

Delayed-onset infections after impacted lower third molar extraction: involved bacteria and sensitivity profiles to commonly used antibiotics

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Objectives. The objectives of this study were to identify the bacteria involved in delayed-onset infections after lower third molar removal and to determine the most suitable antibiotic for such complication.

Study Design. Bacterial samples were collected from 13 patients who developed delayed-onset infections after lower third molar extraction. After the identification of the bacterial isolates, the in vitro antimicrobial susceptibility of the isolated strains was determined.

Results. A total of 11 patients (12 samples) were finally included in the study. Up to 7 bacteria genera were identified. *Fusobacterium* sp. was present in 11 patients, *Prevotella* sp. in 8 cases, and *Peptostreptococcus* sp. in 7. Some strains of these bacteria were not susceptible to amoxicillin, amoxicillin/clavulanate, and metronidazol, whereas no resistances were found to clindamycin.

Conclusions. *Fusobacterium* sp., *Prevotella* sp., and *Peptostreptococcus* sp. are frequently present in delayed-onset infections after lower third molar removal. Based on the results of the microbial susceptibility tests, clindamycin seems to be the most adequate antibiotic for the treatment of this complication. (Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114:43-48)

The treatment of postoperative wound infections after lower third molar extraction has been widely discussed in dental literature. Most articles focus on the prevention of such complications using systemic or local antibiotics.¹⁻⁴ Usually, authors recommend amoxicillin associated with clavulanate as the first line of treatment.^{5,6} Nevertheless, there are very few reports that study the involved bacteria, as well as their sensitivity to commonly used antibiotics.

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Delayed-onset infections are a rare postoperative complication with onset after suture removal (at least 7 days after the surgical procedure), which can be difficult to manage.^{7,8} In fact, one previous report stated that antibiotics are effective in only two-thirds of the patients who developed this particular postoperative complication.⁸ Indeed, to treat this infection, surgical debridement of the extraction site is often necessary, although some studies show that this rate is clearly inferior for conventional postoperative wound infections after lower third molar removal.^{8,9} Therefore, the lack of data on the microbiological features of lower third molar postoperative infections, as well as the need to explain this low success rate of antibiotics, justifies the need to perform a study with the following aims: to identify the bacteria involved in delayed-onset infections after lower third molar extractions and to determine which is the most suitable antibiotic to treat such complication.

MATERIAL AND METHODS

Bacterial samples of 13 consecutive patients who developed delayed-onset infections were collected. These patients had been submitted to an extraction of an impacted lower third molar in the Oral Surgery and Implantology Department of the School of Dentistry of the University of Barcelona, Spain. The main inclusion criterion was an inflammatory swelling of the operated area accompanied by the presence of suppuration that began at any time subsequent to suture removal, 1 week postoperatively. The patients also had to be considered healthy (classification ASA I or II). The exclusion criteria were the

following: patients who took any antibiotic or antiseptic drug before collection of the bacterial sample; patients who developed a surgical wound infection before suture removal; and patients who presented periodontitis or deep caries associated with the first and/or second adjacent molars that could lead to a misdiagnosis.

Surgical technique

All patients had one lower third molar removed under local anesthesia—generally with a 4% articaine solution containing epinephrine 1:100,000 (Artinibsa, Inibsa; Lliça de Vall, Spain). The surgical technique used was similar to that described in a previous report.⁷ After the operation, the patients were prescribed an antibiotic (usually amoxicillin 750 mg every 8 hours for 7 days [Clamoxyl 750; GlaxoSmithKline, Madrid, Spain], except in 1 patient with previous history of allergy to penicillin who was prescribed clindamycin 300 mg every 6 hours for 7 days [Dalacin 300; Pfizer, Madrid, Spain]), a nonsteroidal anti-inflammatory drug (usually sodium diclofenac 50 mg every 8 hours [Diclofenaco Llorens 50 mg; Llorens; Barcelona, Spain]), an analgesic (metamizol 575 mg every 6 hours for 3 to 4 days [Nolotil; Boehringer Ingelheim, Sant Cugat del Vallès, Spain]), and a mouthrinse (0.12% chlorhexidine digluconate every 12 hours for 15 days [Clo-rhexidina Lacer; Lacer; Barcelona, Spain]). Postoperative instructions and use of the prescribed drugs were explained orally and also were provided on a printed sheet of paper that was given to the patient.

Delayed-onset infection treatment

Bacterial samples were collected before performing any specific treatment for the delayed-onset infections. The sockets were initially irrigated with chlorhexidine digluconate in a 0.12% solution, and the patients were prescribed oral antibiotics (amoxicillin 875 mg plus clavulanate 125 mg every 8 hours) for 7 days. If this treatment did not resolve the infection, a second bacterial sample was collected and the area was exposed by means of a full-thickness flap. The granulation tissue and any bone particles or foreign material inside the extraction socket were removed. The socket was then irrigated with sterile saline, the flap was repositioned with 3-0 silk sutures (Silkam; Braun, Tuttlingen, Germany), and clindamycin 300 mg every 6 hours for 7 days was prescribed.

Data sampling

A single surgeon examined all patients. The following data were gathered: age, gender, operated side, smoking habit, history of pain or infection of the lower third molar, position of the lower third molar according to the Winter classification,¹⁰ distal space and depth of inclusion using the Pell & Gregory classification,¹¹ Nolla stage,¹² degree of retention, flap design, bone

removal, tooth sectioning, the time elapsed from removal of the lower third molar to onset of the infection, the antibiotics prescribed to treat the infection, and the need for an additional surgical procedure. Time and date of the sample collection, the number of aerobic and anaerobic colony-forming units (CFU), the identified bacteria, and the patient's sensitivity to different antibiotics (amoxicillin, amoxicillin/clavulanate, clindamycin and metronidazole) were also recorded.

Two samples were excluded from the study because of an inadequate shipping process (more than 24 hours).

Microbiology procedures

To collect the bacterial samples, a sterile endodontic paper point was inserted apically in the area where suppuration was present (usually in the distal aspect of the adjacent second molar) until resistance was encountered. It was left in place for 10 seconds and then inserted into a 2-mL snap-top tube with reduced transport fluid medium (RTF).¹³ Once collected, the samples were refrigerated until shipped to the microbiology laboratory (Department of Microbiology, Dentaïd, Cerdanyola del Vallès, Spain) for inoculation and incubation.

After vortexing for 45 seconds, the samples were 10-fold serially diluted in phosphate buffered saline (PBS; pH 7.2) and 100 µL of appropriated dilutions were plated in duplicate on nonselective Columbia agar (Difco, Detroit, MI, USA) with 5% horse blood supplemented with vitamin K1 (10 mg/L) and hemin (5 mg/L). The samples were also plated on Dentaïd-1 plates (Dentaïd, Cerdanyola del Valles, Spain) for selective isolation of *Actinobacillus actinomycetemcomitans*.¹⁴ Half of the blood agar plates were incubated in aerobic conditions for 3 days at 36°C and the other half in an anaerobic chamber for 14 days at 37°C with 80% N₂, 10% CO₂, and 10% H₂. Dentaïd-1 plates were incubated in air plus 5% CO₂ at 37°C for 5 days.

Subsequently, the total count of aerobic and anaerobic bacteria was made. The most common pathogens present in odontogenic infections were aisled and identified on the basis of their characteristic colony morphology; a Gram stain and an aerotolerance test were performed on each isolate. The anaerobic bacteria were identified using the Rap Id Ana II System (Remel, Oxford SA, Madrid, Spain) and *Streptococcus* were identified using the Rapid STR System (Remel). Pure isolates were kept on plates, or were preserved at -70°C for posterior minimal inhibitory concentration (MIC) determination.

Susceptibility testing

For the in vitro antimicrobial susceptibility testing, antibiotic powders were used (amoxicillin, amoxicillin/

potassium clavulanate [provided by GlaxoSmithKline, Madrid, Spain]; clindamycin [provided by MP Bio-medicals LLC, Illkirch, France], and metronidazole [provided by Sigma-Aldrich Quimica SA, Madrid, Spain]). Then, broth microdilution testing following the guidelines described by the National Committee for Clinical Laboratory Standards^{15,16} was performed.

The MICs of aerobic bacteria were determined by using cation-adjusted Mueller-Hinton broth supplemented with 1% horse serum at 36°C for 24 hours. Reference strains of *Enterococcus faecalis* ATCC29212 and *Escherichia coli* ATCC 25922 were used as controls in each test.

The MICs of anaerobic bacteria were determined by using brain heart infusion broth (Difco) supplemented with cystein (Merck, Darmstadt, Germany) 0.4 g/L, horse serum 1%, vitamin K₁ 1 µg/mL, hemin 5 µg/mL in an atmosphere of 10% CO₂, 10% H₂, and 70% N₂ at 37°C for 72 hours. Reference strains of *Bacteroides fragilis* ATCC 25285 and *Bacteroides thetaiotaomicron* ATCC 29741 were used as controls in each test.

The interpretation of the MIC values was made using the EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints.¹⁷

β-lactamase testing

Nitrocefin (Oxoid, SR0112) was rehydrated and the bacteria were tested emulsified into the nitrocefin drop onto a clean glass slide. The result was considered positive if the color changed from yellow to red. *Bacteroides fragilis* ATCC25285 was included as a positive control.

Statistical analysis

A descriptive analysis of the data was made with the Statistical Package for the Social Sciences (SPSS version 15.0; SPSS, Chicago, IL).

RESULTS

A total of 11 patients (12 samples) were finally included in the analysis. The mean age of the patients was 22.8 years and 7 were females. The mean time elapsed from extraction to the delayed-onset infection was 38.7 days (range 16-79 days). Table I shows the main clinical, radiological, and surgical features of the cases included in our sample.

Ten of the 11 patients were successfully treated with antibiotics. However, in case #9, the prescribed antimicrobials were not effective and the infection was finally solved after surgical debridement (Table I).

The isolated bacterial strains and the number of CFUs are shown in Table II. The most common were *Fusobacterium* sp. (present in 11 of the 12 samples); *Prevotella* sp. (isolated in 8 samples), and *Peptostreptococcus* sp. (present in 7 samples).

The MIC values and sensitivity profiles of the bac-

Table I. Clinical, radiographic, and surgical features of the patients

Case	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11
Age, y	21	17	31	29	16	16	29	16	29	28	19
Gender	M	F	M	M	F	F	F	F	F	M	F
Operated side	Left	Left	Left	Right	Left	Right	Right	Right	Left	Left	Right
Time from extraction – infection, d	28	28	45	54	41	25	21	71	79	18	16
Smoking, cigarettes/d	No	>20	>20	<20	No	<20	No	No	<20	<20	<20
Previous infection	No	No	Yes	No	No	Yes	No	Yes	Yes	No	No
Soft tissue coverage	Total	Total	Partial	Total	Total	Total	Total	Total	Total	Total	Total
Bone coverage	Partial	Total	Partial	Total	Partial	Partial	Partial	Total	Total	Partial	Partial
Pell & Gregory Classification	IIB	IIC	IIB	IIC	IIB	IIB	IIB	IIC	IIB	IIB	IIB
Winters Classification	Horiz.	Mes.	Horiz.	Horiz.	Mes.	Vert.	Horiz.	Horiz.	Mes.	Horiz.	Vert.
Nolla	9	6	10	10	7	8	10	9	10	10	8
Bone removal	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tooth sectioning	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Antibiotic prescribed after surgery	Amox	Amox	Amox	Amox	Amox	Amox	Amox	Amox	Amox	Clind	Amox
Antibiotic prescribed to treat infection	Amox + Clavu	Amox + Clavu	Amox + Clavu	Amox + Clavu	Amox + Clavu	Amox + Clavu	Amox + Clavu	Amox + Clavu	Amox + Clavu	Amox + Clavu	Amox + Clavu
Surgical debridement	No	No	No	No	No	No	No	No	Yes	No	No

Amox, amoxicillin; Clavu, clavulanate; Clind, clindamycin; F, female; Horiz., horizontal; M, male; Mes., mesioangular; Vert., vertical.

Table II. Aisled bacteria in each sample

Case	Age	Gender	CFU/mL aerobic	CFU/mL anaerobic	Isolated strains
#1	21	Male	1.7×10^5	5.5×10^5	<i>Veillonella</i> sp. <i>Prevotella intermedia</i> <i>Fusobacterium nucleatum</i>
#2	17	Female	2.1×10^6	2.4×10^7	<i>Fusobacterium varium</i> <i>Peptostreptococcus micros</i> <i>Fusobacterium</i> sp. <i>Prevotella intermedia</i>
#3	31	Male	4.0×10^6	1.3×10^7	<i>Peptostreptococcus prevotii</i> <i>Fusobacterium</i> sp. <i>Prevotella intermedia</i>
#4	29	Male	2.5×10^6	1.3×10^6	GPB aerobic <i>Fusobacterium</i> sp. <i>Prevotella corporis</i>
#5	16	Female	2.6×10^5	4.3×10^5	<i>Actinomyces israelii</i> <i>Fusobacterium nucleatum</i>
#6	16	Female	7.0×10^5	2.3×10^6	<i>Fusobacterium</i> sp. <i>Prevotella intermedia</i>
#7	29	Female	3.88×10^4	8.5×10^4	<i>Fusobacterium</i> sp. <i>Fusobacterium varium</i>
#8	16	Female	5.28×10^6	1.9×10^7	<i>Fusobacterium</i> sp. <i>Prevotella intermedia</i> <i>Peptostreptococcus micros</i>
#9	29	Female	1.37×10^4	1.8×10^4	GPB aerobic <i>Peptostreptococcus micros</i> <i>Fusobacterium</i> sp.
			7.7×10^5	5.0×10^6	<i>Peptostreptococcus micros</i> <i>Fusobacterium</i> sp. <i>Prevotella intermedia</i> <i>Bacteroides forsythus</i>
#10	28	Male	1.2×10^5	7.6×10^5	<i>Peptostreptococcus micros</i> <i>Prevotella intermedia</i>
#11	19	Female	7.2×10^3	1.9×10^4	<i>Peptostreptococcus micros</i> <i>Porphyromonas endodontalis</i> <i>Fusobacterium</i> sp.

Note that patient # 9 required surgery in addition to antibiotics to treat the infection, so 2 samples were collected in this case.

CFU, colony-forming units; GPB, gram-positive bacilli.

teria are shown in Table III. Clindamycin showed excellent results for all isolated strains, followed by metronidazole and amoxicillin/clavulanate. *Prevotella* sp. and *Fusobacterium* sp. showed particularly high resistance rates to amoxicillin alone.

DISCUSSION

To our knowledge, this is the first study to describe the microbiological characteristics of delayed-onset infections after lower third molar extractions. This is a rare complication with an estimated incidence of 1.5%, which explains the reduced number of patients in our series.⁷ Although the sample size may be considered small, the bacterial strains identified were quite similar in the great majority of patients.

Another limitation of our study is related to the fact that all patients were administered antibiotics after surgery. This could have selected the identified bacteria and also may have affected their sensitivity profiles. However, these amoxicillin-susceptible microorganisms are unlikely

to be the cause of delayed-onset infections. Moreover, the effect of postoperative antibiotics in this particular type of late-onset complications is questionable. On the one hand because most patients had finished taking amoxicillin at least 3 weeks before diagnosis (the mean time elapsed from extraction to infection was 39 days), and on the other hand, because the socket can be easily recontaminated with oral bacteria.

It is commonly accepted that anaerobic bacteria play a major role in the development of orofacial infections.¹⁸ Nevertheless, there are very few reports that actually try to identify the bacteria involved in surgical wound infections through microbiological sample collections. This information could be extremely useful to clinicians, as it allows a more adequate prescription of antibiotics, especially in delayed-onset infections after lower third molar removal where antibiotics do not have a high success rate, as shown in a recent report.⁸ Our sample had very similar clinical and radiological features when

Table III. MIC ranges and sensitivity profiles to amoxicillin, amoxicillin/clavulanic acid, clindamycin, and metronidazole of the most frequently identified bacteria genera

Antibiotic	Bacterial genera (n)	MIC range, µg/mL	S, %	I, %	R, %
Amoxicillin	<i>Prevotella</i> sp. (8)	2-32	0	12.5	87.5
	<i>Fusobacterium</i> sp. (13)	0.0625 to >32	69.2	0	30.8
	<i>Peptostreptococcus</i> sp. (7)	≤0.03125 to 0.25	100	0	0
Amoxicillin Clavulanate	<i>Prevotella</i> sp. (8)	1-32	75	12.5	12.5
	<i>Fusobacterium</i> sp. (13)	<0.03125 to 32	69.2	7.7	23.1
	<i>Peptostreptococcus</i> sp. (7)	<0.03125 to 0.5/0.0045 to 0.072	100	0	0
Clindamycin	<i>Prevotella</i> sp. (8)	<0.0625 to 0.25	100	0	0
	<i>Fusobacterium</i> sp. (13)	<0.0625 to 0.25	100	0	0
	<i>Peptostreptococcus</i> sp. (7)	<0.0625 to 1	100	0	0
Metronidazole	<i>Prevotella</i> sp. (8)	<0.0625 to 0.25	100	0	0
	<i>Fusobacterium</i> sp. (13)	<0.0625 to >64	93.3	0	7.7
	<i>Peptostreptococcus</i> sp. (7)	0.125 to >32	85.7	0	14.3

MIC, minimal inhibitory concentration; n, number of ailed strains; S, susceptible; I, intermediate; R, resistant.

compared with previous articles,^{7,8,19} so it might be expected that the microbiological profile is also comparable.

A mixed anaerobic-aerobic flora is frequently present in odontogenic infections.^{5,20} Among these bacteria, viridans group streptococci and staphylococci are usually predominant. In our study, these bacteria might have been eliminated owing to the administration of post-operative antibiotics and the use of chlorhexidine mouthrinses. Nevertheless, most authors attribute a causative role to other anaerobic bacteria, such as *Prevotella*, *Bacteroides*, *Fusobacterium*, or *Peptostreptococcus*.^{5,21,22} Our results entirely support this opinion, showing that *Fusobacterium* sp. (present in 11 of the 12 samples analyzed), *Prevotella* sp. (found in 8 samples), and *Peptostreptococcus* sp. (present in 7 patients) were common in our samples. In patient # 9, 2 samples were retrieved because the delayed-onset infection initially treated with amoxicillin/clavulanate relapsed after 21 days. This case is of particular interest, as part of the microbiological flora were probably eliminated with the first antibiotic prescribed (amoxicillin/clavulanate). In the second sample, *Fusobacterium* sp., *Prevotella* sp., and *Peptostreptococcus* sp. were still present, which reinforces the hypothesis that these microorganisms could be the cause of this complication. The major risk factors for delayed-onset infections after lower third molar removal are total soft tissue coverage and a mesioangular or vertical angulation of the third molar.¹⁹ Probably, these features allow a primary closure of the surgical wound, leaving a dead space beneath the mucosa, which makes oral hygiene measures (especially chlorhexidine mouthrinses) of that area ineffective. Furthermore, the used flap design detaches the periodontal insertions of the adjacent second molar, which allows the penetration of bacteria through the distal gingival sulcus of this tooth. All these aspects create an ideal environment for the development of anaerobic bacteria.

Regarding the susceptibility to the different antibac-

terial agents, our results showed that all strains of these 3 bacteria were susceptible to clindamycin. Kuriyama et al.²² tested 800 anaerobic isolates found in dentoalveolar infections and, like in our sample, found that clindamycin had very low MIC to the great majority of *Fusobacterium*, *Peptostreptococcus*, *Porphyromonas*, and *Prevotella* strains.

On the other hand, amoxicillin was shown to be an inadequate antibiotic for the treatment of these infections, as it presented extremely high MIC values to 2 of the isolated strains. This could be attributable to the high incidence of β-lactamase-producing bacteria from the genus *Prevotella* and *Fusobacterium*, as shown in several reports.²²⁻²⁴ A fact that supports this statement is that the sensitivity rates clearly improved with the addition of clavulanic acid. In fact, because of the sensitivity profiles of the odontogenic infections, some authors recommend the use of amoxicillin/clavulanate as the first line of treatment.^{5,25,26} In our sample, some strains of *Prevotella* sp. and of *Fusobacterium* sp. were not susceptible to this association. Nevertheless, this combination can be a good alternative to clindamycin. A previous clinical study claimed that amoxicillin/clavulanate and clindamycin had similar results in the treatment of delayed-onset infections, being effective in two-thirds of patients.⁸ Metronidazole can be considered a good option to treat postoperative infections especially when gram-negative anaerobic bacteria are involved. However, this antibacterial drug should be associated with another antibiotic, mainly because it has a reduced effect over gram-positive aerobic bacteria.²⁷

The microbial sensitivity test results of this article seem to support the clinical data published in 2008, where amoxicillin/clavulanate showed disappointing success rates, with 33% of patients needing surgical debridement of the extraction site.⁸ The microbiology outcomes of the present study seem to support the use of clindamycin in the treatment of delayed-onset infections after lower third molar extraction. A future study with a larger sample and without

the use of postoperative antibiotics would be of great value to confirm the present results.

CONCLUSIONS

Fusobacterium sp., *Prevotella* sp., and *Peptostreptococcus* sp. are frequently present in delayed-onset infections after lower third molar removal when postoperative amoxicillin has been administered. Based on the results of the microbial susceptibility tests, clindamycin seems to be the most adequate antibiotic for the treatment of this complication.

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