



Case report

Arcanobacterium haemolyticum bacteremia presenting as severe sepsis: A case report and review of the literature

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ABSTRACT

Objective: to describe a case of severe sepsis and complicated bacteremia caused by *Arcanobacterium haemolyticum* and review similar cases in the literature.

Case summary: A 26-year-old gentleman with a history of epilepsy presented with symptoms of sore throat, productive cough, periumbilical abdominal pain, watery diarrhea, nausea and vomiting, subjective fevers along with progressive jaundice for seven days. The patient had acute fulminant liver failure, septic shock, and Multi-organ failure. He required vasopressors, underwent intubation, and had grown *Arcanobacterium haemolyticum* in the blood and Bronchoalveolar lavage samples. He developed a peritonsillar abscess and cavitary pneumonia and required chest tube drainage followed by thoracotomy for hemothorax. The patient improved on Ampicillin-Sulbactam treatment and was treated with a total antibiotic duration of 6 weeks. He fully improved on post-discharge follow-up.

Discussion: *Arcanobacterium haemolyticum* is a Gram-positive (sometimes Gram variable), catalase-negative facultatively anaerobic, non-motile, non-spore-forming, and variably β -hemolytic and is known to be a cause of pharyngitis and skin and soft tissue infections. Rarely *A. Haemolyticum* can be associated with severe systemic infections such as infective endocarditis, systemic abscesses, osteomyelitis, and septicemia. In previous literature reviews, the source of *A. haemolyticum* depended on the host, and pharyngeal and upper respiratory sources were likely to be associated with immunocompetent hosts.

Conclusion: *A. haemolyticum* should be included in the differential diagnosis of bacterial pharyngitis complicated by severe systemic illness. Penicillins are the most commonly used antibiotics for treating *A. haemolyticum* bacteremia, and macrolides can be used for Penicillin's treatment failure.

Introduction

Arcanobacterium haemolyticum is a pathogen known to cause pharyngitis in young adults [1,2]. The pathogenicity of this organism varies in the literature. Rarely, *A. Haemolyticum* can be associated with severe systemic infections as in infective endocarditis [3], systemic abscesses [4–7], osteomyelitis [8,9], and septicemia [9,10]. We describe a case of a young patient who was transferred to our hospital with severe sepsis and complicated bacteremia caused by *Arcanobacterium haemolyticum*. We also did a Literature review of similar cases.

Case report

A 26-year-old gentleman with a history of epilepsy on Levetiracetam and a remote history of a gunshot wound to his abdomen was transferred to our hospital for acute liver failure after a two-day stay at an outside facility. The patient noted sore throat, productive cough, periumbilical abdominal pain, watery diarrhea, nausea, and vomiting, subjective fevers along with progressive jaundice for seven days before presentation at the outside hospital. The patient indicated that he took acetaminophen (three tablets of acetaminophen 500 mg at different times) for his

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Table 1
Laboratory values on presentation.

Parameter	Ref range	Value
WBC	Ref Range: 3.60–9.50 K/uL	39.9 H
RBC	Ref Range: 4.50–5.70 M/uL	3.42 L
Hemoglobin	Ref Range: 13.0–17.0 g/dL	10.5 L
Hematocrit	Ref Range: 40.0–50.0 %	29.6 L
MCV	Ref Range: 80.0–100.0 fL	87
MCH	Ref Range: 26.0–33.0 pg	31
MCHC	Ref Range: 32.0–36.0 g/dL	36
RDW	Ref Range: 12.0–15.0 %	13.1
Platelet	Ref Range: 150–450 K/uL	75 L
Myelocyte	Ref Range: < 2.0 %	2 H
Metamyelocytes	Units: %	2 H
Bands	Ref Range: 5.0–11.0 %	11 H
Neutrophils	Ref Range: 35.0–65.0 %	70
Lymphocytes	Ref Range: 23.0–50.0 %	6 L
Monocytes	Ref Range: 4.6–12.0 %	9 H
Eosinophils	Ref Range: 0.5–6.5 %	0 L
Basophils	Ref Range: 0.1–1.1 %	2 H
Sodium	Ref Range: 135–145 mmol/L	126 L
Potassium	Ref Range: 3.5–5.1 mmol/L	3.4 L
Chloride	Ref Range: 98–107 mmol/L	81 L
CO2	Ref Range: 22–32 mmol/L	13.3 L
BUN	Ref Range: 6–20 mg/dL	138 H
Creatinine	Ref Range: 0.6–1.3 mg/dL	6.10 H
eGFR	Units: mL/min/1.73 square meters	14
Calcium	Ref Range: 8.6–10.2 mg/dL	9.7
Phosphorus	Ref Range: 2.5–4.5 mg/dL	11
Magnesium	Ref Range: 1.6–2.6 mg/dL	3.4
Glucose	Ref Range: 70–110 mg/dL	105
LACTATE	Ref Range: 0.5–2.2 mmol/L	3.3 H
Procalcitonin	Ref Range: 0.00–0.10 ng/mL	505.81 H
Alkaline Phosphatase	Ref Range: 32–91 IU/L	543 H
AST	Ref Range: 15–41 IU/L	121 H
ALT	Ref Range: 4–45 IU/L	62 H
GGT	Ref Range: 7–50 IU/L	46
Bilirubin, Total	Ref Range: 0.2–1.2 mg/dL	71.0 H
Bilirubin, Direct	Ref Range: ≤ 0.5 mg/dL	> 15.0 H
Albumin	Ref range: 3.5–5.2 g/dL	3.2 L

WBC: White Blood Cells, RBC: Red Blood Cells, MCV: Mean Corpuscular Volume, RDW: Red Blood Cell Distribution Width, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration, BUN: Blood Urea Nitrogen, CO2: Carbon Dioxide, eGFR: Estimated Glomerular Filtration Rate, AST: Aspartate Aminotransferase And ALT: Alanine Aminotransferase, GGT: Gamma-Glutamyl Transferase, Glutamyl Transferase, H: High, L: Low.

abdominal pain. He was incarcerated twelve days before admission for one week at a local county jail. His illness began three days after his release. His COVID-19 test was negative while in jail. The patient history was negative for new medications, ingestions, exposures, IV drug use, smoking, sick contacts, travel, animals, water or hiking activity, tuberculosis and hepatitis. The patient reported using marijuana daily and drank half a pint of brandy once weekly. He reported being sexually active with one female partner with frequent condom use. The patient lived in Arkansas, where he had grown up, with no recent travel.

The patient had a blood pressure of 140/74 mmHg on arrival to the

outside hospital with a heart rate of 106 BPM, respiratory rate of 22 breaths/min, and oxygen saturation of 98 % on room air. Physical examination was remarkable for scleral icterus. The patient had a crusted lesion on his right lateral oral commissure. His left eye showed a small subconjunctival hemorrhage. He had no evidence of oropharyngeal exudate. Chest examination showed regular rate and rhythm, no murmurs, rubs, or gallops, and lungs that were clear to auscultation bilaterally with distant breath sounds. An abdominal exam revealed mild diffuse abdominal tenderness, but he did not demonstrate any stigmata of chronic liver disease.

Laboratory workup showed leukocytosis, anemia, hyponatremia, cholestatic liver injury, acute kidney injury (Table 1), and a negative respiratory pathogen panel. Arterial blood gas revealed primary anion gap metabolic acidosis. Chest X-ray demonstrated patchy interstitial and alveolar opacities throughout the right and left lung that was concerning for multifocal pneumonia. Computed tomography (CT) scan of the chest, abdomen, and pelvis showed bilateral lung parenchymal ground glass consolidative lesions with central cavitation; no abnormalities were noted in the abdomen (Fig. 1). A panel of tests including an autoimmune workup (C3, C4, ANCA), blood cultures, *Histoplasma* and *Blastomyces* urine antigens, *Cryptococcus* antigen, 1,3 Beta D-Glucan, TB-PCR from sputum samples, *Leptospira* PCR, and Lyme serologies were sent. Serologies for *Francisella tularensis*, *Ehrlichia chaffeensis* (in addition to PCR) and *Rickettsia rickettsii* were also sent. Transthoracic echocardiography showed reduced left ventricular function with global hypokinesia and no valve lesions, although the views were limited.

The patient received vancomycin, cefepime, and metronidazole and due to fulminant liver failure, was transferred to our tertiary care facility as noted. His course was complicated by hypothermia, shock, and encephalopathy. He also developed acute renal failure requiring continuous renal replacement therapy and respiratory failure requiring mechanical ventilation.

Bronchoscopy with bronchoalveolar lavage (BAL) was performed, which revealed a neutrophilic predominance with negative GMS and AFB stains and negative cytology. The patient's right lip exudate was swabbed and returned positive for HSV 1 through NAAT testing. Complete etiological workup for other causes of encephalopathy (Brain CT scan), acute liver injury workup including Anti-LKM, Mitochondrial Antibody IgG, Smooth muscle Antibody IgG, A1AT levels, Salicylates, acetaminophen levels, ethanol levels, ceruloplasmin, HIV, Hepatitis Screen, EBV PCR, CMV PCR, and urine drug screen were sent and were all negative. Ammonia level was elevated. Hemophagocytic lymphohistiocytosis (patient had high ferritin reaching > 40,000 ng/mL) workup was ordered and was negative. Amylase and Lipase were also negative.

Thirteen hours after collection of blood cultures, one out of two blood cultures sets was positive with a Gram stain showing gram-positive cocci and gram-positive bacilli. At 23 h after collection, four out of four blood culture bottles were positive. The Gram-positive Bacilli were elongated and tapered on one end. BAL cultures were subsequently positive as well. Using Matrix-assisted laser desorption ionization-time

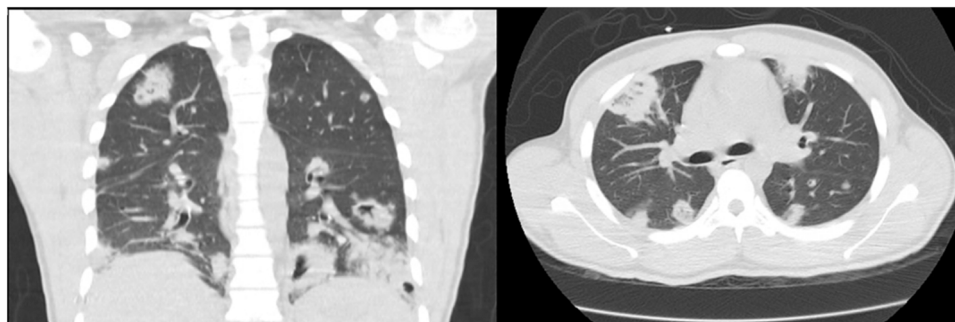


Fig. 1. CT chest showing multifocal cavitary lung lesions.

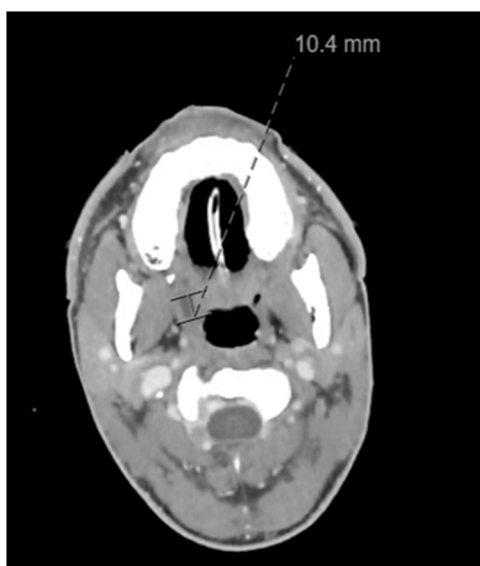


Fig. 2. CT neck with contrast showing a 1.4 cm right palatine tonsillar abscess.

of flight Mass spectrometry (MALDI-TOF) for identification, *Arcanobacterium haemolyticum* was identified in both Blood and BAL cultures. The patient's antimicrobial therapy was narrowed from Vancomycin and Cefepime to Ampicillin-Sulbactam. Due to concern for an oropharyngeal source of *Arcanobacterium* septicemia, a CT scan of the neck was obtained, which showed a 1.4 cm right palatine tonsillar abscess (Fig. 2), prominence of nasopharyngeal adenoids, cervical lymphadenopathy in the bilateral anterior and posterior triangles, mediastinal fat stranding, and sinusitis; furthermore, the visualized portion of the lungs demonstrated the development of multiple abscesses and loculated pleural effusions. The internal jugular veins did not show a thrombus or occlusion. Otolaryngology assessed the patient and deemed the abscess too small for drainage. A dedicated CT chest was performed, which showed bilateral pleural fluid collections concerning for empyema, requiring multiple pigtail catheters to be placed. Chest tubes returned bloody purulent drainage, and eventually, the patient required surgical thoracotomy with evacuation of the hemothorax and pulmonary decortication. Other infectious and autoimmune workup remained negative. He had a Trans-esophageal echocardiogram which didn't show any oscillating echo-densities. There was, however, mild tricuspid, mitral and pulmonary valve regurgitation. There was mention of a tiny, delayed right to left shunt with the Bubble study that was suggestive of a pulmonary AVM. A percutaneous tracheostomy was performed, and the patient slowly improved. The previously mentioned infectious workup was all negative.

The patient's multi-organ failure and septicemia were determined to be due to *Arcanobacterium haemolyticum* infection likely originating from initial pharyngitis. This pathogen was repeatedly isolated from cultures from various body culture sites while the other infectious workup remained negative. Susceptibilities were obtained from the outside hospital, and the organism was penicillin-sensitive. The patient completed an antibiotics therapy course for six weeks with Ampicillin-Sulbactam covering five weeks of that duration. This was associated with clinical improvement. Chest and tracheostomy tubes were removed, and he no longer required renal replacement therapy. He was discharged home after an inpatient stay of over a month. The patient had recovered fully at his two-month post-discharge follow-up.

Discussion

Due to chemical and numerical phenetic data, *Arcanobacterium* was re-classified as a separate genus by itself by Collins in 1982 and was no

longer a species of the genus *Corynebacterium* [11]. The pathogen was previously known as *Corynebacterium haemolyticum*. It was first isolated in 1946 by MacLean et al. from American soldiers and Natives living on certain west and south pacific islands with pharyngeal and skin infections [12].

The name *Arcanobacterium* was coined by Collins et al. and translates to "secretive" (*Arcano-*) bacteria [11]. The organism is Gram-positive (sometimes Gram variable), catalase-negative, facultatively anaerobic, non-motile, non-spore-forming, and variably β -hemolytic, with hemolysis being best observed on human blood agar [12]. Growth and hemolysis are enhanced with the addition of CO₂ [13,14]. The organism grows on most blood-based media, and colonies are usually small, with a characteristic pitting below the colony [14,15].

The patient, in our case, did not have a clear cause of his illness at the beginning. His age is typical for *Arcanobacterium* pharyngitis [2,16,17]. About 51.8 % of patients with *A. Haemolyticum* pharyngitis have a rash [12]. There was no reported rash in our case [2]. Several case reports have reported the presentation of severe sepsis and/or complicated bacteremia with *Arcanobacterium haemolyticum* in the literature (see Table 2). Many of these cases are associated with Lemierre's syndrome. While internal jugular thrombophlebitis was not seen on neck imaging, the patient likely had *Arcanobacterium* pharyngitis complicated by a peritonsillar abscess, which resulted in bacteremia, cavitory pneumonia with empyema, multi-organ failure, and septic shock. We maintained a clinical concern for infective endocarditis due to multiple indirect signs of hematogenous bacterial spread: growth of *Arcanobacterium* in blood and respiratory cultures, the presence of a peritonsillar abscess, and multifocal cavitory lung lesions consistent with septic emboli.

The risk factors for having *Arcanobacterium* pharyngitis in this patient were unclear to us; however, in a review of literature by Therriault et al. in 2008, an attempt to identify two sets of hosts for *Arcanobacterium* infection was made with one set of young immunocompetent adults and adolescents with no risk factors who had Upper respiratory tract infections and the other set being middle-old aged adults with immunocompromising condition (diabetes, chronic steroid use) who had skin and soft tissue infections [17]. Our patient fits the former category. The last set of patients usually has polymicrobial infections. Classification of Biotypes of *Arcanobacterium* based on Colony morphology, beta hemolysis, β -glucuronidase activity, and sucrose/Trehalose fermentation was sought in a study of biotypes, and the author made the distinction between smooth (84 % from wounds) and rough biotype (91 % from the respiratory tract) [36]. Our patient had concurrent HSV stomatitis with possible pharyngitis. This finding could represent a facilitation mechanism for *Arcanobacterium* but could also be coincidental. Our English language literature review did not demonstrate any reported association between HSV stomatitis/pharyngitis and *A. haemolyticum* invasive infection; however, reports of EBV infections preceding *Arcanobacterium haemolyticum* bacteremia do exist. The patient in our case had detectable EBV by PCR but with low levels (was 51 IU/mL, and the range was 49 IU/mL to 1.69E + 08 IU/mL). No serology for EBV or Monospot test was sent.

A recent systematic review conducted by Sayad et al. in 2020 examined *Arcanobacterium* Pharyngitis manifestations and complications among studies found in the literature. The authors included 17 studies and had a total of 191 patients [2]. About 51.8 % of patients with *A. haemolyticum* pharyngitis had a rash. Data on complications were available in seventeen patients, and blood culture(s) were positive in five out of six patients with reported blood culture results. These patients had complications like meningitis, lung cavitation, Lemierre's syndrome, and pneumonia. Patients with negative or no blood cultures reported having only peritonsillar abscess (one case with airway obstruction), or no complications. This indicates the possibility that complications arise when bacteremia develops.

Our case represents an *Arcanobacterium haemolyticum* complicated bacteremia presenting with severe sepsis. We have identified 20 cases in the literature representing severe sepsis and/or complicated bacteremia

Table 2

Cases of *Arcanobacterium haemolyticum* bacteremia with severe sepsis and/or complicated bacteremia with a pharyngeal/upper respiratory or an unknown source: Host, primary source of infection, symptoms, complications.

Author/year	Host/risk factors	Primary infection	Symptoms prior to presentation	Symptoms duration prior to presentation (Days)	Positive blood cultures for <i>A. haemolyticum</i> /other organisms/other cultures.	Complications
Verona, J et al. 2020 [18]	21-year-old immunocompetent male going through a strong emotional shock.	Pharyngitis	Symptoms of pharyngitis, Rash, fever.	More than 7 days	Yes	Anemia, Thrombocytopenia, Cavitory pneumonia, Multiple subpleural abscesses, and left gluteal muscle abscess (following dipyrone injection in the context of thrombocytopenia)
Poplin, V et al. 2018 [19]	20-year-old healthy African American male college football player with infectious mononucleosis and prednisone treatment for ten days	Pharyngitis, sinusitis	Fevers, chills, malaise, anorexia, insomnia, headaches, green rhinorrhea, severe anorexia with swollen and tender posterior cervical lymph nodes.	21	Yes/gram stain of abscess culture was characteristic of <i>A. haemolyticum</i> .	Brain abscesses and Subdural Empyema, Transaminitis, Hyperbilirubinemia
Cortés-Penfield, N et al. (2017) [20]	16-year-old girl presented 48 h after a physical assault that involved head trauma with loss of consciousness	pharyngitis and sinusitis	Cough, congestion, and sore throat (5 days) and nausea, vomiting and altered mentation (2 days PTA)	5	Yes/polymicrobial sinus cultures	Meningitis, altered mental status, cerebritis, and brain abscess.
Zhang, W. han et al. 2013 [21]	Man	Pharyngitis and left tonsillitis	sore throat and enlarged left tonsil with exudate.		yes	Lemierre's syndrome, elevated AST.
Ji, Y.Q et al. 2013 [22]	54-year-old male smoker	Pharyngitis and left peritonsillar abscess	fever and sore throat	10	yes	thrombocytopenia, transaminitis, hyperbilirubinemia, cavitory pneumonia, Lemierre's syndrome
Lee, K. J. et al. 2012 [23]	37-year-old previously healthy male	Pharyngitis and peritonsillar abscess	sore throat, fever, back pain, weakness, dyspnea, and cough The patient had a maculopapular rash during his admission	3	yes	Thrombocytopenia, transaminitis, hyperbilirubinemia, hypotension, elevated LDH, Cavitory pneumonia, exudative pleural effusion, Lemierre's syndrome
Edelman, K. et al. 2012 [24]	19-year-old Hispanic female	Pharyngitis and right peritonsillar abscess	anorexia, myalgias, odynophagia, and sore throat	5	yes	Acute hypoxic respiratory failure requiring intubation, Bilateral pulmonary septic emboli, Lemierre's syndrome, large tension pneumothorax, complicated parapneumonic effusion.
Wong, V et al. 2011 [25]	21-year-old Caucasian female with known congenital heart disease with previous surgical repair	Unrecognized	Fever, lethargy, and a swollen, painful left calf that turned out to be a hematoma.	5	yes	Multiple right-sided frontal abscesses, endocarditis
Lundblom, K. et al. 2010 [26]	19-year-old previously healthy man	Pharyngitis	maculopapular rash, sore throat, non-productive cough, fever, vomiting and prostration	5	Yes/ blood cultures also positive for <i>F. necrophorum</i>	Lung cavitory lesions bilaterally, Lemierre's syndrome, Thrombocytopenia, hyperbilirubinemia, elevated ALP, hypotension, coagulopathy, acute renal failure.
Fernández-Suárez, A. et al. 2009 [27]	23-year-old male from Spain, weighing 84.5 kg and is a sheep- herder	Pharyngitis and tonsillitis	Asthenia, anorexia, weight loss, arthromyalgia, nocturnal fever, and severe sore throat which worsened on swallowing.	6	yes	Thrombocytopenia, hepatomegaly, lemierre syndrome, pneumonia, acute liver failure, acute renal failure
Therriault, B. L. et al. 2008 [17]	18-year-old male with a medical history significant for mild asthma and positive history of having squirrels in his apartment. Recent experiments with hallucinogenic mushrooms	Pneumonia	productive cough, myalgia, nausea, vomiting (history of bloody emesis), diarrhea, fevers, and hallucination, right shoulder and left hip pain in addition to findings of lymphadenopathy.	7	Yes/surface and surgical swabs and bronchial washings cultures were also positive for <i>A. haemolyticum</i>	Cavitory pneumonia. Left lower extremity abscess, thrombocytopenia hyperbilirubinemia, elevated ALP, hypotension.
Van Der Eerden M.M et al. 2006 [28]	20-year-old woman	Pharyngitis	symptoms of pharyngitis and rash	Not available	yes	Cavitory pneumonia
	21-year-old, previously healthy Chinese male	pharyngitis		3		Cavitory pneumonia, right-sided pleural effusion,

(continued on next page)

Table 2 (continued)

Author/year	Host/risk factors	Primary infection	Symptoms prior to presentation	Symptoms duration prior to presentation (Days)	Positive blood cultures for <i>A. haemolyticum</i> /other organisms/other cultures.	Complications
Younus, F. et al. 2002 [29]			Sore throat, maculopapular rash, fever, chills, sweating and diarrhea.		Yes/ blood cultures are also positive for <i>F. necrophorum</i>	Lemierre syndrome, thrombocytopenia, and hypotension.
Skov, R. L. et al. 1997 case 2 [30]	15-year-old previously healthy boy	Pharyngitis and tonsillitis	Symptoms of pharyngitis, rash, Catarrhalia, fever, and prostration	7	Yes/ blood cultures were also positive for <i>F. necrophorum</i> /positive <i>A. haemolyticum</i> from the vestibulum nasi	Meningitis, abducent nerve palsy
Minarik, T. et al. 1997 case 1 [31]	58-year-old male with non-Hodgkin's lymphoma presenting four days after chemotherapy with neutropenia	Unrecognized	Fever, headache, dizziness, disorientation, right-sided focal neurological symptoms, and maculous exanthem.	Not available	Yes/positive CSF culture for <i>A. haemolyticum</i>	Meningitis, exudative pericarditis
Ford, J et al. (1995) [32]	16-year-old boy with no risk factors. The patient presented despite Ampicillin-sulbactam therapy.	Sinusitis	Symptoms of sinusitis, vomiting, diarrhea, fevers, and left upper eyelid erythema and edema	7	Yes/blood cultures also positive for <i>F. necrophorum</i> /positive sinus culture for <i>A. haemolyticum</i>	left orbital cellulitis; subperiosteal abscess in the supratemporal orbit; ethmoid, maxillary, frontal sinusitis, and soft tissue swelling of the eyelid
Worthington, M. G. et al. 1985 [33]	87-year-old male patient with a history of mild hypertension not requiring therapy and angina pectoris	Unrecognized	low-grade fever, malaise, and anorexia	21	Yes/gram-positive rods were seen on the valves on postmortem examination.	Endocarditis on native valve
Givner, L et al. 1984 [25]	16-year-old male with EBV and received oral steroids for seven days.	Pharyngitis and sinusitis	sore throat, tender cervical lymphadenopathy, rash, fever, left orbital erythema.	21	Yes/ blood cultures were also positive for <i>Bacteroides capillosus</i> .	Left maxillary and ethmoidal sinusitis, intraconal abscess, orbital and periorbital cellulitis, DIC, hypotension, intubation, and vasopressor therapy.
Cook, I. F. et al. 1981 [34]	24-year-old male truck driver	Sinusitis	generalized headache, neck stiffness, difficulty focusing, photophobia, and vomiting	3	Yes/gram-positive bacilli on sinus pus gram stain	Bacterial meningitis, sixth cranial nerve palsy
Washington, J. A et al. 1971 [35]	17-year-old boy with a history of focal seizures	Unrecognized	Severe, unremitting, right frontal headache, vomiting, confusion, and agitation.	25	Yes/ blood cultures also positive for <i>F. necrophorum</i> / CSF culture for <i>A. haemolyticum</i>	Right Frontal lobe brain Abscess with leptomeningitis

AST: Aspartate Aminotransferase, CSF: cerebrospinal fluid, LDH: Lactate Dehydrogenase, AKI: Acute Kidney Injury, DIC: Disseminated Intravascular Coagulation, ALP: Alkaline Phosphatase.

due to *Arcanobacterium*. Inclusion of the cases in this review was based on the presence of positive blood culture(s) for *Arcanobacterium haemolyticum* indicating bacteremia from a pharyngeal/upper respiratory tract source or an unknown source and either [11] severe sepsis (defined as sepsis with at least one end-organ dysfunction) and/or septic shock or [12] the presence of complications of bacteremia (e.g., abscesses, Lemierre's syndrome, cavitary lung lesions, etc.). We did not include Cases with mild sepsis and uncomplicated bacteremia in the review [37–40]. Severe sepsis and/or complicated bacteremia can occur secondary to *Arcanobacterium* infections from sources other than the pharynx and upper respiratory tract [41,42]. These patients were not included as well.

We performed analysis of the reported cases; the median age was 20 years (IQR = 7). 80 % of the cases (n = 16) were male patients and the M: F ratio was 4:1. Few case reports have shown EBV infection preceding *A. Haemolyticum* bacteremia [38,40,19,25], and it is hypothesized By Skov R.L et al., 1997 that EBV infection facilitates invasiveness of *A. haemolyticum*. Two patients in our review had EBV infection preceding their *A. haemolyticum* bacteremia. They also received steroids before the presentation [19,25]. The rate of reported complications were as follow: Thrombocytopenia in 35 % (n = 7), Cavitary pneumonia in 35 % (n = 7), Lemierre's syndrome in 35 % (n = 7), intracranial abscesses in 30 % (n = 6), Hyperbilirubinemia in 25 % (n = 5), meningitis in 25 % (n = 5), Transaminitis in 20 % (n = 4), Hypotension in 20 % (n = 4), pleural effusion in 15 % (n = 3), endocarditis in 10 % (n = 2),

coagulopathy in 10 % (n = 2), lower extremity abscesses in 10% (n = 2), orbital/periorbital cellulitis in 10% (n = 2), intubation in 10% (n = 2), AKI in 10 % (n = 2), abducent nerve palsy in 10% (n = 2), acute liver failure in 5 % (n = 1), lung abscesses in 5 % (n = 1), exudative pericarditis in 5 % (n = 1) and vasopressors need in 5 % (n = 1). 85 % of the hosts (n = 17) were immunocompetent with no predisposing factors for bacteremia. The two patients who received steroids were considered immunocompromised. Although before the receipt of steroids (short course for 7–10 days), they would be considered immunocompetent hosts. One patient had NHL and received chemotherapy four days before the presentation. He was neutropenic on presentation [31] and did not have a recognizable source of infection. The source was not recognized in four patients. Otherwise the source was either pharyngitis (65 %, n = 13), tonsillitis (30 %, n = 6), and/or sinusitis (25 %, n = 5). There was one patient who had pneumonia symptoms reported with no mention of upper respiratory or pharyngeal source [17]. Rash was reported in 45 % of the sample, which is consistent with previous studies. Around 15 % of patients (n = 3) had a peritonsillar abscess. There were five patients with meningitis. two of them had sinusitis as the primary source of infection while two had an unknown source and one had an upper pharyngeal source. two of the meningitis patients had developed brain abscesses. One patient in the review, who had EBV, had developed intracranial abscesses after sinusitis and periorbital cellulitis. He also developed an intraconal abscess. A similar patient developed orbital cellulitis after he had sinusitis. Using Fisher's exact test, there was an

Table 3Cases of *Arcanobacterium haemolyticum* bacteremia with severe sepsis and/or complicated bacteremia with a pharyngeal/upper respiratory or an unknown source: management and outcome.

Author/year	Antibiotics use prior to presentation	Empirical antibiotic therapy	Surgical management	Definitive treatment/duration of Antibiotic therapy	Outcome
Verona, J et al. 2020 [18]	The patient received three days of amoxicillin/clavulanic acid with no improvement.	Amoxicillin/clavulanic acid then Ceftriaxone	Abscess drainage	vancomycin plus Piperacillin/tazobactam/13 days course	Discharged home after 19 days of hospitalization and antibiotics were stopped on discharge.
Poplin, V et al. 2018 [19]	Not mentioned	Ceftriaxone, Vancomycin, Doxycycline, Metronidazole	Evacuation of brain abscesses and subdural empyema	ceftriaxone and metronidazole/63 days course	Resolution of intracranial abscesses on F/U imaging. His infection has not recurred during a two-year follow-up period
Cortés-Penfield, N et al. (2017) [20]	Not mentioned	Ceftriaxone, Vancomycin, Ampicillin-Sulbactam	Brain Abscesses surgical drainage	Vancomycin, ceftriaxone, metronidazole for four weeks/ additional two weeks of amoxicillin/clavulanate./total 42 days course	Resolution of infection after four weeks of treatment of definitive therapy. She was discharged home.
Zhang, W. han et al. 2013 [21]	Not mentioned	penicillin G and azithromycin	None	Piperacillin-tazobactam until fevers abated. the patient was treated with anticoagulation	Two follow-up clinic visits over the following four months were unremarkable.
Ji, Y.Q et al. 2013 [22]	Treated with penicillin G with no improvement.	Penicillin, Azithromycin, teicoplanin and then the addition of imipenem/cilastatin	Abscess drainage	anticoagulation/piperacillin-tazobactam until fevers abated. Discharged on the 29th day on Oral amoxicillin for a total period of 6 weeks/total 42 days course.	Hospitalized for 29 days. Resolution of the lung cavities and nodules on F/U imaging several weeks after discharge.
Lee, K. J. et al. 2012 [23]	Treated with cephradine with no improvement.	Ceftriaxone, Metronidazole	None	Anticoagulation was given/ Vancomycin, and gentamicin/total 28 days course	disappearance of the peritonsillar abscess and left IJV thrombosis with an improvement of perivascular inflammatory on F/U CTA After four weeks of antibiotics therapy
Edelman, K. et al. 2012 [24]	Not mentioned	Piperacillin-Tazobactam	Partial decortication	A course of Piperacillin-Tazobactam.	On the twelfth day of hospitalization, she was successfully extubated, and shortly after, she was discharged home to complete a course of IV Piperacillin-Tazobactam.
Wong, V et al. 2011 [25]	Not mentioned	Ceftriaxone, Vancomycin, Metronidazole	Right frontal craniotomy with evacuation	Ceftriaxone and Gentamicin/42 days course	Patient showed mild residual weakness and resting tremor of her right lower limb. There was disappearance of endocarditis on F/U Echo and full recovery at six months
Lundblom, K. et al. 2010 [26]	Not mentioned	Cefotaxime	None	Piperacillin–Tazobactam, for a total of 14 days followed by amoxicillin for another three weeks/total 35 days course	A follow-up visit two weeks after discharge was Unremarkable, including blood tests.
Fernández-Suárez, A. et al. 2009 [27]	He was treated with erythromycin with no improvement.	Amoxicillin/clavulanic acid, Metronidazole then Imipenem, Metronidazole	None	Patient was changed to Imipenem, Metronidazole. The patient was treated with anticoagulation. He was sent home on clindamycin/10 days course.	The patient was discharged home in good general Condition after seven days of hospitalization.
Therriault, B. L. et al. 2008 [17]	Not mentioned	Vancomycin, Levofloxacin, Doxycycline, Piperacillin-Tazobactam followed by TMP-SMX, Imipenem/cilastatin and Vancomycin for Nocardia coverage	Drainage of the abscess	intravenous penicillin G and Azithromycin for 17 days followed by Azithromycin for another three weeks/total 38 days course.	Discharged 17 days after admission on a home antibiotic regimen of azithromycin for three weeks. two follow-up clinic visits in the next two months were unremarkable, and the patient had no long-term sequelae from the infection.
Van Der Eerden M.M et al. 2006 [28]	Not mentioned	Not available	None	Pathogen-directed therapy and no specific class mentioned.	After initiating pathogen-directed therapy, the patient recovered completely
Younus, F. et al. 2002 [29]	Not mentioned	Gatifloxacin, Metronidazole	None	2-weeks of Piperacillin–Tazobactam and vancomycin. was discharged on oral amoxicillin-clavulanic acid for a 12-week course./total 98 days course	Discharged on oral antibiotics for a 12-week course.
Skov, R. L. et al. 1997 case 2 [30]	Not mentioned	Cefotaxime	None	Empiric regimen changed to Cefotaxime and metronidazole based on susceptibility testing.	The patient's recovery was prolonged but uneventful. The abducent palsy resolved after 3 months.
Minarik, T. et al. 1997 case 1 [31]	Not mentioned	Cefotaxime, Pefloxacin	None	Therapy was modified on day 3 to Teicoplanin, penicillin G and ceftazidime/total 16 days course.	Defervescence on day four and the disappearance of rash on day 6 with improved neurological symptoms. Echocardiographic

(continued on next page)

Table 3 (continued)

Author/year	Antibiotics use prior to presentation	Empirical antibiotic therapy	Surgical management	Definitive treatment/duration of Antibiotic therapy	Outcome
Ford, J et al. (1995) [32]	Not mentioned	Ceftizoxime, Ampicillin, Clindamycin	Multiple head and neck surgeries	Started on Ceftizoxime, ampicillin, and clindamycin.	changes disappeared. Antibiotics were stopped on day 16. Six months After the last surgery, the patient's visual acuity was 20/20, and the result of the ocular examination was normal.
Worthington, M. G. et al. 1985 [33]	Not mentioned	Ampicillin	None	By day 3 changed to IV penicillin and gentamicin/total six days course.	Worsening heart failure and death on day 6 of hospitalization (patient and family refused surgery)
Givner, L et al. 1984 [25]	The patient was treated with penicillin and oral ampicillin.	Vancomycin, Chloramphenicol	Underwent bilateral Antral washouts with indwelling trocar needle followed by external left ethmoidectomy.	Treated with penicillin G for four weeks after discharge/28 days course	Patient did well after surgery. Radiological disappearance of the intraconal abscess. There was persistent anesthesia around the ophthalmic branch of the trigeminal nerve on follow up.
Cook, I. F. et al. 1981 [34]	Not mentioned	Gentamicin, Ampicillin, Metronidazole, Probenecid	Sinus drainage and surgery and	was treated with gentamicin, ampicillin, metronidazole, and probenecid	Patient improved after two sinus surgeries, and general condition returned to normal except for persistent sixth nerve palsy.
Washington, J. A et al. 1971 [35]	Not mentioned	Cephalothin, Gentamicin, Chloramphenicol	None	Cephalothin, gentamicin, and chloramphenicol. The patient deteriorated rapidly and passed away.	Passed away at 30 h post admission.

association between having sinusitis as the source of infection and developing intracranial complications (such as meningitis, brain abscesses and orbital/periorbital cellulitis) with a P-value on a two tailed test of .008. This would indicate the likelihood of contiguous spread of infection from the primary source rather than the bacteremia seeding these sites.

Seven patients, out of the 20 cases reported, had Lemierre's syndrome. We also had seven patients developing cavitory lung lesions, and three were without evidence of Lemierre's syndrome. Using Fisher's exact test There was an association between having peritonsillar abscesses and developing Lemierre's syndrome (two tailed test; P = 0.31) but there was not a statistically significant association between having Lemierre's syndrome and developing cavitory pneumonia (two tailed test; P = 0.174). None of the patients with Lemierre's syndrome were reported to have endocarditis. We did have two patients with endocarditis. One of those patients had an age of 87 years which was an outlier, and the source for his bacteremia was not recognized. The other patient had evidence of a repaired congenital heart disease and had pharyngitis as the possible source of her infection [25]. Three of the twenty reviewed cases indicated evidence of pleural effusion, with two having Cavitory pneumonia and the remaining one having bilateral pulmonary septic emboli. This indicates either a possibility of *Arcanobacterium* seeding the pleura or a possibility for it to cause a parapneumonic effusion secondary to lung seeding. *Arcanobacterium*

haemolyticum was the sole organism identified in the blood of 14 cases, while it was associated with *Fusobacterium necrophorum* in five cases and with *Bacteroides capillosus* in one case. *Arcanobacterium* was identified from the source and a seeding site in nine cases either through gram stains or culture growth and PCR identification.

50 % (n = 10) of the reviewed cases required surgical management (Table 3), which mostly involved abscess drainage of seeding and contiguous spread sites. Beta-lactam therapy was used in 85 % of the cases for empiric coverage and was either part of- or the mainstay regimen for definitive therapy in 90% of the cases (n = 18). One patient was treated with pathogen-directed therapy with no mention of the antibiotic. The other one was put on vancomycin and gentamicin based on susceptibility testing. Beta-lactams used were Penicillin G, Amoxicillin-Clavulanate, Amoxicillin, Ampicillin, Piperacillin-Tazobactam, Ceftriaxone, Imipenem, Cefotaxime, Ceftazidime, Cephalothin, and Ceftizoxime. Combination agents included: Macrolides, Metronidazole, Teicoplanin, Vancomycin, Aminoglycosides, and Fluoroquinolones (see Table 3). Full recovery was seen in 90 % of patients (n = 18), and around fifteen patients were explicitly mentioned to be discharged. Two deaths were reported: one in an 87-year-old with endocarditis who refused (along with his family) to do the surgery for his valve, and the other one was a meningitis patient with a brain abscess who rapidly deteriorated and died within 30 h of admission. Among the 18 patients who survived, there were no long-term sequelae in 16

Table 4
Arcanobacterium haemolyticum susceptibilities.

Tested antibiotic	MIC	Interpretation
	≤ 1	S
	≤ 0.500	S
	≤ 0.500	S
	≤ 0.500	S
	≤ 4	S
	≤ 1	S
	≤ 0.120	S
	≤ 2	S
	> 8	R
Ciprofloxacin Clindamycin Daptomycin Erythromycin Gentamicin Linezolid Penicillin Sulfamethoxazole Trimethoprim Tetracycline Vancomycin	0.500	S

S: Susceptible, R: Resistant, I: Intermediate, MIC: Minimum Inhibitory Concentration.

patients, and there were two patients who had persistent 6th nerve palsy (following meningitis) and anesthesia on the ophthalmic branch distribution of the trigeminal nerve following periorbital cellulitis and intraconal abscesses. There was variation in the definitive antibiotic treatment duration among these patients. Among the patients who survived (n = 18), thirteen had reported antimicrobial treatment duration. The mean antimicrobial duration was 36 days (SD of ± 24.1 days).

The susceptibilities for the *Arcanobacterium* isolate were sent to us by the outside hospital. They are shown in Table 4. The literature reports the susceptibility of *Arcanobacterium* to penicillins [43,44]; however, treatment failures are described as well [2,45]. One study attempted to explain that penicillin failure occurs due to the ability of *Arcanobacterium* to reside intracellularly, effectively hiding the organism from penicillin [46]. In addition to the reported low minimum inhibitory concentrations, this makes Macrolides Antibiotics a good candidate for treatment failure [14,36].

Conclusion

Arcanobacterium haemolyticum pharyngitis can be associated with peritonsillar abscess formation and secondary bacteremia. Severe infections can lead to cavitory lung lesions, septic shock, and multi-organ failure. Penicillins can be used for treatment, and our patient fully recovered with Ampicillin-Sulbactam given for five weeks. *A. haemolyticum* should be included in the differential diagnosis for bacterial pharyngitis complicated by severe systemic illness and in patients who demonstrate signs of hematogenous spread of bacterial infection.

CRedit authorship contribution statement

Anas M. Alrwashdeh: Care of the patient, writing of the case, review of the literature, Data analysis. **Prachi Saluja:** Care of the patient, writing of the case. **Lana Hasan:** Care of the patient, review of the literature. **Emily Kocurek:** Care of the patient, Writing – review & editing. **Ryan K. Dare:** Care of the patient, Writing – review & editing.

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Ethical approval

Our institution guidelines do not require ethics committee approval of case reports that include one patient subject.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflicts of interest

No conflict of interest to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.idcr.2022.e01645](https://doi.org/10.1016/j.idcr.2022.e01645).

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