   | Endocarditis, acute kidney injury and glomerulonephritis |
| Sadaune L et al, 2019 [72] | France  | 86, female                         | Gemella haemolysans | Endocarditis and geriatric assessment |
| Samuel L et al, 1995 [73]  | UK      | 34, male                           | gemella haemolysans | Endocarditis and prosthetic valve |
| Satake K et al, 2011 [74]  | Japan   | 76, male                           | Gemella morbillorum | Endocarditis, acute kidney injury and glomerulonephritis |
| Seeburger J et al, 2009 [75] | Germany | 76, male                           | Gemella morbillorum | Endocarditis and prosthetic valve |
| Shahani L, 2014 [76]       | USA     | 73, male                           | Gemella morbillorum | Endocarditis and prosthetic valve |
| Shinha T, 2017 [77]        | USA     | 37, male                           | Gemella spp.        | Endocarditis              |
| Shukla SK et al, 2002 [78] | USA     | 69, male                           | Gemella sanguinis   | Endocarditis              |
| Sroup JS et al, 2007 [79]  | USA     | 50, male                           | Gemella spp.        | Endocarditis              |
| Taimur S et al, 2010 [80]  | Pakistan | 31, female                        | Gemella morbillorum | Endocarditis and bacteremia |
| Terada H et al, 1994 [81]  | Japan   | 64, male                           | Gemella morbillorum | Endocarditis              |
| Ukimura A et al, 1999 [82] | Japan   | 57, male                           | Gemella spp.        | Endocarditis and prosthetic valve |
| Ukudcwea A et al, 2017 [83] | USA     | 63, male                           | Gemella bergeriae   | Endocarditis              |
| Ural S et al, 2014 [84]    | turkey   | 67, male                           | Gemella morbillorum | Endocarditis              |
| Virgilio E et al, 2014 [85] | Brazil  | 50, male                           | Gemella bergeriae   | Endocarditis              |
| Winkler J et al, 2016 [86] | USA     | 67, male                           | Gemella spp.        | Endocarditis, cardiogenic shock and STEMI |
| Yang CH et al, 2014 [87]   | Taiwan  | 67, male                           | Gemella sanguinis   | Endocarditis              |
| Youssef D et al, 2019 [88] | USA     | 81, male                           | Gemella haemolysans | Endocarditis              |
| Zaidi SJ et al, 2018 [89]  | USA     | 23, male                           | Gemella bergeriae   | Endocarditis              |
| Zakir RM et al, 2004 [90]  | USA     | 44, male                           | Gemella morbillorum | Endocarditis and prosthetic valve |
| Zheng M et al, 2008 [91]   | Singapore | 67, male                        | Gemella morbillorum | Endocarditis and end-stage renal disease |
| Zingaro L et al, 1999 [92] | Italy   | 49, male                           | Gemella haemolysans | Endocarditis, acute kidney injury and glomerulonephritis |
2.4. Study Selection

Initial triage of articles was based on whether titles or abstracts met the inclusion criteria. Full-text articles were reviewed, and those that did not satisfy the inclusion were excluded. A summary of study characteristics is given in Table 1.

2.5. Data Collection Process and Data Items

Data extracted from articles included name of first author, year of publication, country, and study design. Variables for which data were sought included viral strain, patient age and sex, presenting complaints on admission, past medical and surgical histories, laboratory tests, diagnostic studies, management of endocarditis, and outcome of the patient.

2.6. Synthesis of Results and Summary of Measures

Data were tabulated, evaluated, and summarized.

2.7. Risk of Bias across Studies

Potential bias across studies were analyzed within study characteristics. Two independent reviewers evaluated the methodological quality of the eligible studies. A third reviewer evaluated papers where there was no agreement. The Joanna Briggs Institute critical appraisal tool for case reports was selected for use in this systematic review. Bias was evaluated using a checklist of 8 questions. Each question is specified in Supplementary Table S1 concerning risk of bias whereby an overall appraisal was made of each article: risk of bias is low (included), high (excluded), or uncertain (more information is required). For the purpose of this study, an answer of “yes” equal to or greater than 50% of the questions was considered to be low risk of bias. Similarly, an answer of “no” equal to or greater than 50% of questions was determined to be high risk of bias, whereas “unclear” answers were equal to or less than 50% response.

3. Results

3.1. Study Selection

From five databases, 118 articles were selected with relevance to Gemella spp. and endocarditis. 83 case reports were selected once assessed for eligibility. [14-92] A PRISMA flow diagram detailing the process of identification, inclusion, and exclusion of studies is shown in Figure 1.

3.2. Study Characteristics

All studies were published between 1989 and 2019. The majority of studies were conducted in Europe and the UK [22,23,24,25,26,27,28,30,32,34,35,36,37,38,40,46,47, 49,52,56,57,58,60,61,66,68,72,73,75,84,92] followed by North America [15,17,19,21,29,31,33,39,43,45,48,54,55, 64,67,69,71,76,77,78,79,83,86,88,90] and Asia. [14,16, 18,20,41,44,50,51,53,62,63,65,74,80,81,82,87,91] USA [15,17,21,29,39,43,45,48,54,55,64,69,76,77,78,79,83,86, 88,89,90] reported the most number of cases in the world, followed by the UK. [23,25,26,58,68,73] Japan [16,41,63,74,81,82] reported the most cases among Asia, Oceania, and South America.

3.3. Risk of Bias within Studies

Results are found in Supplementary Table S1. All articles were rated as low risk of bias, although three studies recorded 50.0% “yes” response to the questions. [14,52,65] Two articles were missing either sex [14] or age [52] with regards to demographic characteristics. Fifteen case reports did not have satisfy the patient’s history and timeline criteria, [18,25,32,34,40,44,45,49, 51,56,58,59,62,65,92] while five articles omitted details of intervention. [14,52,65,77,86] 71.4% of studies did not include the post-intervention clinical condition of the patients and/or adverse or unanticipated events. [14,15,16,18,19,22-26,28-32,34,36-43,46-50,52,53,57-63, 65-68,71-73,76-78,80,81,84,85,87,89,90,92]
3.4. Results of Individual Studies

A summary of findings is presented in Table 1.

3.4.1. Gemella spp. and Endocarditis

Fifty five articles involved the discovery of the gram-positive bacteria Gemella spp. in adult patients with infective endocarditis. [14-20,24,25,29,30,32-34,36,38,39,41,43,46,48,49,52,53,57-60,64-66,68,69,72,73,75-85,87-90] While the majority of these studies reported the presence of the bacteria in predominately native-valves, [14-16,18,20,24,25,29,30,32-34,36,38,41,43,46,48,49,52,53,57-59,64,65,68,72,77-81,83-85,87-89] 12 of those studies highlighted the association of prosthetic valve endocarditis by Gemella spp. [17,19,39,42,60,66,69,73,75,76,82,90]

The remaining 20 studies investigated the possible implication of a second disease in relation to endocarditis as caused by Gemella spp. Three articles investigated the association of endocarditis and cancer, particular colonic carcinoma [40,56] and multiple myeloma, [54] while four studies reported the association aneurysms and strokes. [21,27,44,61] was the subject of one article, while systemic lupus erythematus was the topic the other. [22]

In terms of population studies, six studies observed Gemella spp. in the pediatric population, [35,37,51,55,62,67] while two articles found the bacteria in the intravenous drug users or body piercing populations. [23,28]

3.5. Synthesis of Results

3.5.1. Species

Five different species of Gemella spp. were identified as shown in Table 1. The most common species was Gemella morbillorum (44.6%) [14,16,19,23,24,27,28,30,31,35,37,38,42,43,47,49-53,56,58,63,64,70,74-76,80,81,83-85,87-90] followed by Gemella haemolysans (26.5%). [15,21,22,25,26,32,36,40,46,48,52,54,59,61,68,69,72,73,88,92] The predominant strains in studies published in Europe and North America were Gemella morbillorum [17,19,23,24,27,28,30,31,35,37,38,43,47,49,52,56,57,64,75,76,84,90] and Gemella haemolysans. [15,21,22,25,26,32,36,40,46,48,52,54,60,61,68,69,72,73,88,91] whereas articles from Asia involved mainly Gemella morbillorum. [14,16,18,50,51,63,72,80,81,91]

3.5.2. Patient Profile

The distribution of age, shown in Supplementary Figure S1, was stratified in groups of 15 years of age, as well as according to gender. Nearly three-quarter of studies involved male patients. [14-17,19-21,23-27,29,31,33,36,38,40,43-45,48,49,52,53,55,57-66,68,70,71,73-79,81-92]

3.5.3. Presenting Complaints

The average temperature recorded at admission was 38.2 +/- 0.8°C ranging from 36.0°C to 40.4°C, [16-19,21,24,25,28-30,32-37,39,41,45-49,51,52,55,58,63,65,68,70,76,79-85,87-90,92] while the average heart rate and blood pressure was 103.0 +/- 21.5 bpm [15-17,21,28,30,32-34,39,41,43,45-47,49-51,53,55,57,59,62,65,67,68,76,79-84,86,87,90,92] and 120.6/67.9 +/- 25.3/17.0 mmHg [16-18,24,28,30,32,34,36,39,41,44,45-47,49,51,53,59,65,68,70,74-79,84,86,87,90,92] respectively. Distribution of presenting complaints and associated symptoms are found in Table 2. There were noticeable differences when organized according to age. The predominant symptom was fever, [16,18-24,26,28-42,45,47-53,56,57,59,62-66,68,69,70,72-85,87,90-92] while fatigue, malaise, lethargy, and weakness were common to all age groups. [14,21-23,26,27,29-33,36,40,42,45,47,48,51,53,55,59-61,66,67,71,73-77,83,84,87,88] Nausea, vomiting, diarrhea, and weight change were present in the pediatric [26,35,37,51,55,62,66,67] and geriatric populations, [25,29,31,34,38,40,42,43,45,46,48,52,54,56,58,61,64,68,70-72,74-76,78,81,83,84,86-88,91] while shortness of breath, cough, and dyspnea were exclusively found in the adult population. [14-24,27,28,32,33,36,38,39,41,44,46,47,49,50,52,53,57,59,60,63,65,69-71,73,76-87,89-92] The pediatric and adult populations exhibited chills and sweating, while rigor, myalgia, back pain and joint pain were observed in the adult and geriatric populations.

3.5.4. Past Medical History/Past Surgical History

Twenty studies reported a history of congenital heart disease. [14,15,17,19,20,24,26,37,50,52,53,55,57,66,67,69,80,85,87,89] Bicuspid aortic valve was observed in 50.0% of these studies, [15,17,19,52,57,66,80,85,87,89] followed by ventricular septal defect (VSD) (20.0%) [20,37,53,76] and tetralogy of Fallot (15.0%). [24,55,66]

A history of some form of infection was found in 21 studies. [16,21,31,36,37,39,41,47,49,52,53,60,63,64,67,71,73,76,78,91]. The majority of these patients were found to have had an infection of the mouth (57.14%). [16,21,37,41,49,60,63,64,71,73,76,78]

Table 2. Most common clinical manifestations on admission of all patients, and pediatric, adult, and geriatric populations with Gemella-infected endocarditis

|                          | All patients (n=83) | %       | Pediatric population (n=8) | %       | Adult population (n=40) | %       | Geriatric population (n=22) | %       |
|--------------------------|-------------------|---------|---------------------------|---------|------------------------|---------|---------------------------|---------|
| Fever                    | 76.2              |         | Fever                     | 75.0    | Fever                  | 80.0    | Fever                     | 72.3    |
| Fatigue                  | 41.7              |         | Fatigue                   | 75.0    | Chills and/or Sweating | 47.5    | Fatigue                   | 50.0    |
| Chills and/or Sweating   | 40.5              |         | Chills and/or Sweating    | 62.5    | Chills and/or Sweating | 40.0    | Chills and/or Sweating    | 40.9    |
| Cough and/or Dyspnea     | 38.1              |         | Cough and/or Dyspnea      | 40.0    | Cough and/or Dyspnea   | 35.0    | Cough and/or Dyspnea      | 31.8    |


A history of invasive procedure was recalled in 37 articles, [17,19,20,22,24,26,28,30,35,37,41,42,48-50,55,57,60,66-70,73,74,76,80-84,88-90] the most being aortic valve replacement or aortic arch repair (45.9%) [8,10,11,15,21,28,30,52,59,61,65,66,68,71,73,80] and dental procedure (32.4%). [22,28,35,39,41,48-50,57,68,81,83] Mitral valve replacement, [39,60,67,90] pulmonary repair or pulmonary artery repair, [24,37,55,66] and VSD repair [20,26,37,68] were cited in 4 articles each.

### 3.5.5. Laboratory Tests

A summary of laboratory tests is found in Table 3. All population groups showed anemia, [16-18,23,24,27,28,32-36,41,44,46,49,51,52,54-59,62,67,68,70,71,74,76,79-82,84,87,88,90] leukocytosis [15-19,21,23,24,27,28,29,32-36,41,44-49,50,52,55-59,61,67,74,76,79,80,82,84,87-90,91] and elevated erythrocyte sedimentation rate. [18,24,27,28,29,32,34,35,38,46,47,49,50,52,55-59,61,67,70,79,81,85,89,91] C-reactive protein was elevated in the adult and geriatric populations [16,23,24,28,29,32,34,36,38,44,46,49,50,57,63,68,70,72,74,80-82,84,85,87,89,91] but remained normal in the pediatric population. [35,55]

### 3.5.6. Diagnostic Studies

Sixty-four patients were evaluated by transthoracic echocardiogram [16-19,21,23,25-30,32,34,35,37-39,41,43-48,50-52,53-69,71,72,74,76-78,80,81,83-92] whereas 34 cases used transesophageal echocardiogram. [14,15,18-22,24,30,31,33,39,41-43,48,49,52,56,68,70,71,73,75,76,78,79,82,86,90] The mitral valve was the most common location of vegetation in the pediatric and geriatric populations, whereas the aortic valve vegetation predominated in the adult age group. *Gemella haemolysans, Gemella bergeriae, Gemella sanguinis* were mainly found on aortic valves [15-17,19-22,29,30,33,34,38,39,43,44,49,52,54,56,57,59-61,63,68,69,71-77,80-82,84,85,87,89,91,92] while *Gemella morbillorum* and *Gemella taiwanensis* were discovered predominantly on the mitral valve. [16-18,21,22,25-29,31,32,34,35,37,38,41,43,44,46-52,56,58,67,68,70,71,74,75,78-81,83,86-91]

### 3.5.7. Management of Endocarditis

Management of endocarditis by *Gemella spp.* was governed by antibiotic susceptibility in 43 studies, [17-19,23,24,30,32,35,39,41,42,44-46,48-50,51,53-62,64,67,68,70,71,73,76,81,82,84,87-90] most commonly beta-lactam treatment, as shown in Supplementary Table S2. Five studies, however, demonstrated antibiotic resistance, in particular penicillin, [49,62] aminoglycoside [49] and fluoroquinolone. [41,62]

In studies where patients survived the course of treatment, more patients showed clinical improvement after receiving six weeks or more of antibiotic therapy [16,19,21,25,30-34,38,39,41,47-51,55,57,62,66,67,71,72,76,80,82,87,89] than patients who received under six weeks of antibiotic therapy, [15,23,24,27,35-37,46,52,53,58,59,61,63,65,69,81,84,85,90] as demonstrated in Figure 2.

Of the 45 patients who underwent surgical procedure, 43 required valve replacement or repair. [14-18,21,27-29,32,33,38-41,49,50,52,53,56,59,60,62,63,65,66,68-72,75,76,78,79,81-83,87-89,92] Furthermore, patients who received longer treatment courses [16,19,21,25,30-34,38,39,41,47-51,55,57,62,66,67,71,72,76,80,82,87,89] underwent less surgical procedures for valve repair than shorter treatment courses. [15,23,24,27,35-37,46,52,53,58,59,61,63,65,69,81,84,85,90]

### Table 3. Trends of laboratory values of endocarditis patients infected with *Gemella* combined and as divided by age group

|                      | All patients (n=83) | Pediatric (n=8) | Adults (n=40) | Geriatric (n=22) | (Standard range) |
|----------------------|--------------------|----------------|---------------|-----------------|-----------------|
| Temperature (°C)     | ↓                  | ↓              | ↓             | ↓               | (36.1 - 37.2)   |
| Hemoglobin (g/dl)    | ↓                  | ↓              | ↓             | ↓               | (12.0 - 16.0)   |
| Highest WBC (cells/mm^3) | ↓              | ↓              | ↓             | ↓               | (4,500 - 11,000)|
| ESR (mm/hr)          | ↓                  | ↓              | ↓             | ↓               | (0 - 20)        |
| CRP (mg/dl)          | ↓                  | ↓              | ↓             | ↓               | (<8.0)          |

Figure 2. Comparison between antibiotic therapy 6 weeks or more (dark) to treatment duration under 6 weeks (light) (n=51)
Two-thirds of infective endocarditis in low-income countries are caused by community-acquired penicillin-sensitive streptococci entering via the oral cavity leading to rheumatic heart disease. [97] Infective endocarditis in high-income countries, on the other hand, is due to degenerative valve disease, diabetes, cancer, intravenous drug use, and congenital heart disease. [98] This is in large due to improved living standards and availability of antibiotics for streptococcal pharyngitis resulting in substantially reduced incidence of rheumatic heart disease. [99] In parallel, the incidence of cases attributable to oral streptococci has decreased due to oral antibiotic prophylaxis. [100] Interestingly, we showed that one in four patients reported a history of congenital heart disease, such as bicuspid aortic valve, ventricular septal defect, and tetralogy of Fallot. Furthermore, one in four patients had a recent history of oral infection, and one in two had undergone surgical procedure, such as heart valve replacement or dental repairs. This poses the question whether the incidence and prevalence of infective endocarditis by Gemella spp. is under-reported in low-income countries.

Typically, clinical examination of infective endocarditis shows variable signs of disease, with fever present in 90% of cases and cardiac murmurs in 85% of patients. Splenomegaly or cutaneous manifestations, such as petechiae or splinter haemorrhages, are supportive signs. [101,102] Osler’s nodes, Janeway lesions, and Roth spots are rare, while signs of complications such as heart failure, stroke, or metastatic infection (eg, vertebral osteomyelitis, peripheral abscess) are more prevalent. [5] Patients with infective endocarditis by Gemella spp. showed fever, tachycardia, and normal blood pressure. The most common clinical manifestations for all patients were fever, fatigue, and chills or sweating. Nausea, vomiting, diarrhea or anorexia were more commonly found in children, while adults displayed chills or sweating. The elderly, on the other hand, exhibited fatigue.

Generally, laboratory tests for infective endocarditis is non-specific, showing raised inflammatory markers and normocytic-normochromic anemia. [103] Our systematic review revealed that patients with infective endocarditis by Gemella spp. have anemia, leukocytosis, and elevated erythrocyte sedimentation rate in all age groups, while the adult and geriatric populations have an elevation in C-reactive protein. Diagnostic studies commonly showed mitral valve vegetation in the pediatric and geriatric population, and aortic valve vegetation in the adult age group. Gemella haemolysans, bergeriae, and sanguinis were mainly found on aortic valves, whereas Gemella morbillorum and taiwanensis were discovered predominantly on mitral valves.

The most common Gemella-susceptible antibiotics are penicillin, vancomycin, cephalosporin, macrolide, and aminoglycosides. However, antibiotic resistance was observed against penicillin, aminoglycoside, and fluoroquinolone. This management is similar current approach to patients with uncomplicated community-acquired native valve or late prosthetic valve endocarditis due to highly sensitive streptococci, where combination therapy with a beta-lactam antibiotic and aminoglycoside is used. [104] Finally, patients who received treatment course for at least six weeks or greater showed greater clinical
improvement than patients who received antibiotic therapy for less than six weeks. This finding indicates that special attention should be placed on the duration of treatment for Gemella cases.

One out of two cases in the systematic review underwent either valve replacement or repair where removal of the infected tissues and reconstruction of cardiac morphology were accomplished. Typically, surgery is undertaken in 40-50% of patients with infective endocarditis. [105] In mitral valve infective endocarditis, successful valve repair is achieved in up to 80% of patients. [106]

Finally, patients with infective endocarditis by Gemella spp. commonly suffered complications involving the cardiovascular, neurological, and renal systems. Death occurred in one of eight patients, half of which occurred in the post-surgical period with the majority occurring equal to or greater than 1 week from admission. This is similar to in-hospital mortality of infective endocarditis, which is estimated at 20% and increases to 25-30% at six months. [106,107]

Although the strength of the study is an extensive review of infective endocarditis due Gemella spp. data were limited with regards to recurrent infections with the same organism.

In conclusion, infective endocarditis by Gemella spp. is more likely to infect men ages 31 to 45 years with a history of congenital heart disease, recent oral infection, or surgical procedures, such as heart valve replacement or dental repairs. Laboratory tests will likely indicate anemia, leukocytosis, and elevated erythrocyte sedimentation rate, while diagnostic studies will commonly show mitral or aortic valve vegetation, which is dependent of population or Gemella species. Infective endocarditis by Gemella spp. is managed by empiric treatment with beta-lactam and aminoglycosides combination therapy for at least 6 weeks in duration, or valve replacement or repair, with death occurring in 12.5% of the cases. Therefore, our systematic review highlights the importance of considering rare pathogens, particularly in the presence of predisposing risk factors.

Acknowledgement

This work is supported in part by the efforts of Dr. Moro O. Salifu M.D., M.P.H., M.B.A., M.A.C.P., Professor and Chairman of Medicine through NIH Grant number S21MD012474.

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Chu VH, Cabell CH, Benjamin DK Jr, et al. Early predictors of in-hospital death in infective endocarditis. Circulation 2004; 109: 1745-49.
## Supplementary Table 1. Risk of bias across studies

| Reference, publication year | Missing sex | Treatment procedure(s) clearly described? | Clinical condition clearly described? | Unanticipated events identified? | Total score |
|-----------------------------|-------------|------------------------------------------|--------------------------------------|---------------------------------|-------------|
| Agrawal N et al, 2014 [14]  | ✓           | ✓                                        | ✓                                    | X                               | 50%         |
| Agrawal T et al, 2019 [15]  | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Akyama K et al, 2001 [16]   | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Al Chekakie MO et al, 2009 [17] | ✓         | ✓                                        | ✓                                    | X                               | 100%        |
| Al Soub H et al, 2003 [18]  | ✓           | ✓                                        | ✓                                    | X                               | 63%         |
| Al-Hujailan G et al, 2007 [19] | ✓         | ✓                                        | ✓                                    | X                               | 75%         |
| Almaghrabi R et al, 2009 [20] | ✓         | ✓                                        | ✓                                    | X                               | 100%        |
| Ando A et al, 2016 [21]     | ✓           | ✓                                        | ✓                                    | X                               | 100%        |
| Avgoustidis N et al, 2011 [22] | ✓        | ✓                                        | ✓                                    | X                               | 75%         |
| Bell E et al, 1992 [23]     | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Benes J et al, 2002 [24]    | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Brack MJ et al, 1991 [25]   | ✓           | ✓                                        | ✓                                    | X                               | 63%         |
| Breathnach AS et al, 1997 [26] | ✓        | ✓                                        | ✓                                    | X                               | 75%         |
| Calopa M et al, 1990 [27]   | ✓           | ✓                                        | ✓                                    | X                               | 100%        |
| Carano N et al, 2010 [28]   | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Chadha S et al, 2013 [29]   | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Constantinos M et al, 2015 [30] | ✓       | ✓                                        | ✓                                    | X                               | 75%         |
| Carnevei A et al, 2007 [31] | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Devuyse O et al, 1993 [32]  | ✓           | ✓                                        | ✓                                    | X                               | 63%         |
| Elsayed S et al, 2004 [33]  | ✓           | ✓                                        | ✓                                    | X                               | 100%        |
| Emmanouilidou G et al, 2019 [34] | ✓       | ✓                                        | ✓                                    | X                               | 63%         |
| Farmaki E et al, 2000 [35]  | ✓           | ✓                                        | ✓                                    | X                               | 100%        |
| Fresard A et al, 1993 [36]  | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Gimigliano F et al, 2005 [37] | ✓         | ✓                                        | ✓                                    | X                               | 75%         |
| Godinho AR et al, 2013 [38] | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Gundre P et al, 2011 [39]   | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Helf G et al, 1993 [40]     | ✓           | ✓                                        | ✓                                    | X                               | 63%         |
| Hikone M et al, 2017 [41]   | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Holland J et al, 1996 [42]  | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Hull JE, 2010 [43]          | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Hussain K et al, 2014 [44]  | ✓           | ✓                                        | ✓                                    | X                               | 88%         |
| Jayananda S et al, 2017 [45] | ✓         | ✓                                        | ✓                                    | X                               | 88%         |
| Kaufhold A et al, 1989 [46] | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Kerr JR et al, 1994 [47]    | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Khan R et al, 2004 [48]     | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Kolferidis DP et al, 2006 [49] | ✓       | ✓                                        | ✓                                    | X                               | 75%         |
| Kohlhar VB et al, 2014 [50] | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Kumar G et al, 2017 [51]    | ✓           | ✓                                        | ✓                                    | X                               | 88%         |
| La Scola B et al, 1998 [52] | ✓           | ✓                                        | ✓                                    | X                               | 50%         |
| Li D et al, 2017 [53]       | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Liu D et al, 2016 [54]      | ✓           | ✓                                        | ✓                                    | X                               | 100%        |
| Logan LK et al, 2008 [55]   | ✓           | ✓                                        | ✓                                    | X                               | 100%        |
| Lopez-Dupla M et al, 1996 [56] | ✓        | ✓                                        | ✓                                    | X                               | 88%         |
| Maraki S et al, 2019 [57]   | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Martin MJ et al, 1995 [58]  | ✓           | ✓                                        | ✓                                    | X                               | 63%         |
| Matsis PP et al, 1994 [59]  | ✓           | ✓                                        | ✓                                    | X                               | 63%         |
| Morea P et al, 1991 [60]    | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Mosquera JD et al, 2008 [61] | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
| Mugunthanh M et al, 2016 [62] | ✓         | ✓                                        | ✓                                    | X                               | 63%         |
| Murai M et al, 2006 [63]    | ✓           | ✓                                        | ✓                                    | X                               | 75%         |
Were patient’s demographic characteristics clearly described? | Was the patient’s history clearly described and presented as a timeline? | Was the current clinical condition of the patient on presentation clearly described? | Were diagnostic tests or assessment methods and results clearly described? | Was the intervention(s) or treatment procedure(s) clearly described? | Was the post-intervention clinical condition clearly described? | Were adverse events (harms) or unanticipated events identified and described? | Does the case report provide takeaway lessons? | Total score

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| Reference, publication year | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | Total score |
|-----------------------------|----|----|----|----|----|----|----|-------------|
| Nandakumar R et al, 1997    | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | 100%        |
| Pachirat O et al, 2015      | ✓  | X  | ✓  | ✓  | ✓  | ✓  | X  | 50%         |
| Palma G et al, 2011         | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | X  | 75%         |
| Purcell LK et al, 2001      | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | X  | 75%         |
| Raja NS et al, 2009         | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | X  | 75%         |
| Ramchandani MS et al, 2014  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | 100%        |
| Rosa RG et al, 2015         | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | 100%        |
| Rousseau-Gagnon M et al, 2013 | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | X  | 75%         |
| Sadaule L et al, 2019       | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | X  | 75%         |
| Samuel L et al, 1995        | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | X  | 75%         |
| Satake K et al, 2011        | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | 100%        |
| Sceuberger J et al, 2009    | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | 100%        |
| Shahani L, 2014             | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | 75%         |
| Shinha T, 2017              | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | X  | 63%         |
| Shukla SK et al, 2002       | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | X  | 75%         |
| Stroup JS et al, 2007       | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | 100%        |
| Taimur S et al, 2010        | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | X  | 75%         |
| Terada H et al, 1994        | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | X  | 75%         |
| Ukimura A et al, 1998       | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | 100%        |
| Ukudeeva A et al, 2017      | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | 100%        |
| Ural S et al, 2014          | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | X  | 75%         |
| Virgilio E et al, 2014      | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | X  | 75%         |
| Winkler J et al, 2016       | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | X  | 88%         |
| Yang CH et al, 2014         | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | X  | 75%         |
| Youssif D et al, 2019       | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | 100%        |
| Zaidi SI et al, 2018        | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | X  | 75%         |
| Zahir RM et al, 2004        | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | X  | 75%         |
| Zheng M et al, 2008         | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | 100%        |
| Zingaro L et al, 1999       | ✓  | X  | ✓  | ✓  | ✓  | ✓  | X  | 63%         |

Supplementary Figure 1. Distribution of males (A) and females (B) patients with infective endocarditis by Gemella spp. according to age.
**Supplementary Table S2. Antibiotic susceptibility and resistance of *Gemella* in order of most commonly discovered (n=43)**

| Antibiotic susceptibility | Antibiotic resistance          |
|---------------------------|--------------------------------|
| Penicillin (penicillin, ampicillin) | Penicillin (penicillin, ampicillin) |
| Vancomycin                | Aminoglycosides (gentamicin)    |
| Cephalosporin (cefazolin, cefotaxime, ceftriaxone, cephalotin) | Fluoroquinolone (levofloxacin, ciprofloxacin) |
| Macrolide (erythromycin)  | Chloramphenicol                 |
| Aminoglycosides (gentamicin) |                                |
| Lincomycin (clindamycin)  |                                |
| Fluoroquinolone (levofloxacin, ciprofloxacin) |                                |
| Antimycobacerial (rifampicin) |                                |
| Doxycycline (tetracycline, minocycline) |                                |
| Carbapenem (imipenem, meropenem) |                                |
| Chloramphenicol           |                                |
| Oxazolidinones (linezolid) |                                |
| Penicillin-like (amoxicillin-clavulanic acid) |                                |
| Glycopeptide (teicoplanin) |                                |
| Sulfonamides              |                                |

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