

# Dental Infections: Clinical and Microbiological Evaluation of Responsiveness to Twice Daily Amoxicillin-Clavulanic Acid (Amoxiclave)

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## Abstract

**Objective:** The aim of this study was to determine the types of bacteria causing dental infections in Duhok city, Iraq, and examine its response to twice daily Amoxicillin- Clavulanic acid (Amoxiclav).

**Methods:** The study was conducted in Duhok Dental Health Center from November 2007 to April 2008, and included 47 adult patients with the following dental infections: dry socket, pericoronitis, cellulitis, and periapical abscess. After taking smear or drainage for culture and sensitivity study, patients were prescribed Amoxiclave one gram twice daily for one week.

**Results:** After ten days, culture/ sensitivity studies were repeated. More than three quarter of the total isolates were made up by Streptococcus anginosus (31%), Actinomyces israeli (22%), Staphylococcus aureus (16%) and Bacteroides fragilis (8%); more than half of the isolates had mixed infections.

**Conclusions:** The overall cure rate was (87%); the cure rate was (94%) in acute infections and (86%) in chronic ones. It may be concluded that Amoxiclave, as prescribed here, is effective against most of the isolated dental microbes.

**Keywords:** Dental Infections, Amoxiclave, Polymicrobial Infections.

(J Med J 2010; Vol. 44 (3):305- 312)

Received

July 16, 2009

Accepted

October 25, 2009

## Introduction

Bacterial infections are one of the major problems in dental practice. The oral cavity normally harbors the most varied and vast flora in the entire human body.<sup>1</sup> Pathological conditions in oral cavity, such as pericoronitis and chronic periapical abscess, may create foci of infection that can affect other vital organs mainly the respiratory, renal and cardiovascular systems. Proper and early treatment of chronic oral infections will certainly reduce such complications.<sup>2</sup>

Most infections of the oral cavity, including major dental diseases like periapical abscess and pericoronitis are opportunistic in nature. Thus, microbiological tests can be of great value if interpreted accurately for proper clinical diagnosis as well as the choice of proper treatment.<sup>3,4</sup> This can reflect the fact that it may not be possible to develop uniform protocols for usage of antibiotics in the treatment of severe and chronic dental infections.<sup>5</sup>

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Diagnostic laboratories must be accessible to dentists and must have an active role in addressing the growing burden of antibiotic resistance in both hospitals and the community.<sup>6</sup> Antibiotics are widely needed in dental practice. In Spain, it has been estimated that 10% of all antibiotic prescriptions were related to dental infections.<sup>7</sup> Amoxicillin-Clavulanic acid taken three times daily in a dose of 500 mg has been shown to be effective in treating dental infections.<sup>8,9</sup> Little evidence is available about the effectiveness of the twice daily schedule at a dose of 1 gm.<sup>10,11</sup> The drug has recently been made available in Duhok by Al-Hikma Drug Company as Amoxiclave. The compliance to two daily dosage systems is higher; dentists are now frequently prescribing the drug empirically for almost every dental infection.

The main objectives of the study are to determine the types of bacteria causing dental infections in Duhok and to evaluate its clinical and bacteriological response to the twice daily dose of Amoxicillin-Clavulanic acid (Amoxiclave).

### **Patients and Methods**

The study was conducted at Duhok dental health center (Dental polyclinic) during a six month period from November 2007 to April 2008. This is the main referral dental clinic in Duhok governorate. The latter is one of the three governorates in Kurdistan region, Iraq, with a population of about one million.

A total of 50 patients and 25 controls were included in the study. The following types of dental infections: dry socket, pericoronitis, periapical abscess or cellulites.

On clinical grounds, Amoxicillin-Clavulanic capsules of 1 gm dose prescribed for all patients with a twice daily dose for one week. All patients were booked for another visit within 3-5 days of starting this treatment. The aim was to check their clinical response and to decide on further treatment, if any, depending on clinical and bacteriological results. Those who needed a change or the addition of another antimicrobial were excluded from the study. For the rest of the

patients, another culture and sensitivity was conducted 10 days after the beginning of therapy.

Al-Hikma Drug Company (Jordan) was the only provider of the 1gm Amoxicillin-Clavulanic acid (Amoxiclave-Al-Hikma) in Duhok during the period of the study. The company was approached and agreed to support the study. All patients who were given the 500 mg three times daily Amoxicillin-Clavulanic acid by the pharmacist, instead of the 1 gm twice daily form, were excluded from the study.

Acute cases were defined as infection with no previous episodes for dental infections compared to multiple ones in chronic cases. Controls are volunteers who were apparently healthy with no dental infection detected by clinical examination.

Pus was collected from the site of infection either by using disposable ready made swabs or by direct needle aspiration in abscess formation. All samples were collected in full aseptic technique with utmost care to avoid normal oral flora contamination. Specimens were transported and delivered in less than 30 minutes to Central Public Health laboratories which are located opposite to the dental polyclinic.

Promotion of fastidious microorganism was considered by full immersion of swabs in transport media (anaerobic ally sterile Carey and Blair semisolid media) or full expulsion of air in aspirated syringes. All specimens were then submitted for direct wet preparation examination, direct gram stain and culture. The latter was conducted on appropriate Blood agar, Mocconkey, Chocolate agar and fluid media (Thioglycollate and Brain heart infusion broth) and incubated under aerobic, strictly anaerobic and microaerophilic conditions at 37°C for 72 hours, some cases were incubated up to one week duration. The results were confirmed according to gram stain and culture assessment, Pathogens were isolated and identified using different biochemical and enzymatic techniques including API strips.

A swab was also taken from oral mucus membrane for all controls and was processed

microbiologically following exactly the same steps conducted on patients. All strains were tested for Amoxiclave (AMC) sensitivity using 30 µgm disc (Oxoid). Conventional Agar Diffusion antibiotic sensitivity assay, and Modified Kirby-Bauwer technique, was applied using Mueller hinton agar standard media.<sup>12</sup> The inhibition zone standards for Amoxiclave antimicrobial susceptibility were considered from tables for interpretive zone diameters of Clinical and Laboratory Standards Institute (CLSI'S).<sup>13</sup>

**Results**

A total of 47 patients have fulfilled the inclusion and exclusion criteria during the study period. Table (1) shows the age and gender distribution according to clinical presentation. Periapical abscess with cellulitis was the commonest clinical presentation in all ages representing a total of 35 out of the 47 cases. Dry socket and pericoronitis were found only in the age group 18-40 years, accounting for 4 and 8 cases, respectively. Female to male ratio was 1.6:1.

Table (2) shows that 62 isolates were isolated from 47 patients. The table also reveals that 60% of the cases were suffering from chronic infections and about half of the isolates before treatment were polymicrobial anaerobic infections, where two or three microorganisms acted synergistically to participate in the infection process. More than three quarter of the total isolates were made up of *Microaerophilic Streptococci* (37%), *Actinomyces israeli* (22%),

*Staphylococcus aureus* (16%) and *Bacteroides fragilis* (8%). *Peptostreptococcus* (6%) and *Enterococcus faecalis* 1 (2%). The least were *Fusiforms* and *Anaerobic Lactobacilli* (2%). These isolates were also the commonest bacterial encountered in mixed infections.

Table (3) illustrates patients' response to Amoxicillin-Clavulanic acid according to the type of infection, i.e., single or mixed. A total of 39 patients were included only, as 4 were excluded (sterile samples) in 3 of them and the mere isolation of *Candida albicans* in the other one, and another 4 patients did not attend for follow up culture. A cure rate of 85% was encountered in cases with single infection, while 62% and 31% of cases with mixed infection showed complete and partial cure, respectively. Table (3) also shows that the overall cure rate, complete and partial, was 87%.

The Figures 1, 2 and 3 illustrate the response of clinical cases to the drug.

Furthermore, table (4) shows that the cure rate in acute infections was 94% in comparison with 86% in chronic infections, with no significant difference between the two groups. Clinically, however, all of the 39 patients showed a satisfactory response to Amoxiclave.

Finally, table (5) reveals the cure rates encountered in each type of isolate. The commonest three isolated of *Microaerophilic Streptococci*, *Actinomyces Israeli* and *Staphylococcus aureus* showed cure rates of 94%, 67% and 100%, respectively.

**Table (1): Distribution of the study population according to age, gender and clinical presentation.**

Clinical presentation	Age / Gender									All ages		
	18-40 Years			41-60 years			> 60 years					
	M	F	T	M	F	T	M	F	T	M	F	T
Dry Socket	0	4	4	0	0	0	0	0	0	0	4	4
Pericoronitis	4	5	9	0	0	0	0	0	0	4	5	9
Periapical Abscess/Cellulitis	12	14	26	2	4	6	1	1	2	15	19	34
<b>Total</b>	16	23	39	2	4	6	1	1	2	19	28	47

**Table (2): Types of microbial isolates according to type of infection (single or mixed) and chronicity.**

<i>Type of Isolate</i>	<i>Single Infection</i>			<i>Mixed Infection</i>			<i>Total</i>		
	<i>Acute</i>	<i>Chronic</i>	<i>Total</i>	<i>Acute</i>	<i>Chronic</i>	<i>Total</i>	<i>Acute</i>	<i>Chronic</i>	<i>Total</i>
<i>Microaerophillic Streptococcus</i>	5	6	11	4	8	12	9	14	23(37%)
<i>Actinomyces israeli</i>	4	4	8	0	6	6	4	10	14(22%)
<i>Staph. aureus</i>	3	1	4	2	4	6	5	5	10(16%)
<i>Bacteroides fragilis</i>	1	1	2	2	1	3	3	2	5 (8%)
<i>Peptostreptococcus sp.</i>	0	1	1	1	2	3	1	3	4 (6%)
<i>Candida albicans*</i>	1	0	1	1	1	2	2	1	3 (5%)
<i>Enterococcus faecalis</i>	1	0	1	0	0	0	1	0	1 (2%)
<i>Anaerobic Lactobacilli</i>	0	0	0	0	1	1	0	1	1 (2%)
<i>Fusiform</i>	0	0	0	0	1	1	0	1	1 (2%)
<b>Total</b>	15	13	28	10	24	34	25	37	62
<b>(% out of grand total)</b>	24%	21%	45%	16%	39%	55%	40%	60%	100%

\* The occurrence of *Candida albicans* can be explained by contamination from the oral cavity, which is not considered to have any pathological effect on the development of infection. <sup>18</sup>

**Table (3): Cure rate among patients (n=39)\* according to type of infection, whether single or mixed.**

<i>Type</i>	<i>No. treated</i>	<i>No. cured</i>	<i>Cure rate %</i>
<i>Single infection</i>	26	22	85
<i>Mixed infection</i>	13	8 (complete) 4 (partial) 12 (total)	62 31 92
<i>Both types</i>	39	30 (complete) 4 (partial) 34 (total)	77% 10% 87%

\*Out of the involved 47 patients, four patients were excluded due to no growth in 3 of them and the mere isolation of *Candida albicans* in the other one, and 4 did not attend for follow up culture.

**Table (4): Cure rate according to chronicity infection.**

<i>Type of Cure</i>	<i>Acute infection</i>		<i>Chronic infection</i>		<i>Total</i>	
	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>
<i>Complete or partial</i>	16	94	19	86	35	90
<i>No response</i>	1	6	3	14	4	10
<i>All type</i>	17	100	22	100	39	100

$\chi^2$  N.S

Chi square test is not significant; patients responded in almost every way, whether they had acute or chronic infection. Clinically, all patients (100%) showed satisfactory response, as assessed by the treating dentist.

**Table (5): Cure rate according to microbial isolates.**

<i>Microbial isolate</i>	<i>No. treated</i>	<i>No. cured</i>	<i>Cure rate %</i>
<i>Microaerophillic Streptococci</i>	17	16	94
<i>Actinomyces israeli</i>	12	8	67
<i>Staph. aureus</i>	9	9	100
<i>Bacteroides fragilis</i>	5	3	60
<i>Peptostreptococcus magnus</i>	4	4	100
<i>Strept. viridans</i>	4	2	50
<i>Enterococcus faecalis</i>	1	1	100
<i>Anaerobic Lactobacilli</i>	1	1	100
<i>Fusiform</i>	1	0	0
<b>All</b>	54*	44	82

\*A total of 54 isolated from 39 cases.

**Figure (1),(2), (3): Periapical abscess, Pericoronitis and Dry socket cases before and 10 days after treatment with an oral dose of 1 gm twice daily of amoxicillin- clavulanic acid.**

**Before Treatment**

**After Treatment**



**Figure (1): Periapical abscess.**



**Figure (2): Pericoronitis.**



**Figure (3): Dry socket.**

**Discussion**

Microbiological evaluation is essential in the diagnosis, treatment and follow-up of patients with dental infections. There has been a wide reporting of under usage of diagnostic oral microbiology, even in developed countries.<sup>14</sup>

Aerobic and anaerobic species of oral microbial flora and the opportunistic bacteria isolated from

patients in this study are similar to those reported in other studies.<sup>15, 16</sup> Similarly, a review article on orofacial odontogenic infections indicated that polymicrobial microbial flora were common, predominantly involving strictly anaerobic gram positive cocci and gram negative rods, along with facultative and microaerophilic streptococci.<sup>17-19</sup>

Dental periodontitis presents a more complex etiological and therapeutic situation<sup>17</sup> especially

in cases with polymicrobial infections where certain species of microorganisms, especially Gram-positive facultatives, which have expanded representation, possess greater resistance to antimicrobial agents used during endodontic treatment than anaerobes.<sup>20</sup> This has shifted the focus of scientists to these microorganisms in recent years, in addition to another important factor which started to be evident during the last years is that these microbes can form biofilms consisting of a complex network of different microorganisms.<sup>21</sup> The interaction of *Peptostreptococcus* and *Microaerophilic Streptococci* are common as mixed infections, and as a group, these organisms are the most frequently recovered anaerobes in oral infections and they are often isolated from clinical specimens mixed with other anaerobic or aerobic bacteria.<sup>22, 31</sup> This interaction was noted in our study where almost half of *Microaerophilic Streptococci* were recovered as mixed infection with other pathogens like *Actinomyces Israeli*, *Staph. Aureus*, *Bacteroides fragilis* and *Peptostreptococcus*.

Also, the study showed that the majority of *Actinomyces Israeli* cases were presented as chronic cases with intra or extra oral multiple sinus discharge, this was similar to the report from USA.<sup>23</sup>

The study revealed a high cure rate of dental infections by using Amoxicillin-Clavulanic acid in an oral dose of 1gm given twice daily, which was similar to the results from a French study.<sup>24</sup>

The drug was also found to be effective in combating the anaerobic bacteria involved in dentoalveolar infections and periodontal diseases.<sup>25, 28, 29</sup>

The effectiveness against Actinomycosis cases, especially in chronic cases may be enhanced by longer duration of treatment. This, however, might increase the risk of oral Candidiasis.<sup>16, 31</sup>

The same was also found to be effective in treating other infections like pneumonia in adults with a clinical and bacteriological cure rate of 90.3% and 86.6%, respectively.<sup>26</sup>

The pharmacokinetics of this drug is to provide immediate release of Clavulanic acid and both immediate and sustained release of Amoxicillin to maintain serum concentrations of Amoxicillin that exceed the MIC for the target pathogen for an extended period of the dosing interval, leading to high rates of bacteriologic success against a wide range of pathogens.<sup>9, 27</sup>

Recent studies have also suggested the use of Amoxicillin-Clavulanic acid for prophylaxis of all infection risk associated with bacteraemia of oral origin, due to its boarder range of activity and its pharmacokinetic profile.<sup>11</sup> Moreover, a single oral daily dose of 2000/125 mg Amoxicillin-Clavulanic acid was found to be highly effective for the treatment of infections, including beta-lactamase producing organisms and strains with Amoxicillin MIC $\leq$  4 microgm.<sup>30</sup>

## Conclusion

Amoxiclav given in a dose of 1gm twice daily for one week to adult patients with serious dental infections was found to be effective against most isolated microbial pathogens, mainly to microaerophilic and anaerobic cocci which represented about three quarter of isolates among the groups of dental infections.

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## الإنتانات السننية: دراسة سريرية للمسببات ومدى استجابة الإنتانات متعددة الجراثيم لتناول دواء حامض الأموكسيسيلين كلافولانيك مرتين في اليوم

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### الملخص

كان هدف هذه الدراسة معرفة أنواع البكتيريا المسببة لإنتانات الاسنان في مدينة دهوك، العراق، وفحص استجابتها لأموكسيسيكلاف المعطى على شكل جرعتين يوميا. أجريت الدراسة في مركز دهوك الصحي للأسنان في الفترة من تشرين الاول 2007 الى نيسان 2008 وشملت الدراسة 47 مريضا بالغاً ممن لديهم الانواع التالية من الإنتانات: الحفرة الجافة، التهاب حول التاج، التهاب الخلايا، والخراج حول القمة. تم أخذ مسحات أو عينات من المرضى لغرض الزرع وفحص الحساسية، وذلك قبل اعطائهم غراماً واحداً من الأموكسيسيكلاف كل 12 ساعة لمدة اسبوع، وبعد 10 أيام تم اعادة الزرع وفحص الحساسية. ظهر أن أكثر من ثلاثة أرباع أنواع، (31%) *Streptococcus anginosus*، (22%) *Actinomyces Israeli* البكتيريا المعزولة هي، (16%) *Staphylococcus aureus*، *Bacteroides fragilis* (8%). كما كان أكثر من نصف العينات تمثل إنتانات مختلطة. وبلغ معدل الشفاء الكلي 87%؛ 94% في الحالات الحادة و86% في الحالات المزمنة. يمكن الاستنتاج أن الأموكسيسيكلاف كما أعطي هنا، فعال ضد أغلب إنتانات الأسنان.

الكلمات الدالة: الإنتانات السننية، الأموكسيسيكلاف، الإنتانات متعددة الجراثيم.