CLINICAL CASE REPORT

An Atlantic Canada case of disseminated *Streptococcus equi* subspecies *zooepidemicus* infection

Albert Chang BSc, MD[1], Duncan Webster MA, MD, FRCPC[2]

Streptococcus equi subspecies *zooepidemicus* infections in humans can be contracted through contact with domestic animals or unpasteurized dairy products. Although infection in humans is rare, the course can be fulminant. We describe the case of a 75-year-old immunocompetent male who developed disseminated disease with bacteremia, native aortic valve endocarditis, suppurative pericarditis with cardiac tamponade, meningitis, and bilateral endophthalmitis. Despite treatment with pericardial drain placement, intravenous ceftriaxone, and rifampin, the patient unfortunately did not survive. To date, reported cases of disseminated infection by *S. equi* subsp *zooepidemicus* are few. Furthermore, with review of the literature, this case demonstrates the broadest organ system involvement reported. Of interest, previous studies have suggested an affinity of this organism for certain organ systems and this case corroborates an emerging association of *S. equi* subsp *zooepidemicus* with endophthalmitis. In addition, this is the second Canadian case of documented human infection, with both cases being similar in clinical features, presentation, and geographical location. This case report should serve to warn clinicians about complications and sites of haematogenous seeding in the setting of disseminated *S. equi* subsp *zooepidemicus* infections.

KEY WORDS: endocarditis, endophthalmitis, group C *Streptococci*, meningitis, purulent pericarditis, *Streptococcus equi* subspecies *zooepidemicus*

Chez les humains, il est possible de contracter des infections par les sous-espèces *zooepidemicus* du *Streptococcus equi* par contact avec des animaux domestiques ou des produits laitiers non pasteurisés. L'infection est rare chez les humains, mais l'évolution peut être fulminante. Les auteurs décrivent le cas d'un homme immunocompétent de 75 ans qui a contracté une maladie disséminée incluant une bactériémie, une endocardite de la valve aortique naturelle, une péricardite purulente avec tamponnade cardiaque, une méningite et une endophtalmie bilatérale. Malgré l'installation d'un drain péricardique et un traitement à la ceftriaxone et à la rifampine par voie intraveineuse, le patient n'a malheureusement pas survécu. Jusqu'à présent, peu de cas d'infection disséminée par la sous-espèce *zooepidemicus* du *S. equi* sont déclarés. De plus, après une analyse bibliographique, ce cas s'associait à l'atteinte systémique des organes la plus vaste jamais signalée. Il est à souligner que, selon des études antérieures, cet organisme a des affinités avec certains systèmes organiques et que ce cas corrobore l'émergence d'une association entre la sous-espèce *zooepidemicus* du *S. equi* et l'endophtalmie. De plus, il s'agit du deuxième cas canadien d'infection signalé chez un humain, et les deux cas s'associaient à une présentation, à des caractéristiques cliniques et à un emplacement géographique semblables. Ce rapport de cas devrait alerter les cliniciens des complications et des sièges d'ensemencement hématogène en cas d'infection par la sous-espèce *zooepidemicus* du *S. equi* disséminé.

MOTS CLÉS : endocardite, endophtalmie, méningite, péricardite purulente, sous-espèce de *zooepidemicus* du *Streptococcus* equi, *Streptococci* du groupe C

[1]*Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada;* [2]*Department of Medicine and Division of Infectious Diseases, Saint John Regional Hospital, Saint John, New Brunswick, Canada*

Correspondence: Albert Chang, Internal Medicine, Medical Education, Dalhousie University, 1799 Robie Street, Halifax, Nova Scotia B3H 3G1 Canada. E-mail: albert.chang@dal.ca

CASE PRESENTATION

A 75-year-old male presented to a community hospital in New Brunswick, Canada with pleuritic chest pain on a background history of fatigue, night sweats, and arthralgia for the preceding 3 weeks. His past medical history included hypertension, dyslipidemia, clinical depression, and chronic kidney disease. The patient had no known drug allergies.

On physical exam there was a documented pericardial friction rub. Pertinent investigations displayed widespread ST-segment elevations on electrocardiogram (ECG) (Figure 1) along with a high sensitivity troponin level of 294 ng/L (normal $<$ 14 ng/L) and a creatinine rise to 375 umol/L (normal 80–115 umol/L) from a baseline of 120 umol/L. Additional investigations revealed a C-reactive protein level of 327 mg/L (normal $<$ 5 mg/L) and a white blood count of 17×10^9/L (normal $3.6–10.9 \times 10^9$/L). A urinalysis revealed 51–100 red blood cells per high power field. The patient was admitted with a preliminary diagnosis of pericarditis and acute kidney injury and was started on high-dose Aspirin and colchicine.

The next day on reassessment, the patient became confused and complained of loss of visual acuity in both eyes, particularly worse on the left. An urgent consult to ophthalmology revealed hemorrhagic retinitis in the right eye; the left eye was unable to be thoroughly examined due to a lack of pupillary dilation even with administration of pupillary dilators. The preliminary diagnosis was cytomegalovirus (CMV) retinitis, and intravitreal ganciclovir along with intravenous ganciclovir was started. Given these changes, the patient was transferred to a tertiary care hospital.

On transfer assessment, the patient was increasingly confused and somnolent. He was afebrile, tachycardic, maintaining a blood pressure of 130/67 and requiring 3 L of oxygen. On physical exam, the patient had a positive jolt sign along with pain on neck flexion. There were scleral hemorrhages on the left eye and his pupils were fixed and equal in size bilaterally. Additionally, the patient was tachycardiac with a grade 3/6 systolic ejection murmur heard best at the right upper sternal border, with an elevated jugular venous pulsation along with a pulsus paradoxus of 22 mmHg. His extremities were cool to the touch.

Community hospital blood cultures, taken at the patient's initial presentation, eventually displayed four out of four vials positive for beta-hemolytic group C *Streptococcus* species which was later identified as *Streptococcus equi* subspecies *zooepidemicus*. Additionally, cytomegalovirus (CMV) testing displayed IgG positive antibodies, negative IgM antibodies, and a negative CMV viral load. Varicella zoster virus (VZV) serology displayed positive IgG and negative IgM antibodies. Screening for human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV) were negative.

With the arrival of the patient's family, further questioning revealed that the patient and his wife lived on a small farm and were in contact with horses, goats, and cows. To their knowledge, there were no animals on the farm that were sick. Furthermore, the patient's family revealed that the patient had consumed unpasteurized milk and goat cheese on a regular basis from his farm animals. No other family members or friends were known to have consumed similar unpasteurized products.

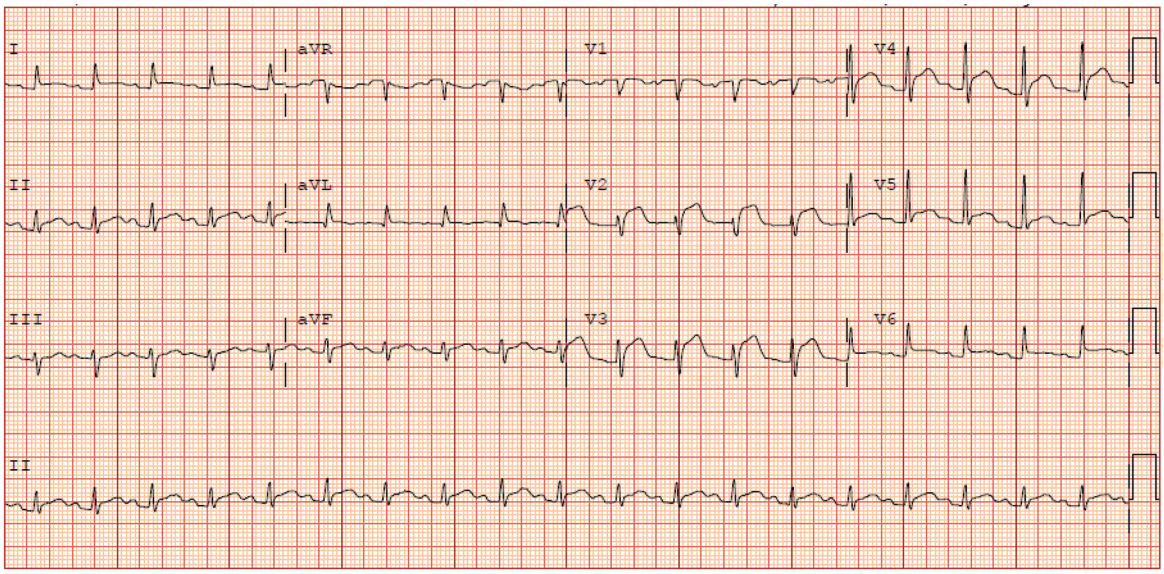

Figure 1: The patient's electrocardiogram on presentation, displaying widespread ST-elevations, PR interval depressions, and reciprocal AVR changes suggestive of pericarditis

Multiple imaging modalities were performed during this admission. An initial portable chest X-ray performed at the community hospital site displayed a globular heart (Figure 2). A transthoracic echocardiogram was performed and showed evidence of moderate pericardial effusion (Figure 3A) (Figure 3B). Additionally, there was evidence of mild aortic insufficiency with evidence of vegetation and early prolapse.

Given the presence of the pericardial effusion and potential tamponade, the patient underwent a pericardiocentesis with pericardial drain placement. With this procedure, 240 mL of purulent fluid was drained initially, followed by an additional 200 mL over the following 24 hours. Analysis of the fluid displayed a leukocyte count of 31×10^9/L (normal $0.000–0.005 \times 10^9$/L) and *S. equi* subsp *zooepidemicus* was isolated within the pericardial culture.

Given the patient's meningeal signs and altered level of consciousness, a computed tomography (CT) scan of the head was performed, which did not display any evidence of septic emboli, increased cerebral pressure, or areas of ischemia. Subsequently, a lumbar puncture was performed and the cerebrospinal fluid (CSF) was noted to be purulent. Analysis of the CSF displayed a leukocyte count of 608×10^6/L (normal $0–5 \times 10^6$/L) and glucose of 1.2 mmol/L (normal 2.2–3.9 mmol/L) and protein of 1.13 g/L (normal 0.15–0.45 g/L). On direct smear, gram-positive cocci were seen; however, the organism failed to grow on culture. CMV polymerase chain reaction (PCR) testing was negative.

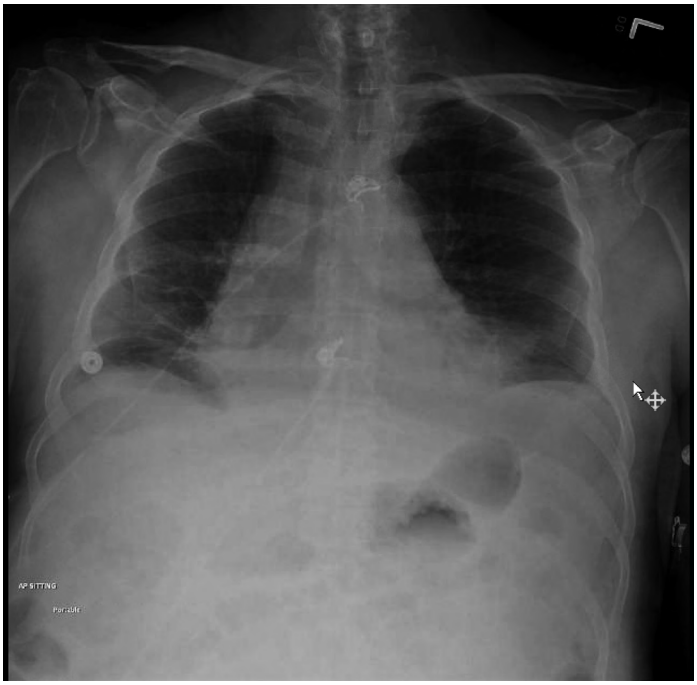

Figure 2: Portable chest X-ray displaying a globular heart suggestive of pericardial effusion

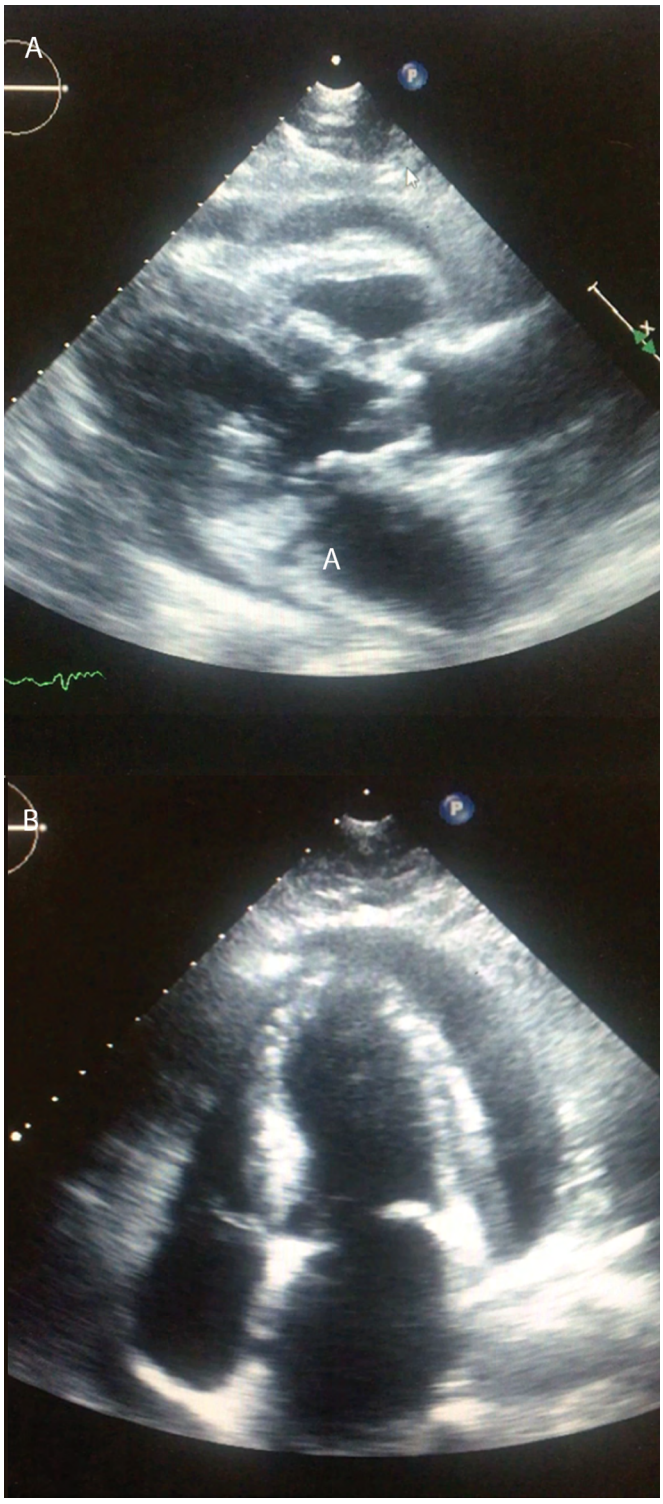

Figure 3: Parasternal long-axis (A) and apical four-chamber (B) views of a transthoracic echocardiogram, showing a moderate size pericardial effusion and vegetation of the aortic valve

It was determined that the patient had acquired a disseminated group C streptococcal infection resulting in bacteremia with meningitis, native aortic valve infective endocarditis,

and suppurative pericarditis with cardiac tamponade. The diagnosis of CMV retinitis was discordant with the general clinical picture and on ophthalmologic re-evaluation, a diagnosis of endogenous bacterial endophthalmitis was considered and the patient received intravitreal vancomycin and ceftazidime injections.

In this setting, the patient was treated with ceftriaxone 2 grams intravenous dosing every 12 hours in conjunction with oral rifampin 600 mg daily. Susceptibility testing of the *S. zooepidemicus* revealed susceptibility to penicillins, beta-lactams, and vancomycin. A cardiothoracic surgical consult was requested given the findings of aortic valve vegetation. After the pericardial drain was placed the patient was transferred to the cardiac care unit for intensive monitoring. The patient's bacteremia cleared within 24 hours. Serial transthoracic echocardiogram was performed, and unfortunately the size of the aortic valve vegetation increased and severe aortic regurgitation developed with a possible partially dehisced aortic valve leaflet.

Unfortunately, the patient's clinical status declined suddenly on post-admission day 3 as he went into cardiac arrest with an underlying rhythm of ventricular fibrillation and pulseless electrical activity. Attempts at cardiopulmonary resuscitation and defibrillation were unsuccessful.

DISCUSSION

Group C streptococci include beta-hemolytic organisms that form large colonies (≥ 0.5 mm) on sheep blood agar. They react with Lancefield group C typing serum. Within this group, *Streptococcus dysgalactiae* subspecies *equismillis* is the most common to colonize and cause human infection. While humans are the primary host of *S. dysgalactiae* subsp *equismillis*, other group C *Streptococcus* organisms such as *S. equi* subspecies *equi* and *S. equi* subsp *zooepidemicus* utilize animals as primary hosts (1). For instance, *S. equi* subsp *equi* are found to cause suppurative lymphadenitis (strangles) in horses (2). Interestingly, human infections with *S. equi* subsp *equi* or subsp *zooepidemicus* can also occur.

S. equi subsp *zooepidemicus* can be found to colonize various animal hosts including horses, cows, pigs, sheep, and dogs (1). Additionally, this organism is known to cause upper respiratory tract infections in horses, and mastitis in cows and mares (1). Although human infection with this organism is rare, *S. equi* subsp *zooepidemicus* can cause invasive infections in humans through zoonotic transmission, either through contact between domestic animals and humans or ingestion of unpasteurized animal products.

In the literature, *S. equi* subsp *zooepidemicus* causing human infections has presented clinically as bacteremia, pneumonia, meningitis, and infective endocarditis (3). A handful of cases have also reported *S. equi* subsp *zooepidemicus* causing suppurative pericarditis (1,4), endophthalmitis (5), myositis (6) and osteomyelitis (7). On closer analysis, *S. equi* subsp *zooepidemicus* shares many characteristics with *Streptococcus pyogenes*, which is known to be an invasive and virulent organism. For instance, on DNA sequencing, *S. equi* subsp *zooepidemicus* shares greater than 80% DNA sequence homology with *S. pyogenes*. Furthermore, *S. equi* subsp *zooepidemicus* also displays virulence factors similar to *S. pyogenes*, such as M-like proteins, superantigens, and hyaluronic acid capsules (2).

There have been multiple *S. equi* subsp *zooepidemicus* outbreaks documented. The first recorded outbreak was in 1988 in West Yorkshire, England, thought to be caused by ingestion of unpasteurized milk from a cow inflicted with mastitis. Seven of 11 cases died and clinical features of these cases were consistent with sepsis, meningitis, and infective endocarditis (8). In 2003, there were outbreaks in both Finland (9) and Spain (10). A contaminated goat cheese farm and inadequately pasteurized cheese from a factory were implicated, respectively. A total of 22 patients from these two outbreaks displayed a variety of clinical features ranging from sepsis to mycotic aortic aneurysms to septic arthritis and meningitis.

In our case report, the patient is suspected to have contracted the *S. equi* subsp *zooepidemicus* infection from physical contact with an infected or colonized animal, or through consumption of contaminated unpasteurized products. Unlike other case reports of human *S. equi* subsp *zooepidemicus* infections, our patient was not immunosuppressed and did not suffer from multiple comorbidities. We speculate that the extent and severity of his infection reflects the underlying invasiveness of the organism and a prolonged delay to treatment. Our patient presented with symptoms suggestive of ongoing bacteremia for weeks leading to a disseminated infection and multiple sequelae including endocarditis, suppurative pericarditis, meningitis, and endophthalmitis. We surmise that the patient died as a result of cardiac arrhythmia resulting from severe acute aortic regurgitation as a complication of infective endocarditis.

In terms of management, the patient's *S. equi* subsp *zooepidemicus* bacteremia cleared within 24 hours of starting intravenous ceftriaxone. His purulent pericardial effusion had been adequately drained. The Infectious Disease Society of America (IDSA) 2015 guidelines for management of infective endocarditis suggest the use of gentamicin for synergy with penicillin or ceftriaxone treatment of group B, C, or G streptococci (Class 2B Level of Evidence C) (11). Given the patient's kidney dysfunction, rifampin was selected as a synergistic agent. While there is a paucity of literature supporting rifampin as a synergistic agent in the treatment of group C streptococcal infective endocarditis, it has been used

Table 1: Previous reports of *Streptococcus equi* subsp *zooepidemicus* endophthalmitis cases in the literature

Author	Year published	Location	Suspected source	Associated infections	Outcome
Mattei et al. (13)	1995	France	Horse	Meningitis	Blindness
Poulin and Boivin (12)	2009	Quebec City, Canada	Horse	Meningitis, infective endocarditis	Blindness
Madžar et al. (5)	2015	Germany	Horse	Meningitis	Left eye visual deficit

in cases where gentamicin is not an option (12). Additionally, the IDSA guidelines suggest there is a "clinical impression" that early surgical intervention may have improved overall survival rates in cases of beta-hemolytic streptococcal infective endocarditis as compared with patients treated in the past. In this case, cardiac surgery was considered though not performed, as the patient decompensated quickly.

Overall, case reports of human *S. equi* subsp *zooepidemicus* infections are rare. On review of the literature, there are several notable aspects of this case. For one, this case appears to demonstrate the broadest organ system involvement among reported cases of disseminated *S. equi* subsp *zooepidemicus* infection to date. Furthermore, it is the fourth reported case of *S. equi* subsp *zooepidemicus* causing endophthalmitis (5,12,13) (Table 1). It has been suggested that endophthalmitis infections may occur more frequently in cases of meningitis caused by *S. equi* subsp *zooepidemicus* as compared to meningitis caused by other organisms (5).

Furthermore, this is the second reported Canadian case of *S. equi* subsp *zooepidemicus* human infection in the literature. The other Canadian case was published in 2009 and displayed strikingly similarities with the presented in this case study. Poulin and Boivin (12) described a 59-year-old female presenting to hospital in Quebec City with generalized weakness over the span of 3 weeks, followed by acute bilateral visual acuity loss. She was diagnosed with *S. equi* subsp *zooepidemicus* bacteremia, endophthalmitis, meningitis and mitral valve infective endocarditis. Of note, she lived on a property that included a stable and multiple horses. She was treated with intravenous ceftriaxone and oral rifampin followed by a mitral valve replacement, triple coronary artery bypass graft, and atrial-septal defect closure. Concomitantly, she was treated with intravitreal injections of vancomycin, ceftriaxone, and dexamethasone, and underwent bilateral vitrectomy. The patient recovered but was left with permanent total blindness on hospital discharge.

Pelkonen et al attempted to study the epidemiology of human *S. equi* subsp *zooepidemicus* infection with three cases in Finland. The authors compared *S. equi* subsp *zooepidemicus* isolates from the human cases with isolates gathered from potential horse contacts. Utilizing molecular characterization of isolates, the authors concluded that two patients had identical isolates with the same isolate obtained in a horse, thus corroborating a zoonotic transmission (2). We also attempted to pursue contact tracing by having the patient's farm animals tested. Regrettably, we could no longer contact the patient's family and this was not performed.

In short, this case report should serve to warn clinicians regarding the complications and sites of haematogenous seeding in the setting of disseminated *S. equi* subsp *zooepidemicus* infections. Furthermore, this case highlights the importance of identifying the subspecies of beta-hemolytic group C streptococcal infections in order to identify possible modes of transmission and potential clinical sequelae.

ACKNOWLEDGEMENTS: Informed consent was obtained from the patient's wife and we would like to thank her and the patient's family for allowing us to publish this case study.

COMPETING INTERESTS: The authors have nothing to disclose.

CONTRIBUTORS: Conceptualization, AC, DW; Methodology, AC, DW; Data Curation, AC, DW; Writing – Original Draft, AC; Writing – Review & Editing, DW; Supervision: DW.

ETHICS APPROVAL: N/A

INFORMED CONSENT: Informed consent to publish this case study was obtained from the patient's wife.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL: N/A

ANIMAL STUDIES: N/A

FUNDING: No funding was received for this work.

PEER REVIEW: This article has been peer reviewed.

REFERENCES

1. Behnes M, Mashayekhi K, Geginat G, Borggrefe M. Horse bacterium causes human pericardial and pleural effusion. Infection. 2010;38(6):501–4. https://doi.org/10.1007/s15010-010-0055-7. Medline:20941523
2. Pelkonen S, Lindahl SB, Suomala P, et al. Transmission of Streptococcus equi subspecies zooepidemicus infection from horses to humans. Emerg Infect Dis. 2013;19(7):1041–8. https://doi.org/10.3201/eid1907.121365. Medline:23777752
3. Rajasekhar A, Clancy CJ. Meningitis due to group C Streptococcus: a case report and review of the literature. Scand J Infect Dis. 2010;42(8):571–8. https://doi.org/10.3109/00365541003754428. Medline:20632899
4. Held J, Schmitz R, van der Linden M, Nührenberg T, Häcker G, Neumann F-J. Purulent pericarditis and pneumonia caused by Streptococcus equi subsp. zooepidemicus. J Med Microbiol. 2014;63(2):313–6. https://doi.org/10.1099/jmm.0.066290-0. Medline:24243287
5. Madžar D, Hagge M, Möller S, et al. Endogenous endophthalmitis complicating Streptococcus equi subspecies zooepidemicus meningitis: a case report. BMC Res Notes. 2015;8:184. https://doi.org/10.1186/s13104-015-1133-9. Medline:25940309
6. Kittang BR, Pettersen VK, Oppegaard O, et al. Zoonotic necrotizing myositis caused by Streptococcus equi subsp. zooepidemicus in a farmer. BMC Infect Dis. 2017;17(1):147. https://doi.org/10.1186/s12879-017-2262-7. Medline:28201995
7. Bhatia R, Bhanot N. Spondylodiskitis secondary to Streptococcus equi subspecies zooepidemicus. Am J Med Sci. 2012;343(1):94–7. https://doi.org/10.1097/MAJ.0b013e31822cf8a8. Medline:21825960
8. Edwards AT, Roulson M, Ironside MJ. A milk-borne outbreak of serious infection due to Streptococcus zooepidemicus (Lancefield Group C). Epidemiol Infect. 1988;101(1):43–51. https://doi.org/10.1017/S0950268800029204. Medline:3402548
9. Kuusi M, Lahti E, Virolainen A, et al. An outbreak of Streptococcus equi subspecies zooepidemicus associated with consumption of fresh goat cheese. BMC Infect Dis. 2006;6:36. https://doi.org/10.1186/1471-2334-6-36. Medline:16504158
10. Bordes-Benítez A, Sánchez-Oñoro M, Suárez-Bordón P, et al. Outbreak of Streptococcus equi subsp. zooepidemicus infections on the island of Gran Canaria associated with the consumption of inadequately pasteurized cheese. Eur J Clin Microbiol Infect Dis. 2006;25(4):242–6. https://doi.org/10.1007/s10096-006-0119-x. Medline:16550347
11. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;132(15):1435–86. Medline:26373316. Erratum in: Circulation. 2015;132(17):e215. Corrected at: https://www.ncbi.nlm.nih.gov/pubmed/27550972.
12. Poulin M-F, Boivin G. A case of disseminated infection caused by Streptococcus equi subspecies zooepidemicus. Can J Infect Dis Med Microbiol. 2009;20(2):59–61. https://doi.org/10.1155/2009/538967. Medline:20514161
13. Mattei P, Beguinot I, Malet T, et al. [Meningitis, septicemia and endophthalmitis caused by Streptococcus equi subspecies zooepidemicus]. Presse Med. 1995;24(23):1089. French. Medline:7567814