CASE REPORT

Lemierre's syndrome and 2016 American College of Physician guidelines for pharyngitis: no to empiric coverage for bacterial pharyngitis. While no role for routine *Fusobacterium* PCR, keep suspicion for this pathogen

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SUMMARY

An 18-year-old woman presented to clinic with acute pharyngitis with 4/4 Centor criteria. Rapid streptococcal antigen test was negative. The patient, who was allergic to penicillin, was prescribed azithromycin. Ultimately, after 5 days and without any corticosteroids, she presented to the emergency department with 10/10 chest pain and was admitted to the intensive care unit. CT showed nodular lung disease and blood cultures on admission grew *Fusobacterium*, likely *Fusobacterium nucleatum*. She sustained two cardiac arrests, three tube thoracostomies, acute kidney injury requiring dialysis and ventilatory failure requiring tracheostomy. After 16 days in hospital and 18 days in long-term acute care, the patient was discharged home. It is unclear how much of this could have been prevented by prescribing an antimicrobial that had activity against *Fusobacterium*. When severe pharyngitis occurs, *Fusobacterium* needs to be considered as an underlying cause. In vitro macrolides have marginal activity against most anaerobes, such as this pathogen, and should be avoided.

BACKGROUND

Recent studies have found bacterial pharyngitis to be caused by *Fusobacterium* more often than by Group A *Streptococcus*.¹ In patients who score highly on the modified Centor criteria (four points plus or minus an additional point for age), empiric treatment is no longer recommended in the absence of a microbiological diagnosis.² Nevertheless, as this case demonstrates, anaerobes can complicate pharyngitis and Lemierre's syndrome has high morbidity, cost and, in some cases, can be fatal.

We feel that antimicrobial coverage for pharyngitis should strive to include therapy against anaerobes. Among the second-line agents, clindamycin has anaerobic coverage. However, macrolides and most oral cephalosporins do not adequately cover anaerobic bacteria, and therefore, should be avoided as monotherapy if possible. Metronidazole can be added.

CASE PRESENTATION

An 18-year-old woman presented to the university clinic for acute pharyngitis with 4/4 Centor criteria. Rapid streptococcal antigen test was negative. The patient, who was allergic to penicillin, was prescribed azithromycin by the advanced care provider and went home for the weekend. Two days later back home and over 100 km away, she presented to urgent care with persisting fever, chills and worsening chest pain. She was diagnosed with pleurisy and sent home with symptomatic treatment.

Three days later (all told 5 days after the symptoms started), she presented to the emergency department with severe chest pain and shortness of breath requiring intensive care unit (ICU) admission. Admission CT showed nodular lung densities and admission blood cultures were positive for *Fusobacterium*. Based on its morphological characteristics (slender with sharp ends), the bacterium was most likely *Fusobacterium nucleatum* and not *Fusobacterium necrophorum* or *Fusobacterium mortiferum*. In the ICU, she experienced cardiac arrest, empyema and pneumothorax requiring three tube thoracostomies, acute kidney injury requiring dialysis and ventilatory failure requiring tracheostomy. She ultimately stabilised and after a stay of 16 days in hospital and 18 days in long-term acute care was discharged home.

INVESTIGATIONS

- ▶ Rapid streptococcal antigen test at the university clinic which was negative.
- ▶ Admitting blood culture: *Fusobacterium* species, susceptible to penicillin at 0.25 µg/mL, metronidazole 0.06 µg/mL, clindamycin 0.016 µg/mL and cefoxitin 0.5 µg/mL. The laboratory did not have susceptibility information for any other antimicrobials (such as the macrolide azithromycin) because it is not the standard procedure to do so for anaerobes.

DIFFERENTIAL DIAGNOSIS

- ▶ Viral pharyngitis.
- ▶ Herpes virus stomatitis (herpes simplex virus 1/2/cytomegalovirus /Epstein-Barr virus).

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Patient's perspective

In April 2017, I was living what I thought was a normal college student life. Everyone knows that college (university) is full of germs and it was likely that you would get sick at some point. I thought that I caught the common cold, but as time went on I knew it was something different. I went to the clinic feeling like I had a fever, my tonsils were huge and had white puss all over them. I thought I had strep throat, which I have never had before, or maybe even mono, which I've also never had. At the clinic, she told me I had the start of an infection and she couldn't do anything about it. I begged and begged for an antibiotic of some sort. Finally, the doctor gave me a z-pack. I remember being freezing cold and sweating at the same time. My throat had never hurt so bad in my entire life. I met with one of my friends for dinner and I could not even walk up stairs to get to the dining hall. I sat in a chair not eating or drinking anything because I couldn't swallow anything. Finally, a day went by and I asked my mom to come and get me and bring me back home. She took me to an ambulatory place and they sent me home saying I had pleurisy of the lungs, and it would heal and I continued taking the z-pack. I knew that there was something more as I had never felt so awful in my life. I went back to college on Sunday night and I was dreading it. On Monday I still managed to go to class. Somehow, I remember seeing a friend on the bus and he was saying that I looked miserable. At this point I did not have the strength to climb into my lofted bed in my dorm room, nor could I even sleep. I did not have a stuffy nose or anything, I just remember my throat hurt, I couldn't breathe, my heart was beating so fast since I couldn't breathe, and this was making me sweat profusely. When Tuesday came around, I had had enough. I was walking around campus and I called my mom. I told her I could not breathe and I needed to go to the emergency. My mom got there in an hour and took me right to the hospital. I remember sitting in the emergency room freaking out over the wait, so anxious to get help. The last thing I remember from the initial intake was getting a hospital bracelet. Then everything else became a blur because it happened so quickly. My family explained to me that they tried just oxygen, then another machine, and then apparently I asked to be intubated because I just could not breathe. From then on it was test after test trying to figure out what was wrong. As I lay there fighting for my life, my family was frantically trying to get answers and notify everyone. At this time in school, I was approaching finals, so my sister had to contact the university and ask them to let me complete all my classes when I was well again. Without her help I would have lost all that work I put in the entire semester. My brother had drove through the night from 8 hours away to get to the hospital because he was finishing his semester in college as well. Surrounded by my family I was unable to hold on, Thursday I coded a few times, but my body knew that I was not done yet, I could get through this. My family believed in the hospital and without them I don't think that I would still be here today. Things in between were very blurry for me because I had so much medicine that I don't remember much. What I do remember are the important things. Those things are that my family never left my side, my mother was right next to me every time I opened my eyes, she never left the hospital. My dad was there every day driving over an hour to see me every day after work. My siblings were holding up the fort at home and coming to see me every couple days. Every time that they walked into my room it gave me hope, hope that I would get better. I would be laying there barely staying awake but I wanted to because I need them to know that I was getting better for them. I had my good days and my bad days, from kidney issues, to getting the tracheotomy, I am sure that I was able to stay strong because of the hospital. The doctors there were so determined to figure out what was wrong and the genuinely cared about my health. Every time the doctors would come into my room I hoped for good news, they would hold my hand and tell me it was going to be okay and I believed them. I remember the first time I walked, I was hooked up to the ventilator and I had my nurse and physical therapy helping me walk around the critical care unit. My mom followed taking pictures and videos of me to send to my family, she was doing this while sobbing. Who knew that it would take so much out of me just to walk a couple steps, my heart rate would shoot up to the 160s. Finally, as the days went on I was able to go to the rehab unit. When I went up there I was off the ventilator in 1 day, and was on only 2 L of oxygen. Things flipped a switch when I got to rehab, they told me that I would be in rehab for an estimated 30 days and I knew I wanted out of there faster. I was standing up on my own to go to the bathroom, I took my physical and occupational therapy very seriously, I wanted to go home. In rehab I struggled with getting all of my levels right in my body, I had blood transfusions, tons of vitamins pumped into my body, and I knew that I needed to pick up the pace. I wanted to eat real food. My entire time in the hospital I did not have an appetite, but the one thing I begged for was a Coke slushy. As soon as I was able to eat again it was the first thing my dad got me. Almost every time someone would come see me they would bring me one. Then when I got my chest tubes out that were draining the fluid from my lungs, I was up and moving more. I would get up and walk every hour. I would stand up, do little arm and leg exercises in my chair, I was getting so anxious to go home. When it came to using my speaking valve and capping the trachea so I was breathing on my own, my mom would wheel me around the hospital, she would take me outside, down to the cafeteria and across the catwalk. It was my favourite part of the day that might have been because the cookies in the cafeteria were to die for. Finally after 36 long days total I was able to go home. I went home on memorial day, 30 May, and I was so ready, I went home on several medications but I was grateful. My trachea was out and I could lift a two pound dumbbell. I was 25 pounds (11.3 kg) lighter and I was determined to get back to normal in no time. Before I got sick, I was running pretty frequently at school. I still think that is what saved my life, being active and in good health. I was told that I would not be able to run again until the end of August. I was not going to accept that, so every day I put in work, I would walk up and down the hallway, ride the exercise bike, and left my dumbbells at home. I was running again by mid-July. I felt great, my trachea was closed by the end of July and I was feeling very strong. In August, I did get surgery on the scar because it did not heal correctly. Finally, I got my last cat scan of my lungs and it came back normal. It looked as if there was no damage, like nothing even happened, the puss pockets were gone and they were fully opened up. I was thankful to have healed so quickly so I could go back to my normal life at college. Now today I am very grateful, grateful that I am fortunate enough to still be here. At first I would look at myself seeing my scar on my neck and think how sad of a time this was. Now I am just reminded of how precious life really is. This research is really important to educate more hospitals on Lemierre's syndrome could benefit lives of many. If anyone is capable of saving lives, it is this hospital because they have forever changed mine.

- ▶ Acute retroviral syndrome (HIV).
- ▶ Gonococcal or Chlamydial infection.
- ▶ *Fusobacterium* or other anaerobic bacterial infection.
- ▶ Group A streptococcus (*S. pyogenes*) and other beta haemolytic streptococci.

TREATMENT

Patient required treatment for septic shock and multiorgan failure secondary to *Fusobacterium*.

OUTCOME AND FOLLOW-UP

- ▶ Patient recovered after 31 days of hospitalisation and currently does not require ventilatory support or dialysis. Today she has returned to her studies at the university with significant comorbid complications.
- ▶ Patient was concerned about her allergy to penicillin and had testing showing no hypersensitivity. She has since taken a course of penicillin on one occasion without problems.

DISCUSSION

This case brings *Fusobacterium* species to light and highlights the importance of appropriate treatment of acute bacterial pharyngitis. It is written in the midst of several competing ideals. One is properly treating patients with Group A Streptococcal (*Streptococcus pyogenes*) pharyngitis to prevent rheumatic fever and the other is the importance of reducing inappropriate antimicrobial prescribing. However, it is important to keep *Fusobacterium* in the differential and treat it. Penicillin is the ideal antimicrobial since it has a narrow spectrum and would cover both *S. pyogenes* as well as anaerobes such as *Fusobacterium* species. However, when penicillin cannot be avoided, none of the second-line agents other than clindamycin would have sufficient anaerobic coverage alone.²

Group A streptococcal (*S. pyogenes*) pharyngitis treatment has prevented countless cases of rheumatic fever, and when given early can ameliorate symptoms. Making the correct aetiological diagnosis, however, can be quite difficult and there is emerging concern that bacterial pharyngitis of non-streptococcal origin can be caused by *Fusobacterium*. In fact, *Fusobacterium* may be more prevalent than *Streptococcus* as a cause of pharyngitis.^{1 3–5} When this occurs, complications like Lemierre's syndrome can cause significant morbidity when patients are given antibiotics that do not have anaerobic coverage.

Lemierre's syndrome is estimated to have a prevalence of approximately 14 million per year in youngsters aged 15–24 (according to a prospective Danish epidemiological survey of all *F. necrophorum* cases from 1998 to 2001, the majority of these cases having an oropharyngeal focus).⁶ It occurs when anaerobic bacteria (typically *Fusobacterium* species) spread from the oropharynx inferiorly through the fascial planes to the jugular veins, mediastinum and the lungs. Our patient developed septic thrombophlebitis of the internal jugular vein, which resulted in septic pulmonary emboli.

Fusobacterium commonly resides in the oropharynx of many individuals and is generally not thought of as a pathogen. However, European and British studies from 2005 to 2014^{3–5 7} estimated that *Fusobacterium* causes at least 9.5% of acute pharyngitis in the young adult age group. In fact, several British microbiology departments have called for the recognition of *Fusobacterium* as 'a true pathogen' and that it should 'not (be) dismissed as a coloniser of the oropharynx'.⁴ In 2015, the University of Alabama surveyed students aged 15–30 and detected *Fusobacterium* by PCR in 21% of 312 students presenting to the health clinic with symptomatic

sore throat and in 9% of 180 asymptomatic students. By comparison, they detected *S. pyogenes* in only 10% of the symptomatic patients and 1% of asymptomatic students.¹ Centor *et al* in 2015 concluded that '*F. necrophorum*-positive pharyngitis occurs more frequently than group A β -haemolytic streptococcal-positive pharyngitis in a student population, and *F. necrophorum*-positive pharyngitis clinically resembles streptococcal pharyngitis'.¹

Macrolides are not strong antianaerobe agents. In vitro sensitivity testing found that azithromycin was the most active of the macrolides against 15 different *Fusobacterium* species. However, the minimum inhibitory concentration 90 of azithromycin was 16 μ g/mL making it unsuitable for widespread use of the drug for an anaerobic infection.⁸ Since *Fusobacterium* can cause up to 20% of cases of pharyngitis in the university population and since uncontrolled infection can cause life-threatening disease, we feel that the use of macrolides and cephalosporins (which have little or no anaerobic activity) should be discouraged in acute bacterial pharyngitis,⁹ if the patient has risk factors for infection with *Fusobacterium* (eg, age 15–30) and presents with severe pharyngitis. If using one of these agents in a patient with penicillin allergy instead of clindamycin, then consider adding metronidazole.

Learning points

- ▶ *Streptococcus pyogenes* (Group A streptococcus) is not the only bacterial cause of pharyngitis. Anaerobic bacteria such as *Fusobacterium* species have been increasingly implicated in symptomatic pharyngitis in the young adult population at least as often as *S. pyogenes*. These infections usually are self-limited and resolve spontaneously, improving over 3–5 days. However, they can rarely lead to life threatening and serious complications such as Lemierre's syndrome. In fact, *Fusobacterium necrophorum* causes Lemierre's syndrome more often than *S. pyogenes* causes rheumatic syndrome.
- ▶ Penicillin should be used in the management of pharyngitis. Among second-line agents, clindamycin has anaerobic coverage. On the other hand, macrolides (such as azithromycin) have very limited antianaerobic activity and in situations where *Fusobacterium* is the origin of the pharyngitis, may not be effective. This leads to the possibility of disseminated anaerobic infection.
- ▶ For the purposes of acute bacterial pharyngitis, penicillin V is the first-line antimicrobial and can be dosed quite conveniently at only 500 mg twice daily for 10 days, as noted by the American College of Physicians (ACP) and has a narrower spectrum than amoxicillin.
- ▶ According to the ACP and US Centers for Disease Control 2016 guidelines, 'Routine testing for *F. necrophorum* is not recommended, but clinicians should remain vigilant and suspect Lemierre syndrome in adolescent and young adult patients with severe pharyngitis'.
- ▶ If a patient with severe acute bacterial pharyngitis is penicillin allergic and receives an oral cephalosporin or macrolide instead, we feel that it is important to consider adding an anaerobic agent such as metronidazole, as macrolides and oral cephalosporins do not have anaerobic coverage. In the words of Centor, 'physicians should avoid macrolides if they choose to treat streptococcus-negative pharyngitis empirically.' Especially in the age group 15–30 years, as *F. necrophorum* and Lemierre's syndrome predominantly occur in this age group.

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