

Rapporteurs:

Chin Hoi Man Bonnie, Kwok Chee Yin, Lam Pok Man, and Tsang Nichol Chun Wai,
with George Pelekos

Affiliation:

Postgraduate programme in periodontology,
University of Hong Kong

study

Are periodontal pathogens no longer susceptible to antibiotic therapy?

Authors:

Karin Jepsen, Wolfgang Falk, Friederike Brune, Rolf Fimmers, Søren Jepsen, Isabelle Bekeredjian-Ding

Background

There is an increased worldwide concern about the use of antibiotics.

Dentistry accounts for 13.2% of all medical prescriptions of antibiotics in the USA and for 8.8% in Germany.

The adjunctive use of systemically administered antibiotics alongside non-surgical periodontal therapy has been shown to improve clinical outcomes, although its routine use has not been recommended because of known side-effects and the development of antimicrobial resistance.

Among the vast choices of antibiotics, the combination of amoxicillin and metronidazole has been recommended for periodontal patients and is generally used without any prior antibiotic susceptibility test. With emerging knowledge of periodontal medicine and the association between periodontal pathogens and several common systemic conditions – such as diabetes mellitus and cardiovascular diseases – the impact of antibiotic susceptibility for periodontal pathogens reaches beyond the scope of periodontics.

Aim

The aim of this study was to understand the change in microbiological composition and its susceptibility to different antibiotics over eight years.

Materials & methods

- An eight-year retrospective surveillance study on microbiological data of 7,804 patients diagnosed with advanced periodontitis from 163 German dental clinics from 2008 to 2015.
- Bacterial specimens were collected from up to five deep periodontal pockets of each patient diagnosed with moderate to advanced periodontitis, prior to treatment with a standardised protocol.
- Samples were then transported via Amies transport medium to the Centre for Oral & Dental Microbiology for microbiological culture and analyses.
- Bacterial culture was conducted for both aerobic and anaerobic bacteria by anaerobic recovery, and nucleic-acid amplification was performed to identify the presence, but not the quantity, of selected bacteria (*A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia*, *T. forsythia*, *F. nucleatum*, *C. rectus*, *Capnocytophaga*, *E. corrodens*).
- The prevalence of bacteria was calculated as the number of positive samples of each species within the population.
- The proportional representation for each species was expressed as the percentage of patients within the population from which the species was identified.
- Antimicrobial susceptibility was investigated using disc diffusion and occurrence of growth inhibition with antibiotics commonly used for periodontal infections, including amoxicillin, amoxicillin/clavulanic acid, metronidazole, doxycycline, clindamycin, azithromycin, ciprofloxacin, and ampicillin.
- Susceptibility was determined by the zone diameter breakpoints for resistance, defined according to different species.
- Linear logistic regression was used to analyse the temporal evolution of antimicrobial susceptibility.

Table: Prevalence of periodontitis patients (n = 7804) harbouring the targeted bacteria in Germany

Year	2008		2009		2010		2011		2012		2013		2014		2015		2008 – 2015	
	(%) of samples positive	%	1266	%	1065	%	1004	%	1038	%	905	%	747	%	933	%	846	%
<i>Aggregatibacter actinomycetemcomitans (Aa)</i>	26.1	331	18.7	199	22.4	225	20.8	216	19.6	177	18.9	141	20.9	195	22.7	192	21.5	1676
<i>Treponema denticola (Td)</i>	70.1	887	73.9	787	71.8	721	81.1	842	78.3	709	79.9	597	80.5	751	79.1	669	76.4	5963
<i>Porphyromonas gingivalis (Pg)</i>	69.3	877	66.6	709	67.9	682	67.1	697	67.8	614	67.1	501	71.5	667	68.1	576	68.2	5323
<i>Tannerella forsythia (Tf)</i>	84.5	1070	86.8	925	86.1	864	89.6	930	89.7	812	89.9	672	89.0	830	90.5	766	88.0	6869
<i>Prevotella intermedia (Pi)</i>	53.5	677	50.9	542	44.3	445	42.7	443	40.5	367	38.4	287	34.7	324	33.1	280	43.1	3365
<i>Campylobacter rectus (Cr)</i>	69.2	876	71.0	756	75.6	759	81.4	845	84.6	766	79.6	595	78.5	732	75.4	638	76.5	5967
<i>Fusobacterium nucleatum (Fn)</i>	99.3	1257	98.8	1052	78.2	785	97.9	1016	98.9	895	98.5	736	98.4	918	97.9	828	95.9	7487
<i>Peptostreptococcus micros (Pm)</i>	42.3	535	46.5	495	21.9	220	77.5	805	81.7	739	74.3	555	72.8	679	56.6	479	57.7	4507
<i>Eubacterium nodatum (En)</i>	12.6	159	10.8	115	37.0	372	37.6	390	47.8	433	38.7	289	36.2	338	32.5	275	30.4	2371
<i>Eikenella corrodens (Ec)</i>	82.4	1043	73.5	783	76.5	768	83.8	870	87.5	792	73.2	547	66.1	617	60.5	512	76.0	5932
<i>Capnocytophaga spp (Cap)</i>	66.3	839	54.5	580	75.2	755	82.8	859	84.0	760	84.3	630	81.8	763	78.8	667	75.0	5853

Results

- All periodontitis-associated species were present in the samples over the eight years, although varying prevalence and proportion was found throughout the population.
- Apart from *A. actinomycetemcomitans*, *P. intermedia*, and *E. nodatum*, all other tested species were identified in samples from more than half of the population.
- The most common bacteria was *F. nucleatum*, which was present in 95.9% of patients, followed by *T. forsythia* in 88.0% of patients, and *T. denticola* in 76.4% of patients.
- In terms of antibiotic susceptibility, isolates from 63.5% of patients were not susceptible to at least one of the antibiotics tested.
- *A. actinomycetemcomitans* showed resistance to metronidazole but not to the other antibiotics.
- *P. gingivalis* and *T. forsythia* showed a low resistance (mean 0.38% and 1.38% respectively) to amoxicillin.
- With the exception of *F. nucleatum*, all other periodontal pathogens tested were susceptible to amoxicillin/clavulanic acid throughout the surveillance period.
- An increasing proportion of patients with isolates resistant to at least one of the antibiotics tested was observed, rising from 37% in 2008 to 70% in 2015.
- A trend of decreasing susceptibility of *P. gingivalis*, *P. intermedia*, and *F. nucleatum* to ciprofloxacin, clindamycin, and azithromycin was shown ($p < 0.05$).
- On the other hand, a trend of increasing susceptibility of *F. nucleatum* to amoxicillin, ampicillin/sulbactam, and amoxicillin was observed ($p < 0.0001$).

Limitations

- Retrospective design with no history of other antibiotic usage or systemic conditions of the patients or other clinical information, which limits the interpretation of the prevalence of certain species in the subgingival microflora and their antibiotic susceptibility profile.
- The use of microbiological cultures instead of microbiome-sequencing technology limits findings to cultivable organisms.

Conclusions & impact

- Within the limitations of this study, a high prevalence of periodontitis-associated species was shown in German periodontitis patients, with individual variations in proportion.
- A trend of decreasing susceptibility of periodontal pathogens to antibiotics was observed over the years. However, susceptibility to amoxicillin and metronidazole remained unaffected.
- The trend of decreasing susceptibility of periodontal pathogens to antibiotics revealed in this study calls for an evaluation of the efficacy of adjunctive antibiotics regimens in periodontal therapy and the need for further prospective research on antibiotic resistance of periodontal pathogens in relation to clinical outcomes.

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