

Pulmonary and thoracic infection by *Fusobacterium nucleatum*

Infeción pulmonar y torácica por *Fusobacterium nucleatum*

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What do we know about the subject matter of this study?

Pneumonias involving the pleura and posterior chest wall invasion, which may reach the skin forming a fistula, are very infrequent.

What does this study contribute to what is already known?

Fusobacterium nucleatum is an anaerobic bacterium that is part of the oral microbiota and dental plaque. It can be a source of local infections, such as caries, gingivitis, periodontitis, and, potentially, distant-site or extra-oral infections, so we present an illustrative case of this condition.

Abstract

Fusobacterium nucleatum is an anaerobic bacillus that is part of the oral microbiota and dental plaque. This can cause local and potentially remote infections, which are exceptional in pediatrics. **Objective:** To present the case of a patient with lung injury with chest wall invasion by *Fusobacterium nucleatum*. **Clinical Case:** An 11-year-old female immunocompetent patient who consulted due to a two-week history of cough, night sweats, without fever or weight loss, and increased volume at the left spleen thoracic level. There was no history of chest wall trauma or travel outside the country. Two weeks before the onset of symptoms, she was treated for dental caries. Imaging studies and CT scan showed left spleen pneumonia, which invades the pleura and the chest wall. A minimal thoracotomy was performed, releasing a thick, foul-smelling liquid. The studies for common germs and tuberculosis were negative. Hematology ruled out tumor lesions. The anaerobic study reported the development of *Fusobacterium nucleatum*. The patient was treated with penicillin followed by amoxicillin presenting good clinical and radiological responses. The dental procedure was suspected as the cause of infection. **Conclusions:** *Fusobacterium nucleatum* can occasionally cause remote or extra-oral infections in immunocompetent patients, such as pneumonia with chest wall invasion, therefore it is necessary to bear it in mind.

Keywords:

*Fusobacterium
Nucleatum*;
Fusobacterium Theory;
Pneumonia;
Empyema

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Introduction

Fusobacterium nucleatum is an anaerobic, Gram-negative, non-sporogenous bacterium. Its name is due to its elongated rod-like shape of different dimensions. It is part of the oropharyngeal, gastrointestinal, and genitourinary microbiota. In the oropharynx, it is important in forming bacterial plaque, where it plays comprehensive and beneficial roles in biofilms, contributing to both periodontal health and disease.

Depending on clinical circumstances, it can have pathogenic activity¹, thus, in periodontal lesions, such as gingivitis, periodontitis, or in dental procedures, it is identified as a possible source of bacteremia and invasive infections². In adult patients, there are reports of pleuropulmonary infections associated with dental problems when occurring bronchoaspiration associated with poor oral health³, and in clinical reports of different bacterial isolates including brain⁴ and hepatic abscess⁵, spondylodiscitis⁶, and endocarditis⁷.

In children, infections due to this microorganism are infrequent. There is a case of endobronchial lesion due to pulmonary infection by *Fusobacterium nucleatum* in a healthy child⁸; a study of 41 cases of necrotizing pneumonia which only one of them was due to *Fusobacterium nucleatum*⁹; and there is also a reference of osteomyelitis of the knee, all in previously healthy children⁹⁻¹¹, and osteomyelitis of the femur¹².

On the other hand, it has been associated with adverse pregnancy events such as chorioamnionitis and stillbirth^{13,20-22}; there is scientific interest in the digestive tract due to associations related to colorectal cancer¹⁴, although experimental investigations are still in progress¹. *Fusobacterium necrophorum* is another species considered pathogenic, which is associated with ear, nose and throat (ENT) infections that may be complicated due to septic thrombophlebitis of the jugular vein, and may present septic emboli in the lung, joints, muscles, soft tissues, liver, spleen, kidneys, and central nervous system¹⁵⁻¹⁸. It is also known as Lemierre's disease or necrobacillosis, which was highly mortal before the antibiotic era.

The objective of this report is to present a case of a pulmonary lesion with chest wall invasion by *Fusobacterium nucleatum*.

Clinical Case

Healthy 11 year and 9 months old schoolgirl, who consulted due to a two-week history of left dorsalgia, associated with cough, night sweats, no fever, no weight loss, and progressive increase in chest wall volume in the left dorsal region, at the T9 level. Chest X-ray (Figure 1) was suggestive of left basal pneumonia,

and chest CT scan (Figure 2) showed left pulmonary consolidation without signs of abscesses and periosteal reaction in the 9th, 10th, and 11th ribs adjacent to the process.

It was observed that the inflammatory involvement went beyond the pleura to the soft tissues of the left posterior chest wall, with increased fat density and thickening of the musculature due to edema. These findings suggested pneumonia due to an unusual germ. *Actinomyces* infection, tuberculosis, mycobacteria, or a neoplastic lesion was suspected.

The dental clinical record was reviewed, finding reports from the age of 8, with 9 procedures due to caries, mostly due to dentin, three extractions of primary teeth, and one extraction of a marginal periodontal abscess a year earlier. There was no report of gingivitis or periodontitis. Two weeks before the onset of symptoms, she was treated for dentin caries by a pediatric dentist. She had no history of chest trauma or travel outside the country.

The following laboratory tests were performed: blood count with normal WBC count and platelets, hemoglobin and hematocrit with mild hypochromic anemia, erythrocyte sedimentation rate and C-reactive protein moderately increased, liver tests, alpha-fetoprotein, and immunoglobulins within normal ranges.

A minimally invasive thoracotomy was performed at the level of the 7th left intercostal space; dissection by planes released a thick, viscous, yellowish, and foul-smelling content. Samples were taken for biopsy, culture for aerobes, anaerobes, smear microscopy, and culture for mycobacteria.

Current aerobic cultures were negative at the 7th and 15th day of incubation. Bacilloscopies were negative and Lowenstein-Jensen medium cultures were negative at 60 days. Mycobacteria cultures were negative at 40 days.

The anatomopathological record reported the presence of a fibro-adipose vascular tissue, with lymphocytic and macrophage inflammatory infiltration, with areas of necrosis and hemorrhagic infiltration. PAS was negative.

Samples of secretion in BACT/ALERT FN PLUS[®] blood culture bottles were sent to the Public Health Institute of Chile (ISP) for anaerobes culture, according to the protocol for the transfer of biological samples, resulting in *Fusobacterium nucleatum* development.

Complementary tests were performed to rule out dissemination to another parenchyma which were normal (abdominal and pelvic ultrasound). Delayed bone scintigraphy showed improvement of rib lesions and ruled out other lesions.

She was treated with intravenous sodium penicillin for 3 weeks, changing to oral therapy with amoxicillin,

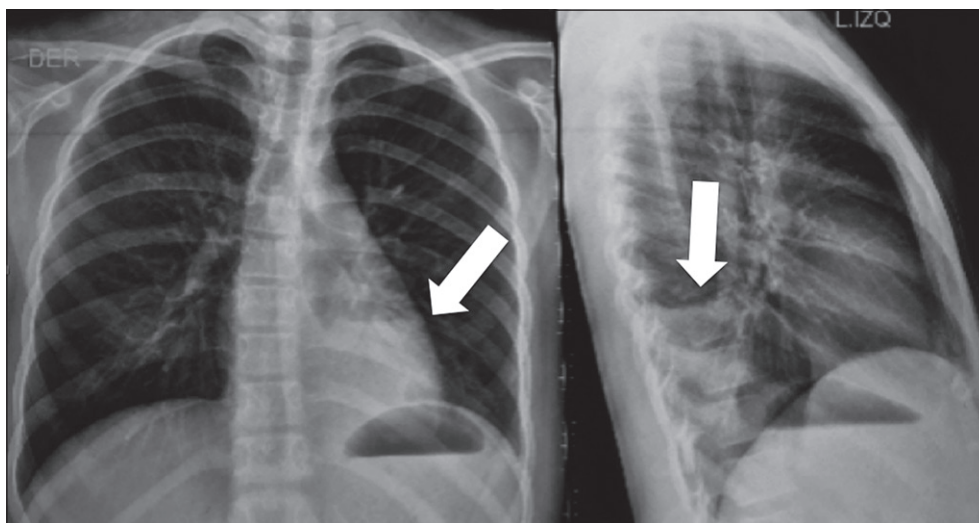


Figure 1. Chest X-ray shows image of pulmonary condensation in the left lower lobe (arrows)

completing 4 months of treatment, evolving favorably. In the last follow-up visit at 9 months post-treatment, the patient was asymptomatic, with complete resolution of pulmonary and thoracic lesions.

Discussion

The genus *Fusobacterium* are Gram-negative anaerobic bacilli, composed of numerous subspecies, among them *Fusobacterium nucleatum* and *Fusobacterium necrophorum*, which are the most identified as pathogens. *Fusobacterium necrophorum* is the main etiological agent of Lemierre's syndrome or necrobacillosis, which is a rare pathology due to oropharyngeal infection that can be complicated by internal or external jugular vein septic thrombophlebitis, usually in young people and previously healthy adults^{15,16}, although there are reports in younger children¹⁷. Septic emboli are one of the complications, where the lung is the most affected organ, and other locations such as joints, skin, bones, and meninges have been described¹⁸.

Fusobacterium nucleatum is part of the oropharyngeal, gastrointestinal, and genitourinary microbiota, and is the most frequently isolated species in the oral cavity, capable of coexisting with different microbial species and adhere to epithelial cells, playing an important role in the formation of bacterial plaque^{1,19}, and in diseases such as dental caries, gingivitis, periodontitis, which can be a source of extraoral infections². Adhesins and lipopolysaccharides of the cell membrane provide its adhesion capacity. The gene encoding the adhesin is FadA, which is also a virulence factor and is a potent stimulator of inflammatory cytokines, IL-6, IL-8, and TNF^{14,23}.

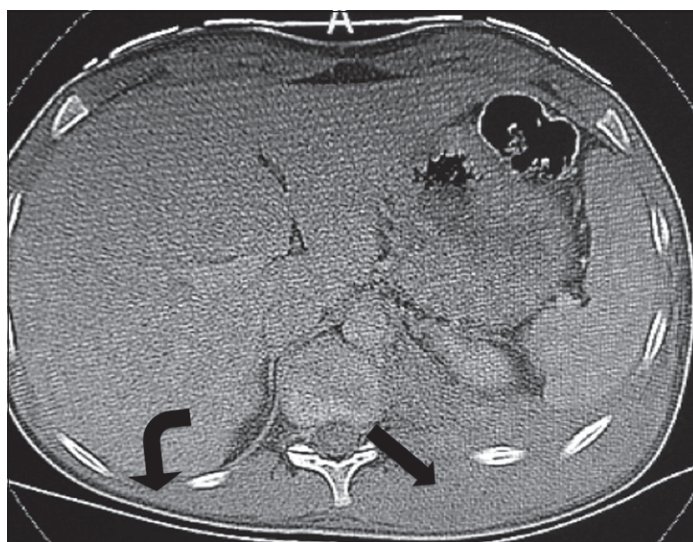


Figure 2. Computed tomography shows compromise of the left thoracolumbar wall, which is manifested as a significant increase in the volume of the soft tissues (arrow), the asymmetry is evident when compared with the right side (curved arrow)

Fusobacterium nucleatum has also been detected as a predominant species in amniotic fluid and fetal membrane associated with preterm delivery and in cord blood associated with neonatal sepsis. According to the results of preclinical studies in pregnant mice, it has been suggested that *Fusobacterium nucleatum* is transferred from the maternal oral cavity to the intra-uterine cavity through hematogenous transmission^{14,23}. Periodontal disease has therefore been associated as one of the risk factors for adverse pregnancy events such as chorioamnionitis, preeclampsia, prematurity, neonatal sepsis, and stillbirth²⁰⁻²².

Fusobacterium nucleatum has been associated with

gastrointestinal disorders; 10-100 times higher levels of FadA and *Fusobacterium nucleatum* have been reported in patients with adenomas and colorectal cancer compared with healthy controls. Therefore, FadA, which is a unique gene of this microorganism, would be a marker to identify individuals at risk of developing cancer²³. Other studies have observed that a high abundance of *Fusobacterium nucleatum* is associated with a worse patient prognosis and cancer recurrence because, in part, it may promote resistance to chemotherapy²⁴.

Infections by anaerobic microorganisms in pediatrics present low incidence but can be serious and mortal. They are associated in newborns with prolonged labor, premature rupture of membranes, maternal chorioamnionitis, prematurity, fetal distress, and necrotizing enterocolitis, and in older children with appendicitis, abdominal trauma with ruptured viscera, in soft tissues with skin abscesses of the buttocks, perirectal areas, vulvovaginal, head, and fingers. Predisposing conditions include chronic disorders such as neoplasms, hematologic diseases, immunodeficiencies, chronic kidney failure, and decubitus ulcers²⁵.

In a study of anaerobic infections over 18 months in children under 1 month and over 5 years of age, 3,898 positive cultures were obtained, of which only 2.9% developed anaerobic agents, mainly from cultures obtained from abdominal fluids, soft tissue, and blood cultures. The most frequent agents included Bacteroides (38.4%), Propionibacterium (15.8%), Clostridioides (14.4%) and *Fusobacterium* (4.8%)²⁶.

Clinical reports of pulmonary infections due to *Fusobacterium nucleatum* in the pediatric age group are rare. There is a report of a previously healthy child with pneumonia and endobronchial lesion⁸. In a French tertiary pediatric care hospital, during 5 years, 41 necrotizing pneumonias were treated, of which only one of them was due to *Fusobacterium nucleatum*, with good clinical evolution⁹. There are also reports of osteomyelitis of the knees in a 4-year-old child¹⁰, others in three children aged 6, 7, and 4 years with osteomyelitis and arthritis of the knees¹¹, and a case of osteomyelitis of the femoral epiphysis due to *Fusobacterium nucleatum*, which was initially suspected as a bone tumor¹².

A Canadian study of bacteremia incidence, which included 95% of all blood cultures collected from both inpatients and outpatients over 10 years, processed and centralized by a single laboratory, concluded that the overall annual incidence of *Fusobacterium bacteremia* was 0.55 per 100,000 population. *Fusobacterium nucleatum* cases had a median age of 53.5 years, while *Fusobacterium necrophorum* cases had a median age of 21 years.

In 72 cases of *Fusobacterium spp.* reported, 61% corresponded to *Fusobacterium nucleatum* and 25% to *Fusobacterium necrophorum*. The latter was identi-

fied in a younger population with no comorbidity or associated mortality, while *Fusobacterium nucleatum* patients were older with comorbidities such as cancer or on dialysis, with mortality of 10%²⁷.

Bacteremia due to *Fusobacterium nucleatum* has been observed in patients with hemato-oncological diseases such as lymphomas or leukemia, and the predisposing factors are severe neutropenia due to immunotherapy and oral mucositis²⁸.

Other diagnoses that can be considered in cases of pleuropulmonary and thoracic symptoms or empyema necessitans, once a tumor lesion has been ruled out, are infection by *Mycobacterium tuberculosis* or Actinomyces, which is identified in most cases^{29,30}. Other agents identified are aerobic agents such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas spp.*, and fungi such as *Aspergillus*. Foreign body aspiration, such as grass inflorescences, can cause complex pulmonary lesions³¹, and inhalation of fungal spores can cause pulmonary lesions such as histoplasmosis. In Chile, there are reports of infections by *Aspergillus* of young people who went hiking in the Ecuadorian jungle³², and a geologist who explored sub-way mines in Central America and Peru³³.

Regarding the treatment of our patient, it was decided to continue with penicillin, initiated at the hospital of origin, while awaiting the results of the bacteriological studies. Only the samples for isolation of anaerobic microorganisms sent to the ISP, according to the transfer protocol³⁴, reported development of *Fusobacterium nucleatum*. Another way to identify microorganisms that are difficult to culture is by broad-range PCR followed by 16S rDNA sequencing^{6,10,12,35}.

The patient evolved favorably, with no complications after surgical emptying and treatment with penicillin and later with amoxicillin. In infections by *Fusobacterium spp.*, there are reports that 95% are sensitive to penicillin, clindamycin, metronidazole, amoxicillin with clavulanic acid, and imipenem. Some strains produce beta-lactamase and are resistant to macrolide antibiotics. Prolonged treatment is recommended depending on the evolution and clinical response^{3,36}.

Regarding the possible odontogenic etiology, although the patient did not report infections such as gingivitis or periodontitis, numerous studies report that asymptomatic and transitory bacteremia occurs during dental procedures such as scaling, dental extractions, and periodontal surgery^{2,37}, and, in people with poor dental hygiene, common activities such as brushing teeth with bleeding or chewing can also be a risk factor³⁸. In healthy individuals, these transient bacteremias have no clinical significance and are eliminated, unlike in patients with affected immune system.

Our patient did not have immunological involvement. Only a dental procedure could be confirmed as

a possible source of thoracopulmonary infection, however, we have not yet clarified how this germ reached the respiratory tract, either via the oral or hematogenous route.

Conclusions

Fusobacterium nucleatum can occasionally cause distant-site or extra-oral infections in immunocompetent patients, such as pneumonia with chest wall invasion, so it is necessary to bear it in mind.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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References

- Brennan C, Garret W. *Fusobacterium nucleatum*-Symbiont, Opportunist and Oncobacterium Nat Rev Microbiol 2019;17(3):156-66.
- Maestre JR, Mateo M, Sánchez P. Bacteriemia secundaria a procedimientos odontológicos periodontales. Rev Esp Quimioter. 2008;21(3):153-6.
- Dolz R, Rubio M, Novella M. Empiema pleural causado por *Fusobacterium* spp. Rev Am Med Respir 2016;16(1):80-3.
- Stefániková L, Freibergarová M, Husa P, Kerkovsky M. Abscesos cerebrales múltiples de origen odontogénico causados por *Fusobacterium nucleatum*. Klin Mikrobiol Infekc Lek 2008;14(4):149-53.
- Jayasimhan D, Wu L, Huggan P. Fusobacterial liver abscess: a case report and literature review BMC Infect Dis 2017;17:440.
- Mediavilla-Santos L, Fernández-Mariño JR, Sánchez-Somolinos M, Herrera V, Díaz-Mauriño J, Marín M. Espondilodiscitis por *Fusobacterium nucleatum*: nueva forma de diagnóstico Acta Ortop Mex 2014;28(4):248-52.
- Varela L, Miguelena J, Cobo J, Romero J. Endocarditis por *Fusobacterium nucleatum* Rev Colomb Cardiol. 2017;24(5):539-40.
- Gedik AH, Cakir E, Soysal O, Umuto lu T. Endobronchial Lesion Due to Pulmonary *Fusobacterium nucleatum* Infection in a Child Pediatr Pulmonol 2014;49(3):63-5.
- Lemaitre CH, Angoulvant F, Gabor F, et al. Necrotizing pneumonia in children: report of 41 cases between 2006 and 2011 in a French tertiary care center Pediatr Infect Dis J 2013;32(10):1146-9.
- Jiménez M, López A, Morales C, Nieto A, Espinosa A. Desbridamiento Artroscópico de Osteomielitis de Rodilla por *Fusobacterium nucleatum* en Niño de 4 Años. Reporte de Caso con 8 Años de Seguimiento. Artroscopia 2020;27(2):64-8.
- Gregory S, Boyce T, Larson N, Patel R, Jackson MA. *Fusobacterium nucleatum* Osteomyelitis in 3 Previously Healthy Children: A Case Series and Review of the Literature. Pediatr Infect Dis J 2015;4(4):155-9.
- Budd E, Johnson D, Thomas E, Sadarangani M. Subacute osteomyelitis of the femur due to *Fusobacterium nucleatum* in a 7 year-old boy. Pediatr Infect Dis J 2015;34(3):324-6.
- Bohrer J, Kamemoto L, Almeida P, Ogasawara K. Acute Chorioamnionitis at term Caused by the Oral Pathogen *Fusobacterium nucleatum*. Hawaii J Med Public Health 2012;71(10):280 -1.
- Han YW. *Fusobacterium nucleatum*: a comensal turned pathogen. Curr Opin Microbiol 2015;0:141-7.
- Harper L, Pflug K, Raggio B, April D, Milburn J Clinical images: Lemierre syndrome: the forgotten disease? Ochner J 2016;16(1):7-9.
- Winter M, Saavedra A, Grau C, Caro J. Síndrome de Lemierre, reporte de un caso. Rev Otorrinolaringol Cir Cabeza Cuello 2013;73(2):164-8.
- Ibsaine O, Aitidir K, Berrah H, Arrada Z. El síndrome de Lemierre: Una patología resurgente. A propósito de una observación pediátrica. Rev Otorrinolaringol Cir Cabeza Cuello 2016;76(2):219-23.
- Andrade J, San Martín J, Grau C. Síndrome de Lemierre, secundario a otitis media aguda. Revisión a partir de un caso. Rev Otorrinolaringol Cir Cabeza Cuello 2013;73:263-7.
- Mujica C, Castillo M, Daille LK, Fuentevilla IA, Bittner M. Co-detección de Patógenos Periodontales en Pacientes Chilenos con Periodontitis Crónica. Rev Clin Periodoncia Implantol Rehabil Oral 2010;3(3):118-22.
- Han YW, Fardini Y, Chen C, et al. Term Stillbirth Caused by oral *Fusobacterium nucleatum*. Obstet Gynecol 2010;115(2Pt2):442-5.
- Ovalle A, Gamonal J, Martínez MA, et al.

- Relación entre enfermedad periodontal, infección bacteriana ascendente y patología placentaria con parto prematuro. Rev Med Chile 2009;137:504-14.
22. Jeewon So A, Gyamfi-Bannerman C, Han YW. *Fusobacterium nucleatum* and adverse pregnancy outcomes: epidemiological and mechanistic evidence. Anaerobe 2018;50:55-9.
 23. Zerón A, Porras D. *Fusobacterium nucleatum*: ¿Un patógeno periodontal promotor de carcinogénesis colorrectal? Revista ADM 2016;73(6):280-5.
 24. Yu T, Guo F, Yu Y, et al. *Fusobacterium nucleatum* promotes chemoresistance to colorectal cancer by modulating autophagy. Cell 2017;170(3):548-63.
 25. Brook I. Clinical review: Bacteremia caused by anaerobic bacteria in children Critical Care 2002;6(3):205-11.
 26. Thirmuoothi MC, Keen BM, Dajani AS. Anaerobic infections in children: a prospective study. J Clin Microbiol 1976;3:318-23.
 27. Afra K, Laupland K, Leal J, Lloyd T, Gregson D. Incidence, risk factors, and outcomes of *Fusobacterium* species bacteremia. BMC Infectious Diseases 2013;13:264.
 28. Candoni A, Fili C, Trevisan R, Sivestri F, Fanin R. *Fusobacterium nucleatum*: a rare cause of bacteremia in neutropenic patients with leukemia and lymphoma. Clin Microbiol Infect 2003;9(11):1112 -5.
 29. Hoffmeister C, Rios G, Contreras J, Jadue C, Joyas A. Actinomicosis torácica. Rev Chil Pediatr. 1989;60(3):173-8.
 30. Pereira N, Cuevas P, Valencia C, et al. Actinomicosis torácica como diagnóstico diferencial de neoplasia: a propósito de un caso. Rev Chil Infectol 2012;29(4):455-8.
 31. Celedón C, Ocaranza D, Vargas F, Zepeda G. Absceso por necesidad secundario a cuerpo extraño en la vía aérea. Rev Otorrinolaringol Cir Cabeza Cuello 2002;62:277-81.
 32. Wolff M. Brote de histoplasmosis aguda en viajeros chilenos a la selva ecuatoriana: un ejemplo de Medicina Geográfica. Rev Med Chile 1999;127:11.
 33. Cabello H, Manieu D, Noguiera M, Meneses M, Peralta M, Larraguibel C. Histoplasmosis Pulmonar Rev Chil Infectol 2002;19(1):54-9.
 34. Normativa técnica para el transporte de sustancias infecciosas a nivel nacional hacia el Instituto de salud Pública (ISP) 2008. www.ispch.cl.
 35. Poggi H, Guzmán AM, García P, Lagos M. PCR Universal o de amplio espectro: un aporte a la detección e identificación de bacterias y hongos en la práctica clínica. Rev Med Chile 2009;137(8):1122-5.
 36. Valle ML, Rodríguez M, Cobos A, de la Fuente J. Empiema causado por *Fusobacterium necrophorum*. Galicia Clin 2014;75(3):131-2.
 37. Heimdahl AG, Hall M, Hedber H, et al. Detection and Quantitation by Lysis-Filtration after Different Oral Surgical Procedures. J Clin Microbiol 1990;28(10):2205-9.
 38. Lockhart P, Brennan M, Thornhill M, et al. Poor Oral Hygiene as a Risk Factor for Infective Endocarditis-Related Bacteremia. JADA 2009;140:1238-44.