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Case Report

Internal Medicine Section

Polymicrobial Endocarditis in Intravenous Heroin and Fentanyl Abuse

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ABSTRACT

Infective endocarditis is a life threatening condition with a high mortality rate. Intravenous Drug Abusers (IVDA) are more likely to acquire endocarditis. Most of the cases of infective endocarditis are caused by a single pathogen; cases of polymicrobial endocarditis are rare and they are associated with a reported mortality rate of more than 30%. Only 21 cases of N. sicca endocarditis have been described in the literature since 1918, and only 15 reported cases of endocarditis which involved *Actinomyces species* have been reported since 1939. We are reporting a case of a 49-year-old male with intravenous heroin and fentanyl abuse, who presented with infective endocarditis caused by *Neisseria sicca*/subflava(N. sicca), Actinomyces, Streptococcus mitis, and *Haemophilus parainfluenzae*, complicated by septic emboli to the lungs and skin, ARDS , splenic infarct and immunocomplex mediated proliferative glomerulonephritis.

Keywords: *Neisseria sicca*, *Actinomysis*, *Streptococcus mitis, Haemophilus parainfluenzae, Septic emboli*

CASE PRESENTATION

A 49-year-old male with a past medical history of bipolar disorder, sickle cell trait and IV heroin, fentanyl and cocaine abuse was admitted to a hospital with fever, headache, toothache, low back pain and a nonspecific facial palsy. The patient reported a habit of injecting a mixture of at least 3 gm/day of heroin mixed with fentanyl, from prescription patches diverted from a medical supply. The patient reported occasional use of intravenous cocaine and an active smoking history of 3 cigarettes per day. He denied alcohol or marijuana use. His last dose of IV drugs was just a few days before admission.

At admission, his white blood cell count was 19,1 k/ul, haemoglobin was 12.2 g/dl, haematocrit was 35.9%, and platelets were 115 k/ul. Alkaline phosphatase was 146 U/L. Gamma glutamyl transferase was 109 k/ul. CRP was 5.9mg/L, ESR was 32mm/hr. CSF cultures from lumbar puncture were negative for bacterial, fungi or viral infections. Head CT and MRI were negative for any acute process. Transthoracic echocardiogram revealed a 0.5 x 0.6 cm vegetation on the medial leaflet of the tricuspid valve, with a strand prolapsing into the right atrium during systole.

On hospital admission day 1, 1/2 blood cultures grew *Haemophilus parainfluenzae* and a species of *Streptococcus*. The second bottle grew *Actinomyces species*. On day 4, 2/4 blood cultures grew *Actinomyces species* and 2/4 bottles grew a nutritional variant of *Streptococcus*. On day 7, 2/2 cultures grew *H. parainfluenzae*. On day 8, 2/4 cultures grew *H. parainfluenzae* and 2/4 cultures grew *Neisseria sicca/subflava* in two bottles. On day 9, 2/4 cultures grew *Actinomyces* and gram positive cocci. Blood cultures were obtained for fungal species, with no growth being reported [Table/Fig-1 and 2].

The patient was treated with IV vancomycin for 6 days before he left against medical advice. His temperature on discharge was noted to be 102.4F. After leaving the hospital, the patient reported using IV heroin again, and presented to our hospital one day later. On admission, he was noted to have a fever of 102.8ºC.

The patient was admitted to the general medical floor, but he soon developed chest pain, dyspnea, hypoxia and diaphoresis. He was transferred to the ICU for monitoring and further management. Physical exam demonstrated crackles at the lung bases, right-sided diffuse chest tenderness and splenomegaly.

Serologies were positive for Hepatitis A, B and C, with a hepatitis C viral load of 1,340,000 IU/mL. Serology for HIV was negative.

Echocardiogram demonstrated 0.5x1.0cm vegetation on the posterior leaflet of the tricuspid valve. CT-chest revealed cavitating

Hosp. Day	Aerobic Culture	Aerobic Gram Stain	Anaerobic Culture	Anaerobic Gram Stain
1	*Haemophilus parainfluenzae* (positive at 33 hours 9 minutes)	Gram positive cocci chains/pairs	*Actinomyces species* (positive at 16 hours)	Gram positive bacilli
4	*Actinomyces species* Nutritionally variant *Streptoccus spp.*	Gram positive bacilli	Nutritionally variant *Streptoccus spp.* (positive at 22 hours)	Gram positive cocci in chains
4	Nutritionally variant *Streptoccus spp.* Actinomyces	Gram positive bacilli	Nutritionally variant *Streptoccus spp.* (positive at 23 hours)	Gram positive cocci
7	*Haemophilus parainfluenzae* (culture positive at 20 hours)	Gram negative bacilli	No growth	Gram negative rods
8	*Neisseria sicca*/subflava (culture positive at 22 hours)	Gram negative diplococci	*Neisseria sicca/subflava* (positive at 36 hours)	Gram negative diplococci
8	*Haemophilus parainfluenzae* (culture positive at 25 hours)	Gram negative bacilli	*Haemophilus parainfluenzae* (positive at 27 hours)	Gram negative bacilli

[Table/Fig-1]: Blood culture results from the first hospital

Patient left against medical advice and then presented to our hospital after 24 hours. The results below are from the second hospitalization.				
1	*Neisseria sicca/subflava* (positive in <24 hours)	Gram negative cocci	*Neisseria sicca/subflava* (positive in <24 hours)	Gram negative cocci
	Neisseria sicca/subflava (positive in <24 hours)	Gram negative cocci	*Neisseria sicca/subflava* (positive in <24 hours)	Gram negative cocci
	Neisseria sicca/subflava (positive in <24 hours)	Gram negative cocci	*Neisseria sicca/subflava* (positive in <24 hours)	Gram negative cocci
2	Species type not performed, presumed *N. sicca/subflava* (positive in <24 hours)	Gram negative cocci	Species type not performed, presumed *N. sicca/subflava* (positive in <24 hours)	Gram negative cocci
	Species type not performed, presumed *N. sicca*/subflava (positive in 4 days)	Gram negative coccobacilli	No growth	none
3	No growth	none	Species type not performed, presumed *N. sicca*/subflava	Gram negative cocci
	No growth	none	Species type not performed, presumed *N. sicca*/subflava	Gram negative cocci
4	No growth	none	Species type not performed, presumed *N. sicca*/subflava	Gram negative cocci
	No growth	none	Species type not performed, presumed *N. sicca*/subflava	Gram negative cocci
5	*Neisseria sicca*/subflava (positive in 4 days)	Gram negative cocci	No growth	none
11	No growth	none	No growth	Gram negative cocci
20	No growth	none	Prevotella denticola (central line blood culture)	Gram negative rods
	No growth	none	Prevotella denticola (peripheral blood culture)	Gram negative rods

[Table/Fig-2]: Blood culture results from Carney Hospital

nodules in the upper lobes of both lungs, "basilar granulomas" and multiple splenic infarcts, consistent with a diagnosis of septic emboli [Table/Fig-3].

The patient was given IV vancomycin for 6 days at another hospital, then IV gentamicin for 4 days at our hospital, which then was discontinued, and the patient was started on IV ceftriaxone for 22 days. However, he was observed to have daily fever of 104.8ºF, with rigors, chills, and diaphoresis, requiring high doses of acetaminophen and ibuprofen and cooling blankets. The febrile episodes would last for a few hours at a time.

On hospital admission day 13, the patient developed respiratory failure, was intubated and was placed on a mechanical ventilator. Chest X ray demonstrated consolidation of the upper lobes, suggestive of aspiration pneumonia [Table/Fig-4]. Chest X ray, arterial blood gas and laboratory results were also consistent with diagnosis of Acute Respiratory Distress Syndrome (ARDS). Levofloxacin was added for anaerobic coverage.

A repeat echocardiogram, showed an increased size of the vegetation on the posterior leaflet of tricuspid valve, now measuring 0.8 x 1.6cm, with moderate tricuspid regurgitation, and markedly elevated pulmonary artery pressure. Repeat chest X–ray was done on day 15 showed improvement following 2 days of levofloxacin therapy [Table/Fig-5].

During the hospitalization, the patient developed severe anaemia and thrombocytopaenia, requiring transfusion of 11 units of packed red blood cells and 1 unit of platelets. A Disseminated Intravascular Coagulation (DIC) panel failed to confirm a diagnosis of DIC. Heparin Induced Thrombocytopaenia (HIT) was considered, but Heparin PF4 Antibody was negative. His anaemia and thrombocytopaenia was considered to be multifactorial.

The patient's renal function started to deteriorate on hospital day 14.

Urine complement C3(123 mg/dL) and C4(27 mg/dL), Anti-Ds DNA and Anti-DNAase were within normal ranges. IgG was measured at 3340 mg/dL, IgA at 512 mg/dL, IgM at 205 mg/dL. Cryoglobulins were negative. However, rheumatoid factor was 63 IU/mL and it was thus elevated. The overall picture was consistent with a diagnosis of ATN as well as immuncomplex-mediated proliferative glomerulonephritis, most likely caused by hepatitis C, although post-infectious glomerulonephritis caused by *N. sicca* could not be excluded. Hemodialysis was begun on hospital day 21 via a femoral catheter.

On hospital day 22, the patient also developed dark skin lesions on his fingers, consistent with features of septic emboli to the skin [Table/Fig-6].

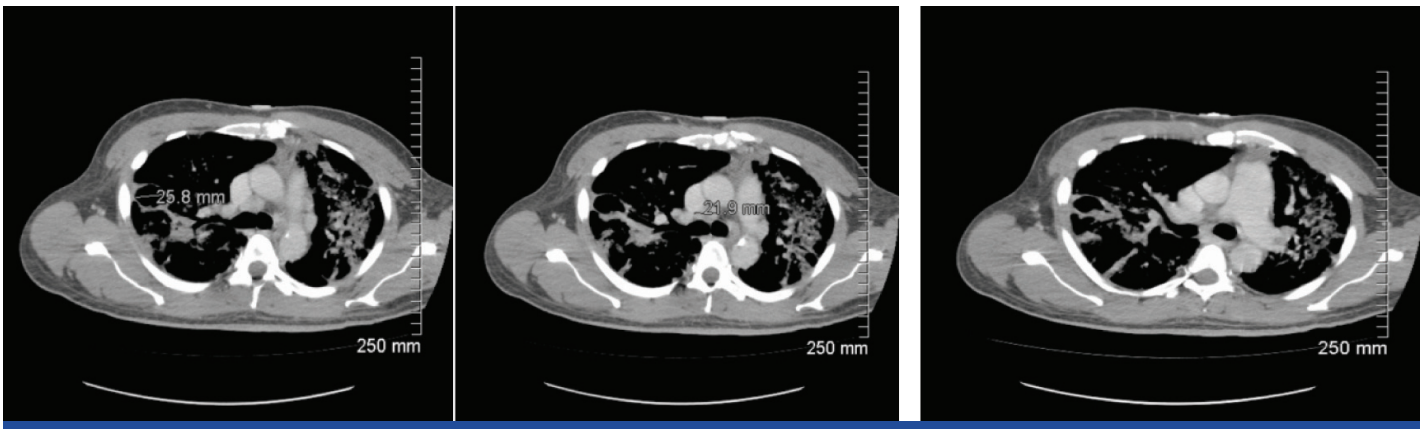
The patient failed seven days of spontaneous breathing trials, and on intubation day 8 (hospital day 21), a tracheostomy as well as a Percutaneous Endoscopic Gastrostomy (PEG) were placed. Repeat CT scan of chest, abdomen, and pelvis, obtained on hospital day 23, showed worsening bilateral cavitary lesions that were new or slightly larger than those seen in the prior study done on hospital day 13 [Table/Fig-7]. A new 1.0x1.5cm left upper lobe nodular opacity was also noted. Small bilateral effusions and left upper lobe parenchymal opacities with air bronchograms worsened since the previous scan as well.

An outside hospital was asked to evaluate the patient for possible cardiothoracic surgery, but it declined to do surgery.

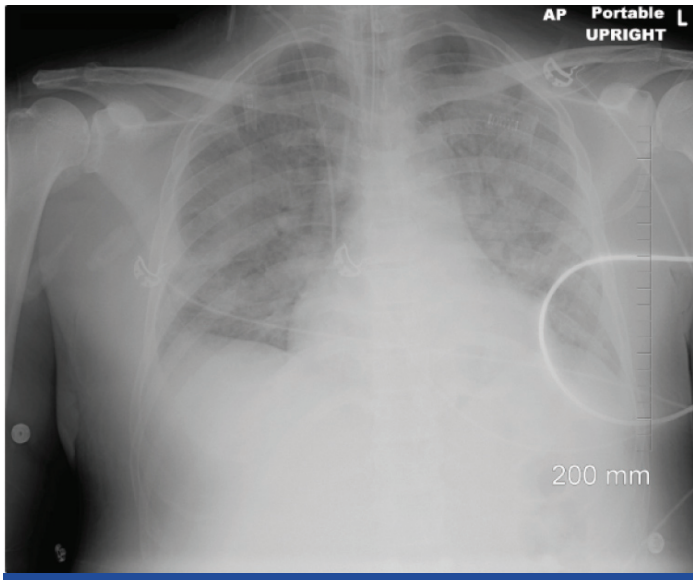
Ceftriaxone was discontinued on hospital day 22 and the patient was started on Ciprofloxacin and on Metronidazole. Four days after initiation of Ciprofloxacin, the patient became afebrile. WBCs trended down. The patient's respiratory status improved and he was able to be weaned off the ventilator machine.

A repeat TTE done on hospital day 31 showed improved systolic function with an EF of 55-60% and a "smaller vegetation" on the tricuspid valve. The tricuspid regurgitation remained moderate in severity. Blood cultures repeated were all negative. The patient's overall clinical course improved and he was screened for rehab.

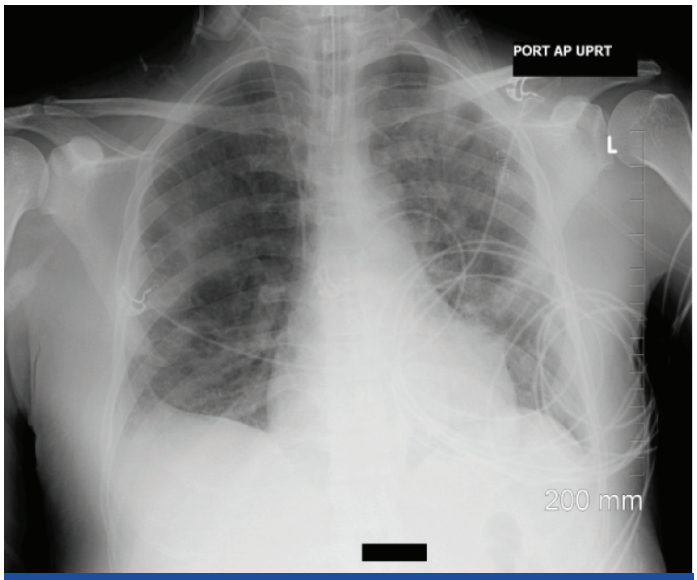
Furthermore, after being on haemodialysis for three weeks, the patient's kidney function returned back to baseline, without the need of any further dialysis.



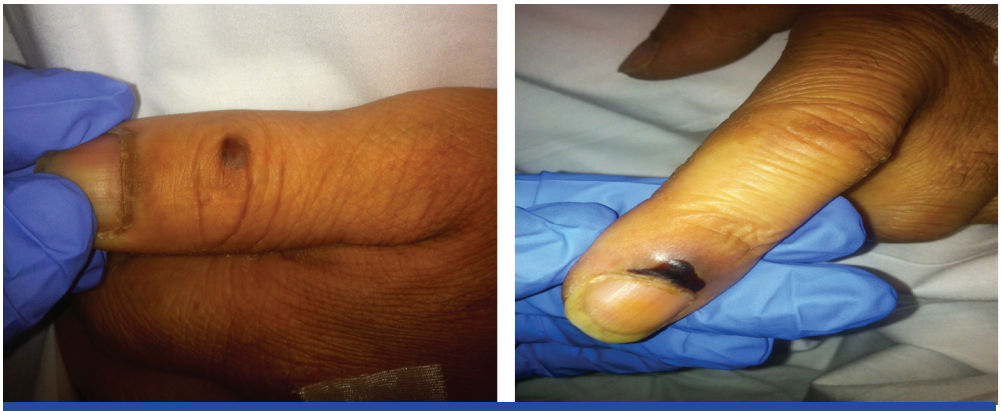
[Table/Fig-3]: Chest CT demonstrating septic emboli and cavitary lesions



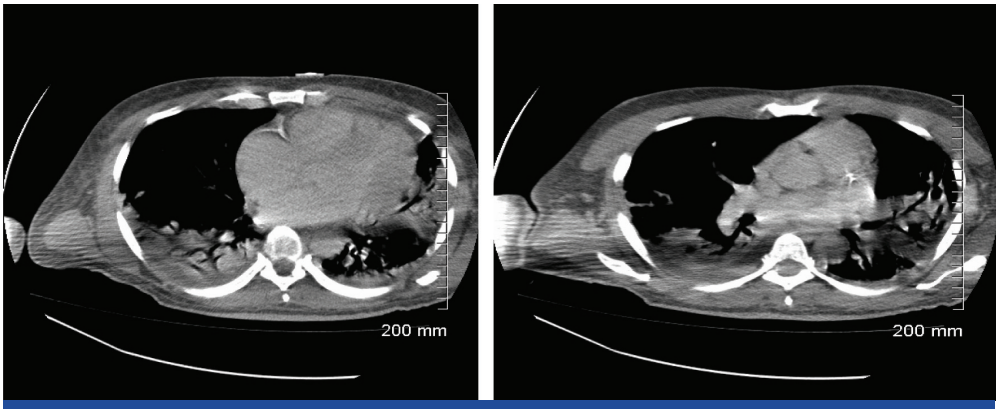
[Table/Fig-4]: Chest x-ray just after intubation



[Table/Fig-5]: Chest x-ray following 2 days of levafloxacin therapy



[Table/Fig-6]: Septic emboli to the skin



[Table/Fig-7]: Chest CT demonstrating worsening bilateral septic emboli and cavitary lesions and mall effusion

DISCUSSION

Neisseria sicca/Subflava

Neisseria species are known to cause meningitis, septicaemia, otitis, broncho-pneumonia, and genital tract disease [1]. However, *N. sicca*, a commensal microorganism of the upper respiratory tract, is an exceedingly rare cause of endocarditis. Only 21 cases of *N. sicca* endocarditis have been described in the literature since 1918 [2]. The most common clinical features of *Neisseria* species endocarditis include fever, headache, chills, murmur, petechiae, and haematuria [1].

N. sicca endocarditis, in particular, has been associated with prolonged fever, pneumonia, intracranial aneurysms, popliteal aneurysms, hepatic artery mycotic aneurysms, liver abscesses, disseminated disease in the immuno-compromised, and fatal embolic phe-nomenon [3,2,4,5], four of which we encountered in our case. This disease has been associated with IV drug use and it is found in non-IV drug users with

carious teeth [3], which were both seen as features in our patient [Table/Fig-8].

A patient who had been reported previously [6] had many symptoms similar to those of our patient, including very high fever, decreased responsiveness, abnormal mentation, ARDS, progressive anaemia requiring blood transfusions and thrombocytopaenia. Some features of other patients recently reported with *N. sicca* endocarditis have been shown in [Table/Fig-8].

Reference	Age/Sex	Valve Involved	Organism	Therapy	Complications	Outcome
Aronson et al., [6]	12 F	Mitral	*N. sicca*	PCN G	Pulmonary hemorrhage, ARDS, DIC, subarachnoid hemorrhage	alive
Sommerstein et al., [7]	75 F	Aortic	*N. sicca*	Amox/clav	Cerebellar/lung emboli	dead
Debellemaniere et al., [2]	41 M	Aortic	*N. sicca*	Cipro, gentamicin	Aortic ring abscess, CHF	alive
Present report	49 M	Tricuspid	*N. sicca/subflava,* multiple	Vancomycin, ceftriaxone ciprofloxacin flagyl	Septic lung emboli, skin emboli, respiratory failure	alive

[Table/Fig-8]: Some recent case reports of *N. sicca* endocarditis

Haemophilus parainfluenzae

H. parainfluenzae is an established cause of infectious endocarditis, being one of the "HACEK" organisms. It tends to produce vegetations more on the mitral and aortic valves than on the tricuspid valve [8]. It is known to present with prolonged, high fever with rigors, organ dysfunction and severe headache [8,6]. In intravenous drug users with salivary contamination of needles, *H. parainfluenzae* has been described as presenting with severe endocarditis, with prominent septic pulmonary emboli [9]. Despite its severe course, the mortality is reportedly low [10] [Table/Fig-9].

Actinomyces

Actinomyces is an exceedingly rare cause of infectious endocarditis. It is associated with systemic emboli to the central nervous system [14]. There have been only 15 reported cases of endocarditis involving *Actinomyces species* since 1939, including this report [15,11]. Five of the reported patients died of the infection [Table/Fig-10].

The species found to cause endocarditis include *A. israelii*, *A. bovis*, *A. viscosus*, *A. pyogenes*, *A. meyeri*, *A. funkei*, and *A. neuii*. *Actinomyces species* are known to be involved in polymicrobial infections in intravenous drug abusers and they are thought to be caused by saliva-to-needle contact [16]. In recent reports, ceftriaxone and ampicillin have been used successfully to eradicate the organism [15]. In our case, however, the patient's condition did not improve on ceftriaxone treatment alone.

Reference	Age/Sex	Valve Involved	Organism	Therapy	Complications	Outcome
Adler et al., [3]	39 M	Tricuspid	*H. parainfluenzae,* multiple	Amp, metronidazole	Cardiac surgery, subclavian abscess	alive
Patel et al., [11]	34 F	Tricuspid	*H. parainfluenzae,* multiple	amp	Pulmonary emboli	alive
Nwaohiri et al., [12]	64 F	Tricuspid	*H. parainfluenzae*	ceftriaxone	none	alive
Christou et al., [13]	54 F	Mitral	*H. parainfluenzae*	ceftriaxone	Cerebral emboli	alive
Present report	49 M	Tricuspid	*N. sicca/subflava,* multiple	Vancomycin, ceftriaxone Ciprofloxacin flagyl	Septic lung emboli, skin emboli respiratory failure	alive

[Table/Fig-9]: Case reports of *Haemophilus parainfluenzae* endocarditis

Reference	Age/Sex	Valve Involved	Organism	Therapy	Complications	Outcome
Uhr	24 M	Aortic/Mitral	*A. bovis*	Sulfathiazole	CNS emboli, CHF	dead
Beamer et al.,	55 M	Aortic/Mitral	*Actinomyces sp.*	none	CNS, renal, GI emboli	dead
MacNeal et al.,	39 M	Mitral	*Actinomyces sp.*	PCN G	CNS emboli	alive
Wedding	37 M	Mitral	*Actinomyces sp.*	Sulfadiazine	CHF, renal, GI emboli	dead
Walters et al.,	43 F	Aortic/Mitral	*A. bovis*	PCN G	GI emboli	alive
Dutton and Inclan	6 M	Mitral	*A. israelii*	PCN G	CHF	dead
Gutschik	70 M	Mitral	*A. viscosus*	PCN G	CNS emboli, CHF	alive
Lam et al.,	65 M	Aortic/Mitral	*A. israelii*	PCN G	none	alive
Reddy et al., [17]	64 M	Aortic	*A. pyogenes*	multiple	CNS emboli, CHF	dead
Hamedka	81 M	Aortic	*A. viscosus*	Ceftizoxime	none	alive
Huang et al.,	55 F	Mitral	*A. meyeri*	Amp-Sulb	none	alive
Mardis and Many	38 M	Mitral	*A. viscosus*	Multiple, PCN G	Cutaneous emboli	alive
Oh et al., [14]	33 M	Tricuspid	*A. odontolytica*	ceftriaxone	Cavitary lung lesions	alive
Cohen et al., [18]	68 M	Aortic (bicuspid)	*A. neuii*	Amp, ceftriaxone, gentamicin	Aortic abscess, acute renal failure	alive
Present report	49 M	Tricuspid	*Actinomyces sp., multiple*	Vancomycin, ceftriaxone ciprofloxacin flagyl	Septic lung emboli, skin emboli, respiratory failure	Alive

[Table/Fig-10]: Case reports of Endocarditis caused by *Actinomyces species*[11]

CONCLUSION

Infective endocarditis is a life threatening condition with a high mortality rate [19]. Polymicrobial endocarditis carries a mortality rate which has been reported to be greater than 30% [20].

While a vast majority of endocarditis cases are caused by a single organism, polymicrobial endocarditis appears to be increasing in incidence, especially amongst intravenous drug users [17]. Over 50% of these patients will require cardiac surgery for controling the infection or for repairing damaged valves [10].

The polymicrobial infection in our patient was caused by *Neisseria sicca*, *Haemophilus parainfluenzae*, *Actinomyces species*, and *Streptococcus viridans*. With the exception of *S. viridans*, these organisms are rare causes of endocarditis, even amongst intravenous drug abusers.

While *N. sicca* infections remain relatively rare, they have the potential to cause severe diseases with very high mortality. Furthermore, endocarditis caused by this species is known to cause numerous symptoms and complications. In our review of the literature and from our own experience, polymicrobial endocarditis was found to be characterized by severe, prolonged illness requiring intensive care, with mortality rates as high as 90% [17]. Unfortunately, our knowledge on this area is still limited to case reports.

Our patient reported injecting a mixture of heroin and fentanyl. The patient's heroin dealers would scrape fentanyl off of a prescription fentanyl patch, freeze it, and then mix it with heroin prior to his injecting it. While endocarditis associated with intravenous heroin use has been well documented, this is the only case which has been reported, that involves infectious endocarditis associated with intravenous fentanyl abuse. Clinicians should be aware of the growing trend among injection drug users of using fentanyl in this matter.

Finally, it is s noteworthy that the patient's condition did not improve on treatment with ceftriaxone. There was insufficient growth of the sample, for testing its susceptibility in vitro, but studies have shown that the species was resistant to ceftriaxone [21]. It is important for clinicians to remember that, although most other oral organisms that cause endocarditis are readily susceptible to this drug, this species is or may be resistant. Indeed, our patient's condition began to improve shortly after the institution of ciprofloxacin treatment.

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