American Journal of Medical Case Reports, 2021, Vol. 9, No. 9, 467-478
Available online at http://pubs.sciepub.com/ajmcr/9/9/8
Published by Science and Education Publishing
DOI:10.12691/ajmcr-9-9-8

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

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Received April 14, 2021; Revised May 17, 2021; Accepted May 25, 2021

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.** 5 species of *Gemella* were identified. Typical patient affected were male 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. 1 in 4 reported a history of congenital heart disease, and a recent oral infection. 1 in 2 patients underwent surgical procedure. Laboratory tests revealed anemia, leukocytosis, and elevated erythrocyte sedimentation in all age groups, as well as elevated C-reactive protein in 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 therapy of at least 6 weeks resulted in superior clinical improvements than durations under 6 weeks. Finally, 1 in 2 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: *infective endocarditis, Gemella spp, heart valve vegetations, clinical features, mortality, risk factors*

Cite This Article: Pramod Theetha Kariyanna, Bayu Sutarjono, Naga Pranavi Ellanti, Apoorva Jayarangaiah, Amog Jayarangaiah, Sushruth Das, Harshith Priyan Chandrakumar, and Isabel M. McFarlane, "Risk Factors and Patient Profile of Infective Endocarditis by *Gemella spp.*" *American Journal of Medical Case Reports*, vol. 9, no. 9 (2021): 467-467. doi: 10.12691/ajmcr-9-9-8.

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, it is important that for the initiation of targeted antibiotic therapy for infective endocarditis, the organism is isolated from blood cultures, requiring 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 the genus is a more important cause of clinical disease than is presently recognized. These are organisms of the mouth, gastrointestinal tract, and genitourinary tract of humans and other warm-blood animals, although serious systemic infections such as endocarditis are the most prevalent clinical presentation. [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.

It is important that to understand the pathogenicity of the microorganism in order to identify risk factors that predisposes an individual to an infection of a rare bacterium. Therefore, a systematic review was conducted to investigate 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 *Gamella 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."

Table 1. Summary of description characteristics of included articles (n=83)

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 haemolysans*	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 Soub 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 haemolysans*	Endocarditis, aneurysm and stroke
Avgoustidis N et al, 2011 [22]	Greece	56, female	*Gemella haemolysans*	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 haemolysans*	Endocarditis
Breathnach AS et al, 1997 [26]	UK	6, male	*Gemella haemolysans*	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
Constantinos M et al, 2015 [30]	Cyprus	80, female	*Gemella morbillorum*	Endocarditis and tricuspid valve
Czarnecki A et al, 2007 [31]	Canada	75, male	*Gemella morbillorum*	Endocarditis and septic arthritis
Devuyst O et al, 1993 [32]	Belgium	53, female	*Gemella haemolysans*	Endocarditis
Elsayed S et al, 2004 [33]	Canada	32, male	*Gemella bergeriae*	Endocarditis
Emmanouilidou 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 haemolysans*	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
Gundre PR et al, 2011 [39]	USA	28, female	*gemella sanguinis*	Endocarditis
Helft G et al, 1993 [40]	France	71, male	*Gemella haemolysans*	Endocarditis and colonic cancer
Hikone M et al, 2017 [41]	Japan	52, female	*Gemella taiwanensis*	Endocarditis

Reference, publication year	Country	Patient profile (age in years, sex)	Species of *Gemella*	Diagnosis and association
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
Kolhari 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
Purcell 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
Stroup JS et al, 2007 [79]	USA	50, male	*Gemella spp.*	Endocarditis
Taimur S et al, 2010 [80]	Pakistan	31, female	*Gemella morbillorum*	Endocarditis and bicuspid aortic valve
Terada H et al, 1994 [81]	Japan	64, male	*Gemella morbillorum*	Endocarditis
Ukimura A et al, 1998 [82]	Japan	57, male	*Gemella spp.*	Endocarditis and prosthetic valve
Ukudeeva 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 then read, and those that did not satisfy the inclusion/exclusion criteria 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 were 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 1 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 greater than 50% response.

3. Results

3.1. Study Selection

From 5 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 [22-28,30,32,34-38,40,46,47,49,52,56-58,60, 61,66,68,72,73,75,84,92] followed by North America [15,17,19,21,29,31,33,39,43,45,48,54,55,64,67,69,71,76-79,83,86,88-90] and Asia. [14,16,18,20,41,44, 50,51,53,62, 63,65,74,80-82,87,91] USA [15,17,21,29,39, 43,45,48,54, 55,64,69,76-79,83,86,88-90] 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.

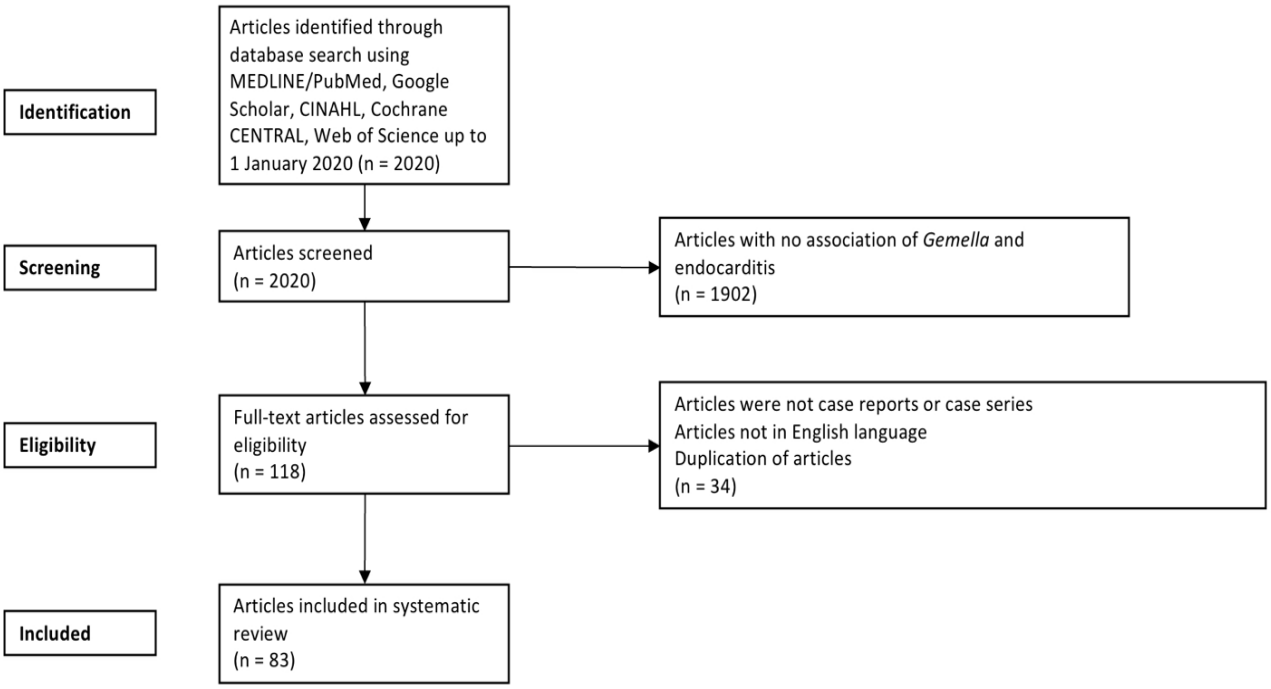

Figure 1. Flow diagram of literature search and selection criteria adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

3.3. Risk of Bias within Studies

Results are found in Supplementary Table 1. All articles were rated as low risk of bias, although 3 studies recorded 50.0% "yes" response to the questions. [14,52,65] 2 articles were missing either sex [14] or age [52] with regards to demographic characteristics. 15 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 5 articles omitted details of intervention. [14,52,65,77,86] 71.4% of studies did not include post-intervention clinical condition and/or adverse or unanticipated events. [14-16,18-19,22-26,28-32,34,36-43,46-50,52-53,57-63, 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 given in Table 1.

3.4.1. *Gemella spp*. and endocarditis

55 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 predominantly 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*. 3 articles investigated the association of endocarditis and cancer, particular colonic carcinoma [40,56] and multiple myeloma, [54] while 4 studies reported the association aneurysms and strokes. [21,27,44,63] The effects on the kidneys were discussed in 4 studies, [71,74,91,92] while 4 articles reported concurrent implications of the heart, such as cardiogenic shock, STEMI, and hypertrophic cardiomyopathy. [47,50,70,86] Finally, 3 articles investigated the contribution of other infections within the body, such as septic arthritis, respiratory tract infection, and presence of anti-streptolysin-O antibodies. [26,31,45] Hemochromatosis [61] was the subject of 1 article, while systemic lupus erythematous was the topic the other. [22]

In terms of population studies, 6 studies observed *Gemella spp.* in the pediatric population, [35,37,51,55,62,67] while 2 articles found the bacteria in the intravenous drug users or body piercing populations. [23,28]

3.5. Synthesis of Results

3.5.1. Species

5 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, 38,42,43,47,49,50,51,52,53,56,58,63,64,70,74-76,80,81, 84,90,91] 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* [17,19,23,24,27,28,30,31,35,37,38,43,47,49,52,56,58,64, 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 1, 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 [15,16,17,21,28,30, 32-34,36,39,41,43-45,47-49,51-53,55,57,59,62,65,67,68, 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.

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	Nausea, Vomiting, and/or Change of Weight	75.0	Chills and/or Sweating	47.5	Fatigue	50.0
Chills and/or Sweating	40.5	Fatigue	62.5	Cough and/or Dyspnea	40.0	Nausea, Vomiting, and/or Change of Weight	40.9
Cough and/or Dyspnea	38.1	Chills and/or Sweating	40.0	Fatigue, or Myalgia and/or Arthralgia	35.0	Myalgia and/or Arthralgia	31.8

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

20 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, [15,17,19,52,57,69,80,85,87,89] 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]

A history of invasive procedure was recalled in 37 articles, [17,19,20,22,24,26,28,30,35,37,39,41,42,48,49,50,55,57,60,66-70,73-74,76,80-84,88-90] 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%). [22,28,35,39,41,48,49,50,57,68,81,83] Mitral valve replacement, [39,60,67,90] pulmonary repair or pulmonary artery repair, [24,37,55,66] and VSD repair [20,26,37,67] 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, [16,17,18,23,24,27,28,32-36,41,44,46,49,51,52,54-59,62,67,68,70,71,74,76,79-82,84,87-88,87-88,90] leukocytosis [15-19,21,23-24,27-29,32-36,41,44-49,52,54-59,61-63,67-72,74,76,79-88,90-91] and elevated erythrocyte sedimentation rate. [18,24,27,28,29,32,34-35,38,46,47,49,50,52,55-59,61,67,70,79,81,85,89-90] 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

64 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 predominately on the mitral valve. [16-18,21,22,25,27-29,31-32,34-35,37-38,41,43-44,46,48-52,56,58,67-68,70-71,74-75,78-81,83,86-91]

3.5.7. Management of Endocarditis

Management of endocarditis by *Gemella spp.* was governed by antibiotic susceptibility in 43 studies, [17-19,23-24,30,32,35,37,39,41-42,44,46-48,50-51,53-62,64,67-68,70-71,73,76,81-82,84,87-90] most commonly beta-lactam treatment, as shown in Supplementary Table 2. 5 studies, however, demonstrated antibiotic resistance, in particular penicillin, [49,62] aminoglycoside [49] and fluoroquinolone. [41,62]

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 (n=45)	↓	↓	↓	↓	(36.1 - 37.2)
Hgb (g/dl) (n=40)	↓	↓	↓	↓	(12.0 - 16.0)
Highest WBC (cells/mm3) (n=55)	↓	↓	↓	↓	(4,500 - 11,000)
ESR (mm/hr) (n=27)	↓	↓	↓	↓	(0 - 20)
CRP (mg/dl) (n=30)	↓	—	↓	↓	(<8.0)

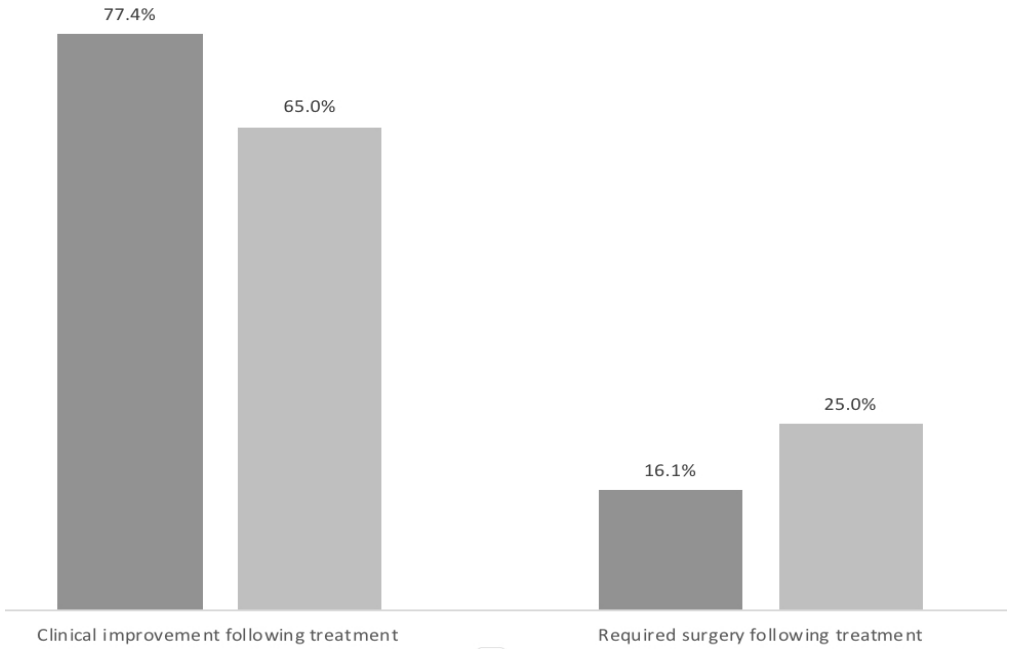

Figure 2. Comparison between antibiotic therapy 6 weeks or more (dark) to treatment duration under 6 weeks (light) (n=51)

In studies where patients survived the course of treatment, more patients showed clinical improvement after receiving 6 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 6 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. [15,23-24,27,35-37,46,52-53,58-59,61,63,65,69,81,85-86,90]

3.5.8. Outcome

23 studies reported complications following treatment. [17,20,21,27,33,35,44-45,51-52,55-56,64,69-70,74,75,79,82,83,86,88,91] This included implications to the cardiovascular (10.8%), [17,21,33,52,56,70,76,86,88,91] neurological (9.6%), [20,27,44,45,74,75,79,82] and renal (6.0%) [21,33,55,64,75] systems. However, there were no reported recurrent infections following successful antibiotic treatment. [14,15,16,21,23-27,29-39,41,43,46-52,53,55,57-63,65-69,71-73,75-76,80-82,84-85,87,89-90] Death of the patient was reported in 13 articles, [17,20,44,45,54,56,70,74,79,83,86,88,91] 46.2% of which occurred post-surgical procedure. [17,56,70,79,83,88] The clear majority of deaths occurred equal to or greater than 1 week from admission (76.9%) [20,44,54,56,70,74,79,86,88,91] in comparison to death occurring under 1 week (23.1%). [17,45,83]

3.6. Risk of Bias across Studies

Due to the nature of descriptive studies, the results being presented are liable to investigator, procedure, and selection bias.

3.7. Limitation of the Study

- Statistical analyses were not performed as there were no control/comparison group in the included studies.

4. Discussion

5 species of *Gemella* were identified in our systematic review, the most common being *Gemella morbillorum* and *haemolysans*. Both species have been members of the genus *Gemella* since 1988. [93] *Gemella spp.* are opportunistic pathogens, similar to many other commensal bacteria of the human microbiota, causing severe localized and generalized infections. [94] Less is known about *Gemella bergeri*, *sanguinis*, and *taiwanensis*. *Gemella bergeri* and *sanguinis* were assigned to the *Gemella* genus in 1998, while *Gemella taiwanensis* was identified more recently in 2014. [95] The misidentification of *Gemella spp.* can be attributed to the inaccuracy of commercial biochemical tests using phenotypic identification systems. [49] *Gemella haemolysans* and *morbillorum* have been identified as the causative pathogens in most of the previous cases caused by *Gemella spp.*, yet these findings may be biased by which test are commercially available.

We discovered that predominantly males were more prone to infective endocarditis by *Gemella spp*. The reduced susceptibility of females could be attributed to the protection from X chromosome and sex hormones, which play an important role in innate and adaptive immunity. [96] We also found that the age of the patients was between 31 and 45 years. Infective endocarditis predominantly inflicts young adults in low-income countries, [97] while the average age in high-income countries is older than 70 years. [98] The majority of studies in this systematic review originated in high income countries such as USA, UK, and Japan.

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 1 in 4 patients reported a history of congenital heart disease, such as bicuspid aortic valve, ventricular septal defect, and tetralogy of Fallot. Furthermore, 1 in 4 patients had a recent history of oral infection, while 1 in 2 patients underwent 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.

We revealed that the most common *Gemella*-susceptible antibiotics were 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 by to highly sensitive streptococci, where combination therapy with a beta-lactam antibiotic and aminoglycoside is used. [104] Finally, we revealed patients that received treatment course for at least 6 weeks or greater showed greater clinical improvement than patients who received antibiotic therapy for less than 6 weeks. This result indicates that special attention should be placed on duration of treatment for future, and we urge more research on that matter.

1 in 2 cases in the systematic review underwent either valve replacement or repair. The primary objectives of surgery are total removal of infected tissues and reconstruction of cardiac morphology. 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 complication following treatment affected the cardiovascular, neurological, and renal systems. Death occurred in 1 in 8 patients, half of which occurred post-surgical procedure, 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 6 months. [106,107]

Although the strength of the study is the extensive review of infective endocarditis with *Gemella spp*, data were limited with regards to recurrent infections

In conclusions, 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 1 in 8 patients. Therefore, our systematic review highlights the importance of considering rare pathogens, particularly in the presence of predisposing risk factors.

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Supplementary

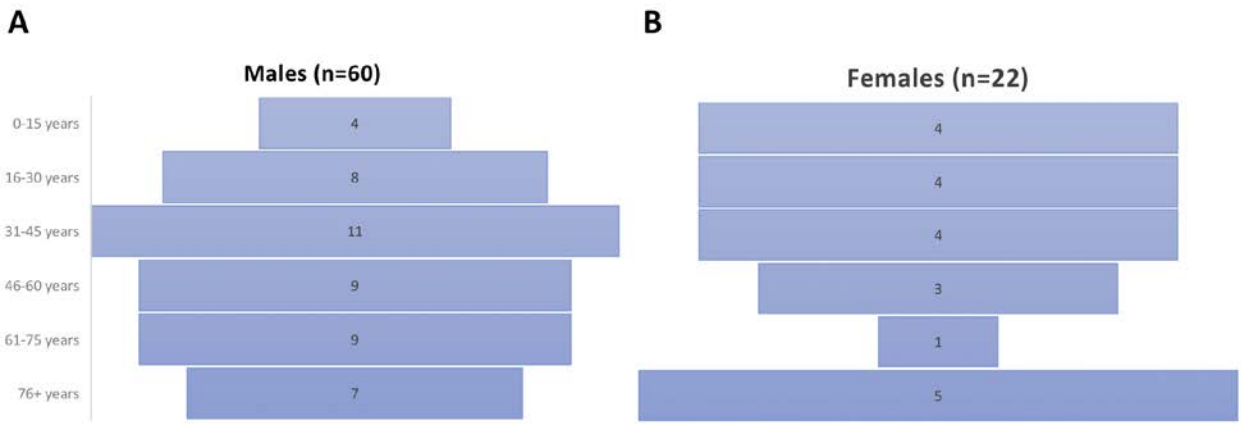

Figure S1. Distribution of males (A) and females (B) patients with infective endocarditis by *Gemella spp.* according to age

Table S1. Risk of bias across studies

Reference, publication year	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
Agrawal N et al, 2014 [14]	Missing sex	✓	✓	✓	Surgery only, no antibiotics	X	X	✓	50%
Agrawal T et al, 2019 [15]	✓	✓	✓	✓	✓	X	X	✓	75%
Akyama K et al, 2001 [16]	✓	✓	✓	✓	✓	X	X	✓	75%
Al Chekakie MO et al, 2009 [17]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Al Soub H et al, 2003 [18]	✓	X	✓	✓	✓	X	X	✓	63%
Al-Hujailan G et al, 2007 [19]	✓	✓	✓	✓	✓	X	X	✓	75%
Almaghrabi R et al, 2009 [20]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Ando A et al, 2016 [21]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Avgoustidis N et al, 2011 [22]	✓	✓	✓	✓	✓	X	X	✓	75%
Bell E et al, 1992 [23]	✓	✓	✓	✓	✓	X	X	✓	75%
Benes J et al, 2002 [24]	✓	✓	✓	✓	✓	X	X	✓	75%
Brack MJ et al, 1991 [25]	✓	X	✓	✓	✓	X	X	✓	63%
Breathnach AS et al, 1997 [26]	✓	✓	✓	✓	✓	X	X	✓	75%
Calopa M et al, 1990 [27]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Carano N et al, 2010 [28]	✓	✓	✓	✓	✓	X	X	✓	75%
Chadha S et al, 2013 [29]	✓	✓	✓	✓	✓	X	X	✓	75%
Constantinos M et al, 2015 [30]	✓	✓	✓	✓	✓	X	X	✓	75%
Czarnecki A et al, 2007 [31]	✓	✓	✓	✓	✓	X	X	✓	75%
Devuyst O et al, 1993 [32]	✓	X	✓	✓	✓	X	X	✓	63%
Elsayed S et al, 2004 [33]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Emmanouilidou G et al, 2019 [34]	✓	X	✓	✓	✓	X	X	✓	63%
Farmaki E et al, 2000 [35]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Fresard A et al, 1993 [36]	✓	✓	✓	✓	✓	X	X	✓	75%
Gimigliano F et al, 2005 [37]	✓	✓	✓	✓	✓	X	X	✓	75%
Godinho AR et al, 2013 [38]	✓	✓	✓	✓	✓	X	X	✓	75%
Gundre P et al, 2011 [39]	✓	✓	✓	✓	✓	X	X	✓	75%
Helft G et al, 1993 [40]	✓	X	✓	✓	✓	X	X	✓	63%
Hikone M et al, 2017 [41]	✓	✓	✓	✓	✓	X	X	✓	75%
Holland J et al, 1996 [42]	✓	✓	✓	✓	✓	X	X	✓	75%
Hull JE, 2010 [43]	✓	✓	✓	✓	✓	X	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	X	✓	75%
Kerr JR et al, 1994 [47]	✓	✓	✓	✓	✓	X	X	✓	75%
Khan R et al, 2004 [48]	✓	✓	✓	✓	✓	X	X	✓	75%
Kofteridis DP et al, 2006 [49]	✓	✓	✓	✓	✓	X	X	✓	75%
Kolhari VB et al, 2014 [50]	✓	✓	✓	✓	✓	X	X	✓	75%
Kumar G et al, 2017 [51]	✓	X	✓	✓	✓	✓	✓	✓	88%
La Scola B et al, 1998 [52]	Missing age	✓	✓	✓	X	X	X	✓	50%
Li D et al, 2017 [53]	✓	✓	✓	✓	✓	X	X	✓	75%
Liu D et al, 2016 [54]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Logan LK et al, 2008 [55]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Lopez-Dupla M et al, 1996 [56]	✓	X	✓	✓	✓	✓	✓	✓	88%
Maraki S et al, 2019 [57]	✓	✓	✓	✓	✓	X	X	✓	75%
Martin MJ et al, 1995 [58]	✓	X	✓	✓	✓	X	X	✓	63%
Matsis PP et al, 1994 [59]	✓	X	✓	✓	✓	X	X	✓	63%
Morea P et al, 1991 [60]	✓	✓	✓	✓	✓	X	X	✓	75%
Mosquera JD et al, 2008 [61]	✓	✓	✓	✓	✓	X	X	✓	75%
Mugunthan M et al, 2016 [62]	✓	X	✓	✓	✓	X	X	✓	63%
Murai M et al, 2006 [63]	✓	✓	✓	✓	✓	X	X	✓	75%
Nandakumar R et al, 1997 [64]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Pachirat O et al, 2015 [65]	✓	X	✓	✓	Surgery only, no antibiotics	X	X	✓	50%

Reference, publication year	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
Palma G et al, 2011 [66]	✓	✓	✓	✓	✓	X	X	✓	75%
Purcell LK et al, 2001 [67]	✓	✓	✓	✓	✓	X	X	✓	75%
Raja NS et al, 2009 [68]	✓	✓	✓	✓	✓	X	X	✓	75%
Ramchandani MS et al, 2014 [69]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Rosa RG et al, 2015 [70]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Rousseau-Gagnon M et al, 2013 [71]	✓	✓	✓	✓	✓	X	X	✓	75%
Sadaune L et al, 2019 [72]	✓	✓	✓	✓	✓	X	X	✓	75%
Samuel L et al, 1995 [73]	✓	✓	✓	✓	✓	X	X	✓	75%
Satake K et al, 2011 [74]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Seeburger J et al, 2009 [75]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Shahani L, 2014 [76]	✓	✓	✓	✓	✓	X	X	✓	75%
Shinha T, 2017 [77]	✓	✓	✓	✓	X	X	X	✓	63%
Shukla SK et al, 2002 [78]	✓	✓	✓	✓	✓	X	X	✓	75%
Stroup JS et al, 2007 [79]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Taimur S et al, 2010 [80]	✓	✓	✓	✓	✓	X	X	✓	75%
Terada H et al, 1994 [81]	✓	✓	✓	✓	✓	X	X	✓	75%
Ukimura A et al, 1998 [82]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Ukudeeva A et al, 2017 [83]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Ural S et al, 2014 [84]	✓	✓	✓	✓	✓	X	X	✓	75%
Virgilio E et al, 2014 [85]	✓	✓	✓	✓	✓	X	X	✓	75%
Winkler J et al, 2016 [86]	✓	✓	✓	✓	X	✓	✓	✓	88%
Yang CH et al, 2014 [87]	✓	✓	✓	✓	✓	X	X	✓	75%
Youssef D et al, 2019 [88]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Zaidi SJ et al, 2018 [89]	✓	✓	✓	✓	✓	X	X	✓	75%
Zakir RM et al, 2004 [90]	✓	✓	✓	✓	✓	X	X	✓	75%
Zheng M et al, 2008 [91]	✓	✓	✓	✓	✓	✓	✓	✓	100%
Zingaro L et al, 1999 [92]	✓	X	✓	✓	✓	X	X	✓	63%

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	