Chapter 3. Results

Overview

This chapter presents the findings for the key question in this evidence report concerning the added effectiveness of therapy adjunctive to scaling and root planing (SRP) in the treatment of chronic periodontitis over time. The key outcomes are reductions in probing depth (PD), gains in clinical attachment level (CAL), and secondarily, microbial changes, chiefly reductions in the percentage of spirochetes present in crevicular fluid or plaque samples.

We present results in separate sections according to the specific agents used adjunctively and to the mode of delivery (either systemic or local) and when more than just one or two articles addressed a particular agent or combination of agents. The agents we report on in separate sections include tetracycline, minocycline, metronidazole, the combination of metronidazole and amoxicillin, and chlorhexidine. We grouped studies of azithromycin, spiramycin, amoxicillin clavenate, and doxycycline, which did not have enough studies to treat separately, into a sixth section called other antibiotics. Finally, we present a seventh section for other kinds of antimicrobial agents such as povidone iodine, hydrogen peroxide, and fluorides. Chapter 7 has the full evidence tables for each main category of treatment; brief summary tables appear at the end of this chapter.

Description of the Evidence

We reviewed 599 published clinical trials for possible inclusion in this evidence report. The final number of unduplicated studies included was 70. We tried to include as many trials as possible; thus, we retained some that did not report actual data on the comparisons of interest but that did make statements about statistical tests of those comparisons. Numerous studies examined the effectiveness of more than a single antimicrobial agent; thus, we have dealt with more comparisons between treatment and control groups than studies *per se*.

In all, we included 16 different adjunctive antimicrobial agents in this review. They include tetracycline, minocycline, metronidazole, amoxicillin, chlorhexidine, spiramycin, doxycycline, sodium bicarbonate and hydrogen peroxide, stannous fluoride, amine fluoride, triclosan, povidone iodine, azithromycin, tetrapotassium peroxydiphosphate, amoxicillin and clavulanic acid, and ofloxacin. These agents were tested as either systemic or local interventions (or both) and involved a variety of modes of delivery – capsule, gel, rinse, irrigant, paste, fiber, chip, and strip.

All test and control teeth received SRP. SRP was delivered all at once (e.g., two visits within 24 hours), one quadrant at a time at intervals of 2 weeks, on only selected teeth or all teeth, by hand or by hand and ultrasonic scaler, and with or without anesthesia. The extent of SRP varied from study to study, but so far as we can tell it was performed the same way within the test and control groups in a given study.

Limitations of the Evidence

As we indicated earlier, all primary studies in this report were controlled trials of some kind, mostly described as randomized, and often described as double or fully blinded. Thus, they represent in some ways a very high level of investigational activity about the added effectiveness over time of adjunctive antimicrobial therapies relative to SRP alone. In addition, we have to the best of our ability eliminated studies that involved patients with conditions (e.g., diabetes, HIV) or risk factors or behaviors (e.g., smoking) that are known to affect the prognosis of chronic periodontitis or with forms of periodontitis diseases not described as chronic or adult (e.g., juvenile, early onset, refractory). In this way, we attempted to ensure that the disease being treated and the associated risk factors in the studies are similar. Nonetheless, the studies we included were quite different along many important dimensions, and that fact has made drawing solid conclusions particularly difficult.

For only five agents – tetracycline, minocycline, metronidazole, the combination of metronidazole and amoxicillin, and chlorhexidine – did more than two studies qualify for inclusion in the main analyses. Moreover, even these particular drugs were often used in different doses, incorporated into different treatment regimens, and delivered via different modalities. We observed particularly great variation in delivery mode for local drug applications: microspheres, chips, fibers, and strips, gels, rinses, irrigants, ointments, and pastes.

Study periods differed greatly from just a few weeks to several years. Often, investigators either did not report intermediate points or gave only partial results for those points. As the ultimate time points did not correspond across studies, neither did intermediate results.

Outcomes measured varied enormously across the studies. Some focused exclusively on microbiological measurements; others focused exclusively on clinical measures. In both situations we encountered many more measures than we could reasonably analyze, and even the studies we ultimately included did not report on all key outcomes. Among the clinical measures reported were gingival indices, plaque indices, periodontal disease indices, bleeding indices, measures of periodontal PD and CAL, and a variety of microbial counts.

As discussed in Chapters 1 and 2, we narrowed the focus of our report to the two clinical measures – PD and CAL – that we believed are of practical importance to clinicians and that studies tended to measure in reasonably similar ways. To reflect microbiological measures, we included the one that was apparently the most frequently reported: percentage of spirochetes. Even though these outcomes were nominally the same, the way they were measured varied across studies. For example, some measurements of attachment level used the cemento-enamel junction as the fixed reference point, whereas others employed some other marker. In addition, different kinds of probes were used. As the variable of interest is change over time (PD reduction; CAL gain), however, these particular variations would not necessarily pose critical analytic problems.

Subjects in the studies differed in important ways too. Some had received prior periodontal treatment, as they were recruited through periodontal patient registries. Because there was no indication that the same sites were being treated again for active disease and because the term refractory was not mentioned, we retained the articles on the assumption that these were new sites or routine maintenance of formerly active sites. By contrast, for other subjects the investigational treatment was explicitly stated as their first for periodontal disease. Rarely was

any demographic information reported on study samples beyond the mean age, or the age range, and sex of subjects. Often such information was for the entire sample and not for each treatment group.

Another variation in the measurements was when they were taken, e.g., before or after SRP. In some cases we could not determine the timing.

The greatest variation occurred in how investigators reported their results. Many studies in this review had not originally been intended to address the question that we wanted to answer, but they had findings seemingly relevant to the question. Many were investigations of whether some form of antimicrobial agent performed as well as SRP alone, and we would have excluded these articles. In some cases, these studies had a SRP-only treatment group and a treatment group that included SRP plus the antimicrobial; when we saw those study groups, we would include the article and then use only the data from those two groups in our analysis.

Investigators often reported testing the change in PD or CAL from baseline to the endpoint for treatment and control or comparison groups and whether those within-group differences were statistically significant. By contrast, they often did not report whether any *differences between the changes from baseline to the end of the study for these groups* was significant. Although sometimes investigators gave the data needed to do that statistical test, such as a mean and a measure of variance (either standard deviation or standard error), often they did not. This was especially a challenge for split-mouth designs, for which observations in groups are not independent and an estimate of the covariance is needed to estimate correctly the confidence intervals around the difference in changes for the two groups.

Determining whether teeth, sites around teeth, or persons were the unit of analysis was often difficult, as investigators may have included only one tooth per mouth, one tooth per quadrant in split-mouth designs, or multiple teeth. Often the criterion for inclusion in the study was the presence of multiple qualifying teeth (by virtue of PD or bleeding, for instance) and all were included, but sometimes the number of teeth included for study was fewer than "all" or indeed only one. With respect to initial or baseline PD, inclusion requirements in these trials differed (e.g., from greater than 4 mm to greater than or equal to 7 mm), thereby presenting different clinical entities for study. It was also difficult, if not impossible, to distinguish when investigators calculated means across all the teeth or across means of multiple teeth in a single mouth, thereby making the group mean a mean of means across people rather than a mean across teeth.

Some investigators reported results only by depth of initial pocket rather for the entire group of subjects. This posed a problem for this review because the grouping of initial pockets often differed from study to study. Usually not enough information was provided to enable us either to aggregate or to split the data to make them more comparable to other studies.

In the presence of a variety of terms used to describe what we reasonably could consider to represent the equivalent of SRP – subgingival scaling and mechanical debridement – rarely could we find enough detail on the extensiveness or thoroughness of the procedure to assess comparability across studies. Some investigators noted the number of sessions and their spacing, average total time spent per subject, time spent per tooth, or time spent per quadrant performing the SRP. Only occasionally did researchers note whether they had used hand instruments, ultrasonic scalers, or both. Some articles mentioned use of an anesthetic in the SRP, but this was

not routine. Studies differed in whether the entire mouth received SRP, or only study teeth, or a particular jaw or quadrant. Terms such as "thorough," "meticulous," "rigorous," and "careful" were only rarely used to describe the SRP. Yet another source of variation may have been the use of dental hygienists in some studies but not others, although we did not document this variable in evidence tables. Overall, if we detected, within a given study, that the SRP differed between the treatment group and our designated control group, we excluded it.

Some studies reported attrition from the original study groups; some gave the number of subjects finishing the trial. In general, then, few research teams presented an intent-to-treat analysis. As one would expect, the longer the study period, the greater the loss to follow-up, and we were not always certain of the comparability of final treatment and control/comparison groups. In presenting numbers of subjects in this chapter, we use counts of completers insofar as possible.

Finally, sorting publications to eliminate duplicate studies (so as not to give multiple studies using the same data extra weight in the evidence pool) was difficult for several reasons. Authors often did not clearly acknowledge earlier or less complete versions in their later or more complete studies. We found several cases of articles published with early data that were published later in the completed study. Also, in some cases of multi-site studies, sites published their own results separately or conducted later follow-ups with their patients. For evidence tables, where one "row" constitutes a study, we combine data and give the multiple citations unless those citations give precisely the same information, in which case we cited the more recent or the more comprehensive publication. In the text, we cite the publication in which the data in question actually appeared.

Organization of this Chapter

The remainder of this chapter takes up the major anti-infectives – tetracycline, minocycline, metronidazole, metronidazole with amoxicillin, and chlorhexidine – and then the two groups of other antibiotics and other microbials. We present first our narrative synthesis of the evidence, accompanied by summary tables (at the end of the chapter) giving PD and CAL data. The qualitative results describe the studies, present PD and CAL data, and give spirochete data when available; we also present additional results for studies that may not have measured PD or CAL in typical ways but do provide insights into the likely effect of drugs adjunctive to SRP. The descriptive analysis focuses on results for the full length of every included study, which ranged from a few weeks to several years.

We conducted meta-analyses when more than two similar studies involved the same antimicrobial and mode of delivery. They focused on the two clinical measures (PD reductions and CAL gains) and were limited to studies with results reported at or around 6 months (plus or minus 3 months) after the initiation of the treatment. Meta-analytic results follow the qualitative discussions within the drug-specific sections. They are presented in Forrest plots (figures at the end of this chapter), which report the mean effect and its 95 percent confidence interval (CI) for each study in the meta-analysis and an overall mean effect and its 95 percent CI calculated across all of the studies. We explain included and excluded studies and, when possible, put those results in a broader context of the confidence intervals and the impact of SRP alone.

Tetracycline

Systemic Tetracycline

Qualitative and Descriptive Results

Five clinical trials appearing between 1978 and 2001 of systemic tetracycline, a broad-spectrum antibiotic of long standing that is effective against a wide array of bacteria, met the inclusion criteria (Table 5 and Evidence Table 1a). Four trials were randomized;[43-46] the most recently reported trial was not.[47] Taken together, the studies comprised 190 subjects who completed the studies, 81 on tetracycline regimens with SRP and 109 receiving SRP alone or with placebo. Subjects in the trials differed in periodontal disease experience. Three studies included subjects with advanced or severe periodontitis, one included "relatively young individuals" with severe disease,[43] and the fifth included only subjects who had demonstrated active disease with attachment loss equal to or greater than 2.5 mm at one or more sites in a pretrial monitoring period.[46]

The studies differed in the selection of sites used to characterize a subject's response to therapy. One study included only two sites per subject, both interproximal sites with PDs of 7 mm or more.[45] A second study based analyses on patients with at least three pairs of contralateral teeth with PDs of 5 mm or greater.[43] A third study included six measurement sites for all teeth present except third molars;[46] a fourth included two teeth per subject with 6 mm or greater PDs;[44] and the fifth study did not report the basis for the selection of sites.[47]

SRP procedures differed across these studies. In one trial, the investigators used modified Widman flap surgery for all sites determined to be active in the pre-intervention period and for all sites with PDs of 4 mm or greater;[46] SRP was repeated at 3, 6, and 9 months. Another study provided repeated SRP during the observation period at 15 and 22 weeks.[43] In the other studies, SRP was provided once, at baseline, and no other details were noted.

The experimental regimen varied across the five trials. The standard dose was 250 mg, with a frequency of either three or four times per day for different treatment periods lasting 14 days,[45] 21 days,[47] and 30 days.[46] One regimen repeated an initial 14-day dosing pattern at the beginning of the sixth week;[43] a fifth approach continued past 14 days to the end of the study (day 350) with a single 250 mg dose per day.[44] Finally, the trials varied in longest follow-up period: 24 weeks to 52 weeks. Three trials reported results from interim periods.

For four studies reporting overall PD measurements, experimental subjects had 0.8 mm,[44] 0.3 mm,[47] 0.29 mm,[46] and 0.2 mm[43] greater mean reductions in the experimental group; of these, three were not significant and one[44] was not tested. A fifth study reported PD reduction by original PD values, and the largest PD reduction was 0.19 (not significant) for those with initial PDs of 7 mm or greater.[45] No interim measures differed significantly between experimental and control groups.

Five studies examined CAL gains, but only three reported data on CAL gains. One trial found a 0.31 mm net gain at 52 weeks ($P < 0.001$) for the experimental group.[47] In the other two trials reporting CAL values, one noted a 0.3 mm net improvement[44] and the other reported gains from 0.04 mm to 0.49 mm (depending on initial PD value), but all were not significant.[45] No interim measure for these studies was reported as being significantly different between groups.

Of the two studies that did not report data, one did state that difference in CAL gain between the groups was not significant.[46]

Three trials analyzed the proportion of spirochetes in the oral microflora. One trial found that significant differences favoring the experimental group at 2 and 8 weeks had disappeared by week 24.[45] Another team reported a larger proportional change in the experimental group (48 percent to 0 percent) than in the control group (37 percent to 8 percent), but they did not test the difference statistically.[44] A third study found similar overall change in both groups (34.8 percent or 36.3 percent to 6.3 percent or 6.5 percent), with the experimental groups showing a larger decline to 0 percent (not tested) at an interim examination.[43] Finally, one trial examined oral microflora but did not separate results for the tetracycline groups from results for another experimental group assessing amoxicillin clavenate.[46] The percentage of sites colonized with several putative pathogens decreased significantly for both group combined.

Quantitative Analysis of Systemic Tetracycline Effects

Probing Depth. Of the five studies reporting on PD reduction reviewed above, we included three in the meta-analysis of PD effect size (Figure 3).[43-45] Both excluded studies had study periods greater than 9 months.[46,47]

The estimate of overall effect size for PD is 0.15 mm (95 percent CI, -0.29 mm to 0.58 mm). Effect sizes of the two studies favoring use of adjunctive local tetracycline range from 0.20 to 0.90. The third study demonstrated a greater reduction in PD for SRP alone (-0.05 mm).[45] Based on their 95 percent CIs, none of these PD effect sizes differed significantly from zero. Because of its appreciably smaller standard error of the difference and larger sample size, the Al-Joburi et al. study contributed more weight to the meta-analysis results.[45] Given the mixed direction of the differences and small study samples, the nonsignificant overall effect size in this meta-analysis is not surprising.

Clinical Attachment Level. Only two of the four studies examining gain in CAL reviewed above had data and ran for the appropriate length of time.[44,45] As explained earlier, we thus did no meta-analysis for CAL gain resulting from adjunctive use of systemic tetracycline.

Local Tetracycline

Qualitative and Descriptive Results

Sixteen clinical trials, published between 1985 and 2002, met the inclusion criteria (Table 6 and Evidence Table 1b). All but three used randomized designs. In 10 studies, the examiner(s) were not aware of treatment assignment, and in 13, placebos were not used. Most of the trials assessed the effects of the intervention on sites with at least 5 mm PDs; four studies either included patients with shallower PDs (as small as 3 mm)[33,48,49] or did not report site selection criteria.[50] Three studies assessed only sites with class II furcation involvements.[35,51,52] One study required demonstration of active disease immediately before inclusion.[53]

Five trials reported site-based analyses,[31,52,54-56] one used teeth, and the rest used the subject as the unit of analysis, with one tooth or site per quadrant per subject being most commonly assessed.

The extensiveness and methods used for the SRP varied, ranging from ultrasonic scaling during one visit to multiple visits over 4 to 7 hours for hand scaling. Tetracycline intervention vehicles included fibers, irrigation, collagen film, ointment, gel, and strips. In one study arm, tetracycline was combined with citric acid;[33] in all others, tetracycline was used alone. In one irrigation study, tetracycline was administered every 2 weeks for 22 weeks.[31] Effects were assessed over durations as short as 4 weeks and as long as 52 weeks. All but one of the studies that reported statistically significant differences had used tetracycline fibers.

Of these 16 studies, 12 reported PD data sufficient to determine the net reduction (i.e., the difference between the experimental and control groups' baseline to follow-up differences). Of these 12 studies, four found statistically significantly greater PD reductions associated with the experimental group. The differences were 0.93 mm at 12 weeks (combined with citric acid gel, $P < 0.05$),[33] 0.73 mm at 6 months ($P < 0.01$),[57] 0.67 mm at 26 weeks ($P = 0.008$),[53] and 0.41 mm at 7 weeks ($P = 0.047$).[56] In eight studies in which differences were either not tested or not significant, reductions in the experimental group were greater than those in the control group; some of these were of a magnitude similar to the statistically significant differences: 1.04 mm;[50] 0.7 mm;[52] 0.6 mm;[34] 0.4 mm and 0.5 mm with irrigation and fibers, respectively;[55] 0.43 mm and 0.87 mm with one and multiple strips, respectively;[58] 0.4 mm;[31] 0.4 mm;[35] and 0.27 mm without citric acid.[33] One study found a nonsignificant 0.43 mm difference favoring the control group.[59] The four remaining studies reported nonsignificant differences but did not give the magnitude or direction of those differences.[48,49,51,54] Interim results also showed statistically significant greater reduction in PD associated with the experimental arm in two studies.[35,53] In one of these,[35] the significant difference was not maintained at the final assessment.

Sixteen studies reported results of some kind for CAL gain, some for two different patient groups or treatments. Of these, two reported significantly greater CAL gains associated with local tetracycline treatment compared to SRP alone: 0.48 mm at 26 weeks ($P < 0.05$)[57] and 0.15 mm at 26 weeks ($P < 0.05$).[53] Nine studies reported nonsignificant or untested differences favoring the experimental group: 1.8 mm,[50] 1.0 mm,[34] 0.73 mm (with citric acid),[33] 0.44 mm and 0.48 mm for a single and multiple strips, respectively,[58] 0.34 mm and 0.33 for groups with initial PD values of greater than 3 mm and greater than 6 mm, respectively,[48] 0.3 mm,[31] 0.2 mm,[56] and 0.14 mm (gel).[33] Three studies reported nonsignificant differences favoring the control group: 0.23 mm,[59] 0.2 mm for tetracycline irrigation,[55] and 0.1 mm.[35] Finally, three studies reported nonsignificant differences but did not report the magnitude or direction of those differences.[49,51,60] No reported interim results were significantly different between the experimental and control groups.

Finally, five studies examined microbiological outcomes,[31,33,49,52,54] but none reported significant differences in these outcomes at final assessments. An interim (3-month) assessment in one study found a significantly greater reduction in the proportion of *P. gingivalis* in the experimental group.[49]

In general, the studies that reported side effects noted some irritation associated with the application of the experimental therapy and, less frequently, candidiasis. These conditions resolved when therapy ended.

Quantitative Analysis of Local Tetracycline Effects

Probing Depth. Of the 16 studies reporting on PD reduction reviewed above, we included six in the meta-analysis of PD effect size (Figure 4).[31,33,34,53,57,59] One study included two different adjunctive local tetracycline treatments – one without and the other with citric acid added to the tetracycline[33] – so the meta-analysis had seven entries. Of the 10 studies excluded, five had study periods of less than 3 months,[50,52,54-56] and four provided no data from which to calculate effect size measures or variances.[48,49,51,58] We excluded the final study because a test for heterogeneity showed that it was at too great variance with the other studies, suggesting that it represented a different intervention.[35]

The estimate of overall effect size for PD is 0.47 mm (95 percent CI, 0.22 mm to 0.72 mm). Effect sizes of included studies favoring use of adjunctive local tetracycline range from 0.27 to 0.93. All but one of the study effect sizes represented results that demonstrate greater PD reduction using adjunctive local tetracycline with SRP than using SRP alone. One study demonstrated a greater reduction in PD for SRP alone (-0.43).[59] Based on the 95 percent CIs, the PD effect sizes of only two studies differed significantly from zero.[33,57] Two studies with appreciably smaller[57] or larger[31] standard errors of difference between means contributed relatively more and less weight, respectively, to the meta-analysis results.

The statistically significant PD result supports the added effectiveness of locally applied tetracycline as an adjunct to SRP in the treatment of chronic periodontitis in adults. It does not address, however, whether a mean change of 0.47 mm is clinically meaningful. In contrast to this less than half a millimeter difference between using and not using some form of local tetracycline as an adjunct to SRP, the effects of SRP alone on reduction in PD in these studies ranged from 0.71 mm to 2.30 mm for the same periods of time.

Clinical Attachment Level. Of the 16 studies examining gain in CAL reviewed above, we were able to include nine in this meta-analysis (Figure 5).[31,33-35,48,53,57-59] Two studies included two different adjunctive local tetracycline treatments: citric acid in one gel group and none in the other,[33] and single and multiple tetracycline strips.[58] Thus, the final meta-analysis had 11 entries. Among the seven excluded studies, five had study periods of less than 3 months,[50,52,54-56] and two had no way for us to calculate CAL effect size measures or variances.[49,51]

The estimate of overall effect size for CAL is 0.24 mm (95 percent CI, 0.07 mm to 0.42 mm). Effect sizes of included studies favoring use of adjunctive local tetracycline ranged from 0.01 mm to 1.00 mm. All but two of the study effect sizes represented greater CAL gain using adjunctive local tetracycline with SRP than using SRP alone. Of these two, one demonstrated a greater reduction in CAL for SRP alone (-0.23 mm),[59] and one favored neither study group.[35]

Based on the estimated 95 percent CIs, only two studies had CAL effect sizes that differed significantly from zero.[33,34] One study had an appreciably smaller[35] standard error of difference between means and another had a standard error that was appreciably larger[31] than the others, so they contributed considerably more or less weight, respectively, to the meta-analysis results.

The statistically significant CAL result supports the added effectiveness of locally applied tetracycline as an adjunct to SRP in the treatment of chronic periodontitis in adults, but whether a mean gain of 0.24 mm is clinically meaningful remains unclear. In contrast to this 0.24 mm

difference, the effects of SRP alone on gain in CAL in these studies ranged from -0.13 mm to 1.61 mm for the same periods of time.

Minocycline

Systemic Minocycline

Qualitative and Descriptive Results. Two studies of systemic minocycline met inclusion criteria (Table 7 and Evidence Table 2a).[61,62] The 1982 trial by Ciancio et al. was a randomized, placebo-controlled, double-blinded trial,[61] whereas the 1996 Atilla et al. study did not report study blinding but noted that it was neither placebo controlled nor randomized. These were small trials of patients with moderate to severe periodontitis, comprising in all 47 subjects who completed the trials, 23 on minocycline regimens with SRP and 24 with SRP only. The studies differed in numerous ways: dosage and duration of minocycline (200 mg a day for 7 days[61] versus 100 mg a day for 4 days[62]); focus on probing depth (4 mm to 5 mm versus 6 mm or higher[62]); nature and periodicity of SRP; and outcomes assessed (the only overlap being PD).

With respect to PD levels, Ciancio et al. assessed outcomes at baseline and at 7, 14, 35, 49, and 70 days but only reported "no significant changes in any study group during the experimental period."[61] The Atilla et al. study reported PD differences according to the initial PD.[62] Among subjects with initial PD of 4 mm to 5 mm, those receiving systemic minocycline experienced 0.06 mm *less* reduction than those receiving SRP only (not significant). By contrast, among patients with initial PD of 6 mm or greater, those receiving adjunctive minocycline experienced 0.49 mm greater reduction than controls (not significant); nonetheless, the authors commented that systemic minocycline might be a useful adjunct to nonsurgical SRP "in the presence of deep pockets, especially for reinfected cases."

Neither study reported CAL data. One reported that patients receiving both SRP and minocycline had notable, long-lasting changes in subgingival microbiologic findings (e.g., cell counts of spirochetes).[61] Owing to the small size of these trials, their nonsigifncant findings on PD (and no data on CAL), and other differences, we did not do any meta-analysis.

Local Minocycline

Qualitative and Descriptive Results. We included eight studies of local applications of minocycline, all appearing between 1993 and 2002 (Table 8 and Evidence Table 2b).[32,53,63-68] All were randomized; five were placebo-controlled;[32,63-66] and all but one[67] were reported to be double-blind studies. Taken together, the eight trials involved 760 subjects who completed the trials; of these 396 received adjunctive minocycline (237 in the Williams et al. trial alone[66]) and 379 received only SRP (230 in the Williams et al. trial). The Williams et al. trial is described as an intention-to-treat design and is a multi-center trial.

Subjects were variously described as having moderate to severe chronic (or advanced) periodontitis. Specifics about site criteria for inclusion, such as minimum number of teeth or sites, minimum PD levels, or bleeding, differed across the studies.

Four trials reported SRP details: subjects were hand-scaled in both van Steenberghe et al. studies (for a maximum of 15 minutes per quadrant in the 1999 study),[63,65] and in the other studies, subjects had both hand and ultrasonic SRP for 90 minutes.[67,68] The trials differed in

many respects (when details were reported); for example, assessment times and duration of measurement included seven times (baseline through 15 months[65]), five times (baseline through 9 months[66]), for two studies three times (baseline through 6 months[53,67] and baseline through 12 weeks[32]), and for one study four times (baseline through 6 months).[68] Moreover, the experimental regimen also differed across the trials. Two studies used gels (2 percent at baseline and at 2 and 4 weeks[32,53]); two other studies used ointments (2 percent at baseline and at various weekly or monthly points thereafter;[63,65] one study used 1 mg of minocycline as a single application at baseline;[64] one used 1 mg of 2-percent minocycline microspheres in a 3-mg polymer gel (at baseline and months 3 and 6[66]); and two used single applications of 1-mg microencapsulated minocycline.[67,68]

With respect to PD effects, four trials reported a greater effect of adjunctive local minocycline – i.e., more reduction among experimental than control groups that was statistically significant for at least some patients. Experimental subjects experienced 1.0 mm more reduction at 12 weeks (for those with 7 mm or greater initial PD, $P = 0.0001$),[63] 0.77 mm and 1.10 mm more reduction at 65 weeks (respectively, for subjects with 5 mm or greater and 7 mm or greater initial PD, $P < 0.0001$ in both cases),[65] 0.7 mm at 26 weeks ($P = 0.05$),[67] 0.32 mm at 39 weeks ($P < 0.001$) and 0.3 mm at 12 weeks (for those with initial PDs of 5 mm or greater, $P = 0.0018$).[63] The remaining trials showed net PD reductions favoring the local minocycline groups for which significance was not reported or the test was not significant: 0.39 mm,[53] 0.34 mm,[32] and 28 mm.[68] The last study did not report data but did indicate the difference between the groups was not significant.[64] In the largest trial lasting 9 months, the investigators reported that the percentage of sites with PD reductions of 1 mm or greater, or 2 mm or greater, was higher in the treatment group by, respectively, 10 percent and 11.6 percent; both values reflected a statistically significant difference ($P < 0.001$) from those for patients receiving SRP and placebo.[66]

Of the six trials that reported actual CAL data, three reported significantly greater net gains in CAL for the minocycline treatment groups: 0.8 mm at 26 weeks ($P = 0.04$),[67] 0.49 mm at 65 weeks (patients with baseline pockets of 5 mm or greater, $P < 0.0001$), and 0.43 mm at 65 weeks (baseline pockets of 7 mm or greater, $P < 0.0001$),[65] and 0.39 mm at 12 weeks ($P < 0.05$).[32] Others reported no or nonsignificant differences in gains favoring the minocycline groups: 0.48 mm,[68] 0.4 for patients with initial PDs of 7 mm or greater,[63] 0.36 mm,[53] and 0.0 mm for patients with initial PD of 5 mm or greater.[63] Of the two remaining trials that did not report data on CAL gain, one indicated that the between group difference was not significant[64] and the other did not say.[66]

None of these trials reported on percentage changes in spirochetes. One trial reported that concentrations of *P. gingivalis* and *P. intermedia* were lower following a minocycline ointment treatment than following SRP with placebo ointment at 2, 4, 6, and 12 weeks post-treatment, as was the concentration of *A. actinomycetemcomitans* at weeks 6 and 12.[63] The van Steenberghe team then later reported significant differences in several microbiological outcomes (e.g., *P. gingivalis, P. intermedia, C. rectus, T. denticola, E. corrodens, F. nucleatum,* and *A. actinomycetemcomitans)* at various follow-up points from month 1 to month 15 between patients receiving adjunctive minocycline ointment and nonsurgical SRP treatment alone.[65] There were significantly greater reductions in the *P. gingivalis, T. denticola,* and *C. rectus* counts from baseline,[65] but for the other microbial outcomes the changes were not significant. The Jones team used DNA probes for microbiological assessments of *A. actinomycetemcomitans, P. gingivalis, P. intermedia, E. corrodens,* and *C. rectus.*[64] The *P. gingivalis* prevalence was

completely nondetectable at 1 month and had a 60 percent reduction at 6 months for the treatment group. The SRP-alone group reductions were never significant from baseline.

Attrition was not well reported in these studies. Authors reported a wide array of adverse effects (among both treatment and control groups), some relatively serious and some not. They included dental infection, abscesses, gingivitis, gingival edema, stomatitis, root sensitivity, tooth sensitivity, dental pain, local irritation, headache, diarrhea, and other "minor" clinical reactions (e.g., redness).

Quantitative Analysis of Local Minocycline Effects. Six of the eight studies examining the effect on PD of locally applied minocycline reviewed above were included in the meta-analysis (Figure 6).[32,53,65-68] Reasons for excluding the other two studies were that one had no data for us to calculate an effect size measure[64] and the other had too great variance with the rest of the studies according to a test of heterogeneity, suggesting that it represented a different intervention.[63]

The estimate of overall effect size for PD is 0.49 mm (95 percent CI, 0.40 mm to 0.58 mm). Effect sizes of included studies favoring use of adjunctive local minocycline range from 0.28 to 0.70. Despite the fact that all of the study effect sizes represent greater PD reduction using adjunctive local minocycline with SRP than using SRP alone, based on the 95 percent CIs, the PD effect sizes of only two of those studies differed significantly from zero.[65,66] Those same two studies had appreciably smaller standard errors of difference between means and larger study samples, and consequently they contributed almost all of the weight to the meta-analysis results.

The statistically significant PD result supports the added effectiveness of locally applied minocycline as an adjunct to SRP in the treatment of chronic periodontitis in adults. It does not address, however, whether a mean change of 0.49 mm is clinically meaningful. One context for judging the import of this half-millimeter difference is that the effects of SRP alone on reduction in PD in these studies range from 0.71 mm to 2.30 mm for the same periods of time.

Of the eight studies examining the effect on CAL of locally applied minocycline reviewed above, we included five in the meta-analysis (Figure 7).[32,53,65,67,68] Of the three excluded studies, two had no way for us to calculate CAL effect sizes,[64,66] and one had a test for heterogeneity of variances suggesting that that study represented a different intervention than that of the other studies.[63]

The estimate of overall effect size for CAL is 0.46 mm (95 percent CI, 0.32 mm to 0.60 mm). Effect sizes of included studies favoring use of adjunctive local minocycline range from 0.04 mm to 0.80 mm. All these effect size estimates represent greater CAL gains using adjunctive local minocycline with SRP than using SRP alone, but based on the 95 percent CIs, the CAL effect sizes of only one of those studies differed significantly from zero.[65] That study had an appreciably smaller standard error of difference between means and a larger study sample and consequently contributed almost all of the weight to the meta-analysis results.

The statistically significant CAL result supports the added effectiveness of locally applied minocycline as an adjunct to SRP in the treatment of chronic periodontitis in adults. As with the PD results, which were of about the same magnitude, the clinical ramifications of a change of this size remains unclear in the context of CAL reductions in these studies for SRP alone of -0.13 mm to 1.61 mm.

Metronidazole

This section concerns the adjunctive use of metronidazole, an antiprotozoa agent with bacteriocidal effects on anaerobic species such as spirochetes, when used either systemically or locally in conjunction with SRP in patients with periodontitis. We present qualitative and descriptive results for both systemic and local metronidazole and a meta-analysis of eligible studies for local metronidazole. Metronidazole used in combination with amoxicillin is presented in the following section.

Systemic Metronidazole

Qualitative and Descriptive Results. Eight studies, published between 1984 and 2002, used systemic metronidazole as the sole antibiotic in conjunction with SRP and otherwise met our inclusion criteria (Table 9 and Evidence Table 3a).[69-76] Six trials were randomized, placebo-controlled, and double-blind trials.[69-74] Two trials were randomized but not placebo-controlled,[75,76] one was blinded only for examiners,[76] and the other did not report blinding.[75]

In all, these trials had 305 completers, of whom 153 were treatment subjects. Subjects had adult periodontal disease characterized as moderate to severe (or advanced). All control subjects received SRP with or without a placebo; experimental subjects received SRP with metronidazole alone.

The trials differed markedly in both therapeutic regimens and outcomes. As to dose, frequency, and duration of the antibiotic: three studies used 200 mg three times a day, one trial for 5 days[71] and two for 7 days;[70,76] one team, in three trials, used 250 mg three times a day for 7 days;[69,73,74] another group used the same dosage but repeated SRP;[75] finally, one study used 400 mg three times a day for 7 days.[72] The studies lasted from 6 weeks to 156 weeks. The trial outcome measures also varied considerably: average mm PD reduction per subject or per site; average mm CAL gain per subject or per site; various microbial measures; the percentage of sites per patient gaining, losing, or not changing PD or CAL; the percentage without disease; the number of sites with a given level of disease; and the percentage of sites needing surgery.

With respect to PD differences, only one of the trials failed to report any PD data although it did report a significant difference between the groups favoring the metronidazole treatment.[70] Of the others, two studies from the same group reported statistically significant net PD reductions favoring the metronidazole group. For patients with initial PD levels of 4 mm to 6 mm, the earliest study reported 0.14 mm gain at 30 weeks (not significant) and the latest study, 0.47 mm at 104 weeks ($P < 0.01$); for subjects with initial PD values greater than 6 mm or 7 mm and higher, the figures were, respectively, 1.64 mm ($P < 0.03$) and 1.05 ($P < 0.01$).[69,74] Other studies reported net gains of 0.6 mm,[75] 0.41 mm,[71] 0.41 mm for patients with initial PDs of 7 mm or higher,[73] and 0.05 mm,[72] but either these values were not significant or significance was not reported. The 1991 Loesche et al. study reported a greater PD reduction of 0.06 mm in the control group at 52 weeks, though the results were not statistically significant.[73] One trial only presented percent change of original PD.[70]

Six of the eight trials reported CAL results.[69,70,73-76] The studies from the Loesche et al. teams reported the following net gains favoring the metronidazole groups:[69,73,74] for those with initial PDs of 4 mm to 6 mm, 0.47 ($P < 0.01$), 0.10 mm (not significant), and 0.13 (not

significant), and for those with initial PDs of either greater than 6 mm or 7 mm and higher, 1.19 ($P = 0.05$), 0.32 (not significant) and 0.66 (not significant). Two other trials reported net gains of 0.41 mm (test not reported)[75] and 0.16 mm (not significant).[76] The sixth study did not report data on the gain in CAL but did indicate that it was not significant.[70]

Five investigations reported on microbial results (specifically spirochetes).[69,72-74,76] For example, the proportions of spirochetes dropped from baseline to the final observation from 59.1 to 22.0 for the test group and from 60.0 to 34.8 for controls, with the difference between groups approaching significance ($P = 0.06$).[74] Similar findings were reported for the 1991 and 1984 studies from this research team.[69,73] Palmer et al. also reported reductions in percentages of spirochetes between baseline and 8-week and then 24-week follow-up for both experimental and control patients, but the 24-week findings (from 47.1 percent to 25.8 percent for the metronidazole group and from 47.2 percent to 25.6 percent in the SRP-only group) reflected no significant difference between the two study groups. Finally, Soder et al. reported that the total number of microorganisms counted at the follow-up visits did not differ significantly between the metronidazole and placebo groups.[72]

Other results covered numerous heterogeneous outcomes. For example, at 6 weeks the percentage of teeth per patient needing surgery was lower for the treatment than the control group.[73] At 24 weeks, the percentages of sites with PDs of 4 mm or greater and the percentages of sites improved per patient were greater for experimentals than controls.[76] Two studies examining a total of 18 experimental subjects in terms of the percentage of deep sites suggested that metronidazole in conjunction with SRP is less effective than scaling alone at 156 weeks[71] and 260 weeks.[72]

Finally, three trials reported some adverse effects.[69,72,74] They included severe diarrhea, gastric discomfort, and, less seriously, "metallic taste."

Local Metronidazole

Qualitative and Descriptive Results. In all, we identified 11 clinical trials appearing between 1986 and 2000 that used local metronidazole in conjunction with SRP and that met the inclusion criteria (Table 10 and Evidence Table 3b).[28,34,36,37,53,75-80] One trial was a randomized, placebo-controlled, double-blind design;[77] most of the studies were randomized, not placebo-controlled, and single-blind designs.[28,36,53,76,78-80] The studies lasted over a range of 6 weeks to 39 weeks (9 months). Overall, the completing number of subjects (treatment and control groups) was 368; units of analyses included subjects, sites, and surfaces.

All subjects had adult or chronic periodontal disease ranging from "mild to moderate" to "moderate to severe," but most authors did not comment on severity. Most research teams used a 25 percent gel of metronidazole as the intervention therapy, each with reapplications after 1 week or more often.[28,34,36,53,75,76,78-80] Other groups used a variety of dosages and modes, such as 0.05 percent solution used with jet irrigation subgingivally[77] and 20 percent ethylcellulose film.[37] Control subjects or sites received SRP with or without a placebo; the experimental subjects received SRP with metronidazole alone.

For the PD outcomes, all 11 studies gave some results. Three reported data showing a statistically significant difference in the net PD reduction that favored the treatment group: 0.8 mm at 13 weeks ($P < 0.03$),[80] 0.5 mm at 39 weeks ($P < 0.001$),[79] and 0.18 mm at 37 weeks ($P <$

0.05).[36] One additional study reported that the net difference between treatment and control groups was significant at 12 weeks ($P < 0.01$) but did not report the difference.[77] Four trials reported net PD reductions in favor of metronidazole that were not statistically significant: 0.9 mm,[37] 0.78 mm,[75] 0.22 mm,[53] for "defect sites" at 26 weeks,[34] and one study did not report the data.[76] Two studies reported nonsignificant net PD reductions favoring the control groups - 0.12 mm[28] and 0.1 mm for "nondefect sites"[34] - and one reported no net difference at all.[78]

Eight of these 11 studies provided information on CAL gains. Only two studies reported significant net gains for the treatment groups: 0.66 mm at 6 weeks ($P < 0.01$)[75] and 0.4 mm at 39 weeks ($P < 0.001$).[79] Several other studies reported nonsignificant CAL gains favoring local metronidazole groups: 0.17 mm,[78] 0.07 mm,[36] 0.03 mm, [37] 0.004 mm,[53] and 0.7 mm and 0.0 mm for defect and nondefect sites.[34] One study reported a nonsignificant greater net gain in the attachment level for the control group of 0.04 mm.[76]

As to changes in the presence of spirochetes, one trial showed that treatment lessened the percentage of spirochetes in both treatment and control groups. At 8 weeks of follow-up, the change was significantly less in the locally delivered metronidazole group, but at 24 weeks the differences were not significant.[76]

Generally, none of these studies reported adverse events. One group noted that about half of the patients receiving metronidazole as a gel reported a bitter taste.[36]

Quantitative Analysis of Local Metronidazole Results. Seven of the 11 studies examining the effect on PD of locally applied metronidazole reviewed above were included in the meta-analysis (Figure 8).[34,36,37,53,78-80] Two studies were not included because they lacked data allowing us to calculate PD effect size measures,[76,77] one was too short,[75] and the final one did not provide data on variation.[28]

The estimate of overall effect size for PD is 0.32 mm (95 percent CI, 0.20 mm to 0.44 mm). Effect sizes of included studies favoring use of adjunctive local metronidazole range from 0.18 mm to 0.90 mm. All but one of the study effect sizes represented results that demonstrate greater PD reduction using adjunctive local metronidazole with SRP than using SRP alone. The one exception found a zero difference between the treatment and control groups.[78] Based on the 95 percent CIs, the PD effect sizes of four studies differed significantly from zero.[37,53,79,80] The two studies with appreciably smaller standard errors of difference between means contributed relatively more weight to the meta-analysis results.[53,79]

The statistically significant PD result supports the added effectiveness of locally applied metronidazole as an adjunct to SRP in the treatment of chronic periodontitis in adults. It does not address, however, whether a mean change of 0.32 mm is clinically meaningful. In contrast to this approximately one-third of a millimeter difference between using and not using some form of local metronidazole as an adjunct to SRP, the effects of SRP alone on reduction in PD in these studies ranged from 0.71 mm to 2.50 mm for the same periods of time.

Of the eight studies examining CAL effects of local metronidazole, we used seven in the meta-analysis (Figure 9).[34,36,37,53,76,78,79] The excluded study was too short.[75]

The estimate of overall effect size for CAL is 0.12 mm (95 percent CI, 0.01 mm to 0.24 mm). Effect sizes of included studies favoring use of adjunctive local metronidazole range from

0.07 mm to 0.70 mm. Five of the study effect sizes suggest greater gain in CAL using adjunctive local metronidazole with SRP than using SRP alone. One of the exceptions found a zero difference between the treatment and control groups;[53] the other was an effect size favoring SRP alone.[76] Based on the 95 percent CIs, the CAL effect sizes of 0.4 mm and 0.7 mm in two studies differed significantly from zero.[34,79] The two studies with appreciably smaller standard errors of the difference between means again contributed relatively more weight to the meta-analysis results.[53,79]

As with PD effects of locally applied metronidazole, the statistically significant CAL result supports its added effectiveness as an adjunct to SRP, but the clinical importance of a mean change of 0.12 mm is open to question. By contrast, the effects of SRP alone on CAL gains in the same time periods ranged from 0.20 mm to 1.60 mm.

Metronidazole and Amoxicillin

We identified four studies that combined systemic metronidazole with amoxicillin as an adjunctive intervention to SRP (Table 11 and Evidence Table 4).[70,81-83] All were randomized trials; three were placebo-controlled;[70,81,83] two were double-blind, one was single blind,[82] and one did not report on blinding.[81] In all studies, patients received SRP (usually under local anesthesia). In total, 133 patients completed the trials (64 in treatment groups and 69 in control groups).

The combined antibiotic regimens differed in dosage, frequency, and duration. Three studies used the combination of 250 mg of metronidazole and 375 mg amoxicillin three times a day for 7 days,[83] 8 days,[82] and two times a day for 2 weeks;[81] one used 200 mg metronidazole and 250 mg amoxicillin three times a day for 7 days.[70]

Two trials gave data on mean PD outcomes. The net PD reduction favoring the treatment groups were 0.7 mm at 13 weeks ($P < 0.05$)[83] and 0.5 mm at 104 weeks (significance not reported).[81] In the remaining trials, data were not reported, although one noted that the net difference for initial probing depths of 6 mm or greater was significant favoring the treatment ($P = 0.001$).[70]

Similarly, two studies reported data on CAL gains: a net gain of 0.3 mm at 104 weeks where significance was not reported[81] and one of 0.4 mm at 24 weeks (not significant).[83] Of the two studies not giving CAL data, one said the net difference was significant ($P = 0.05$) for probing depths greater than 6 mm[70] and one said it was not significant.[82]

None of the studies examined spirochetes, but all four reported on other microbiological outcomes.[70,81-83] One team found that the treatment eliminated *A. actinomycetemcomitans, P. gingivalis* and *P. intermedia* at 8 weeks (significance not reported).[81] For subjects with *A. actinomycetemcomitans* microbes, another team found that a significantly higher incidence of CAL gain of 2 mm or more was achieved in the experimental group over control ($P < 0.05$), but the opposite was true for subjects with *P. gingivalis*, who had a loss of attachment ($P < 0.05$) at 52 weeks.[82] A third team reported significant differences for the treatment versus control for microbiological outcomes (*A. actinomycetemcomitans, P. gingivalis, P. intermedia* and others) only at 1 month and not for the final assessment at 6 months.[70] Finally, the remaining team found significant differences between the experimental and placebo groups in the decreased

number of subjects who were positive for other microbiological outcomes (*P* value not reported).[83]

Some of these trials also reported positive findings for other measures. In one study, for example, at 12 weeks the percentage of deep sites per patient and mean deep and shallow site attachment levels were all improved for the treatment group compared to controls.[83] In another, at 26 weeks the percentage of sites for those with initial PD 6 mm or greater dropped from 15.9 percent to 1.3 percent for the treatment group; figures for the full placebo-control group were 19.3 percent and 12.4 percent, for a net difference favoring the dual antibiotic group of 7.7 percentage points (reported as statistically significant);[70] similar findings were reported for sites with 3 mm or less PD initially. CAL findings indicated that patients in the combination antibiotic group had significant improvements—i.e., decreased percentage of sites with high attachment losses and increased percentage of sites with low attachment losses—compared with levels for the placebo group. Finally, some research teams reported greater elimination or suppression of some periodontal pathogens (e.g., *A. actinomycetemcomitans*).[81,82]

Various adverse effects were reported in these trials. They fell mainly into the category of gastrointestinal problems (e.g., diarrhea),[82,83] with two cases of skin rash and one case of nausea after alcohol use.[83]

Chlorhexidine

In all, we included 17 studies of chlorhexidine, a topical, iodine-free disinfectant (antiseptic) with broadly effective antimicrobial properties, applied locally to either the gingivae or the mouth in general through several modalities (Table 12 and Evidence Table 5). These included rinses, mouthwashes, irrigation, and application or introduction of chips or gels in various ways.

Below we discuss the nine studies, published between 1985 and 1994, that included chlorhexidine applied solely as a rinse or through irrigation.[30,31,54,77,84-88] Those are followed by seven studies involving direct applications via chips or gels (without additional chlorhexidine rinse or irrigation)[59,89-94] and then by one trial that involved complex one-stage "full-mouth disinfection" within 24 hours, comprising gel, rinse, spray, and/or irrigation in combination.[95]

Of these 17 studies, 15 are described as randomized and 10 as placebo-controlled; seven are double-blind; an additional five are single-blind studies (chiefly of examiners). All patients had periodontitis described variously as mild, moderate, severe, or advanced (or severity was not reported). In all, the total number of patients completing these studies was 767, but many analyses were done on sites, surfaces, or pockets.

Two trials were large and multi-site investigations (one of 419 subjects [211 treatment and 208 control][91] and one of 94 subjects [401 treatment pockets and 412 control pockets][90]); one was medium-sized (60 subjects);[88] and the remainder were small (no more than 24 completers, but most were in the 10-subject range).

The approaches to experimental treatments varied considerably in terms of timing, frequency, and relationship to SRP; some trials included Bass brushing as part of the test approach. However, dosage of irrigated chlorhexidine was variable (ranging from 0.02 percent to 2.0 percent); some trials using chips identified it as Perio-Chip® (2.5 mg chlorhexidine); and

gels tended to be either 0.2 percent or 1 percent chlorhexidine. Control subjects tended to receive SRP alone or with some form of saline or water irrigation.

Similarly, the trials measured a wide array of clinical and microbiological outcomes at quite heterogeneous follow-up periods. Of the trials that reported on PD changes, some reported data in terms of the percentage of sites with smaller depths after treatment, rather than actual depths in millimeters; few studies reported on CAL in millimeters; and virtually no studies reported on spirochetes. Only a small number of research teams looked for or commented on adverse events, but as chlorhexidine is considered easily tolerated, this may not be surprising.

Irrigation and Mouthwash

We determined that ten trials of chlorhexidine irrigation and/or mouthwash with SRP versus SRP alone, all published between 1985 and 1994, met our inclusion criteria (Table 12).[30,31,54,77,84-88] Of these, seven used split-mouth designs. These studies ran from 4 weeks to 52 weeks.

With respect to PD, four studies reported net reductions favoring the chlorhexidine solution groups, but none was significant: 1.0 mm,[31] 0.3 mm,[30] and 0.1 mm.[85,87] Three other studies provided no tabulated or quantitative data but reported that the differences in the change from baseline to follow-up between the treatment and control groups were not significant.[54,77,84] One team noted that the percentage of sites with PD reductions was significantly greater for a chlorhexidine-irrigation group than for a water-irrigation group at 2 and 4 weeks.[88] One of the trials reported a nonsignificant net reduction in PD of 0.1 mm favoring the SRP-only group.[86]

Six chlorhexidine irrigation trials provided data on CAL gains.[30,31,54,85-87] Net CAL gains favoring the treatment group (none statistically significant) were 0.9 mm,[31] 0.2 mm,[30] and 0.1 mm.[86,87] One study reported nonsignificant net CAL gains favoring the control group by 0.1 mm.[85] Finally, one team remarked only that CAL did not differ significantly between groups.[54]

With respect to microbial outcomes, three teams reported on percentages of spirochetes at baseline and at last follow-up.[30,31,87] Patients in the chlorhexidine treatment groups all experienced decreases in the percentages of spirochetes; the largest decrease was from 32 percent to 2 percent.[31] Nonetheless, at the end of the studies, the net reductions in proportions of spirochetes for the chlorhexidine groups relative to the control groups were not significant; irrigation with chlorhexidine did not appear to have more than limited microbiological effect compared to SRP alone.

In short, the results of these trials suggest that, with respect to PD and CAL, using local irrigation with chlorhexidine as an adjunct to SRP confers virtually no material benefit over SRP alone.

Direct Gingival Applications

Chlorhexidine Chips. Five trials appearing between 1997 and 2002 tested a chip application of chlorhexidine as an adjunct to SRP against either SRP alone or SRP with a placebo chip (Table 12).[90-94] These were 2.5 mg chips inserted into pockets of varying depths at baseline and at various points after that; the trials lasted from 26 to 39 weeks.

With respect to PD, two trials reported statistically significant net improvements for the treatment group: 0.33 mm at 26 weeks ($P = 0.05$)[92] and 0.26 mm at 39 weeks ($P < 0.0056$).[91] Another study cited a 0.2 mm improvement in favor of the control group but did not report significance,[94] and a fourth gave no data but reported a nonsignificant difference.[93] Finally, the fifth study reported a 0.46 mm net PD reduction favoring the SRP-only group ($P < 0.001$).[90]

Three of the chip trials cited net CAL gains favoring the chlorhexidine chip groups: 0.28 mm at 26 weeks ($P = 0.048$),[92] 0.20 mm at 39 weeks ($P < 0.012$),[91] and 0.16 mm at 26 weeks ($P < 0.05$).[90] Of the other two studies, one did not report all final data in millimeters but commented that the changes were not significant[93] and the other showed only a nonsignificant 0.4 mm net PD reduction favoring the control group.[94]

No chip trial reported on percentages of spirochetes. One research team reported toothache, upper respiratory tract infection, and headache as adverse events but noted that such side effects generally happened with similar frequency for the treatment and control groups except for toothache (e.g., pain, tenderness, and sensitivity similar), which was significantly higher in the chlorhexidine group ($P = 0.042$).[91]

Chlorhexidine Gels. Two trials used chlorhexidine gel as an adjunct to SRP and tested this modality against SRP alone or SRP with placebo gel (Table 12).[59,89] One study did not give tabulated data on PD reductions but the net difference was noted as not significant;[89] in the other, the 0.25 mm net reduction (not significant) favored the control group.[59] One trial noted only a nonsignificant 0.34 mm CAL gain favoring the control group.[59] The one trial that addressed percentages of spirochetes showed a decrease over time for the treatment group, but no significant net benefit emerged for the treatment group at the conclusion of the study.[89] Neither study reported on adverse effects.

Chlorhexidine Combination Treatment. The one study that employed an all within-24 hours full mouth disinfection also employed multiple forms of chlorhexidine.[95] These included chlorhexidine gel for brushing, subgingival chlorhexidine irrigation, and chlorhexidine rinse and spray, the latter twice a day for 60 days. In this study, net PD reductions favoring the control group of 0.1 mm (single-root teeth) and 0.5 mm (multi-root teeth) were not significant. The same was true for CAL gains of 0.3 mm (single-root teeth) and 0.3 mm (multi-root teeth) that favored the control group.

Quantitative Analysis of Local Chlorhexidine Effects. Of the 17 studies examining the effect on PD of locally applied chlorhexidine reviewed above, we retained eight in the meta-analysis (Figure 10).[30,31,59,90-92,94,95] Of the nine excluded studies, one had a study period of less than 3 months,[54] two were longer than 9 months with no intermediate data reported,[86,87] and six did not report data that could be used to calculate a PD effect size.[77,84,86,88,89,93]

The estimate of overall effect size for PD is 0.24 mm (95 percent CI, 0.13 mm to 0.35 mm). Effect sizes favoring use of adjunctive local chlorhexidine range from 0.14 to 1.00 mm. Five of these effect sizes reflected greater PD reduction using adjunctive local chlorhexidine with SRP than using SRP alone; the other three studies had PD effect sizes of from -0.10 mm to -0.25 mm that favored SRP alone.[59,94,95] Based on the 95 percent CIs, the PD effect sizes of only three studies differed significantly from zero; all favored SRP with local chlorhexidine.[31,90,91] The two studies with appreciably smaller standard errors of difference between means contributed considerably more weight to the meta-analysis results.[90,91]

The statistically significant PD result supports the added effectiveness of locally applied chlorhexidine as an adjunct to SRP in the treatment of chronic periodontitis in adults. As with other adjunctive therapies with a mean changes in this range (0.24 mm), however, whether they are consequential clinically remains debatable, given that the effects of SRP alone on reduction in PD in these chlorhexidine studies ranged from 0.70 mm to 3.00 mm for the same periods of time.

Of the 13 studies examining the CAL effects of locally applied chlorhexidine reviewed above, we included seven in the meta-analysis (Figure 11).[30,31,59,90-92,94] Among the six excluded studies, one had a study period of less than 3 months,[54] two had study periods longer than 9 months with no intermediate data reported,[85,87] and three did not report data that could be used to calculate a CAL effect size.[86,93,95]

The estimate of overall effect size for gain in CAL is 0.16 mm (95 percent CI, 0.04 mm to 0.28 mm). Effect sizes of included studies favoring use of adjunctive local chlorhexidine range from 0.16 mm to 0.90 mm. Two of the study effect sizes, ranging from 0.34 to 0.40, represented results that demonstrate greater CAL gains using SRP alone.[59,94] Based on the 95 percent CIs, the CAL effect sizes differed significantly from zero for only two studies.[31,91] The two studies with appreciably smaller standard errors of differences between means and larger sample sizes contributed relatively more weight to the meta-analysis results.[90,91]

The statistically significant CAL result supports the added effectiveness of locally applied chlorhexidine as an adjunct to SRP, but the clinical significance of a mean change of 0.16 mm is also debatable. The effects of SRP alone on CAL gains in these chlorhexidine studies ranged from 0.31 mm to 1.40 mm for the same periods of time.

Other Antibiotics

Systemic Antibiotics

Seven clinical trials of other antibiotics, all given as systemic agents, met the inclusion criteria (Table 13 and Evidence Table 6a).[45,46,70,96-99] Two studies used spiramycin alone as the adjunctive therapy.[45,97] The others used different agents for the adjunctive systemic therapies: a combination of spiramycin and metronidazole,[96] doxycycline (a synthetic derivative of tetracycline),[98] azithromycin (an antibiotic related to erythromycin),[99] amoxicillin with clavulanic acid,[46] and amoxicillin with a placebo and chlorhexidine rinse.[70] All were randomized, placebo-controlled trials; all but one was a double-blind trial.[98]

Taken together, the trials comprised 359 completing subjects, 204 on antibiotic regimens with SRP (just under half from the Bain et al. trial[97]), and 199 receiving SRP with placebo. Subjects in the trials differed in terms of their periodontal disease experience or severity from severe or advanced periodontitis to moderate. One study included subjects with at least two sextants with scores on the Community Periodontal Index of Treatment Needs (CPITN) of 4.[99] All studies used the subject as the unit of analyses.

All studies reported details of the SRP procedures. In two studies, SRP was started at baseline appointment and completed in two sessions of 3 hours each, performed within 1 week of each other by one operator.[45,96] In another, SRP was started at baseline and performed in 3 to 5 hours during the 2 weeks of drug therapy; this involved seven operators in different centers.[97] In another study, 152 teeth received one session of SRP performed under local anesthesia using ultrasonic and hand instruments.[98] Finally, in the most recent study, SRP was performed by one hygienist using hand instruments.[99]

Experimental regimens differed widely across these trials. Two studies had the standard dose of 500 mg of spiramycin, twice a day for 14 days;[45,97] another had a combination dose of 750,000 IU of spiramycin and 125 mg of metronidazole twice a day for 14 days.[96] Other regimens included: 200 mg of doxycycline the first day followed by 100 mg per day for 6 weeks;[98] 500 mg azithromycin capsules once a day for 3 days at week 2 after the final session of SRP;[99] 250 mg amoxicillin with clavulanic acid three times per day for 30 days[46] and the other had 250 mg amoxicillin with a placebo three times a day for 7 days along with a chlorhexidine rinse.[70] Studies ranged in length from 22 to 43 weeks.

Only five studies reported PD data.[45,46,97-99] While the remaining two studies did not report data, they did report that the difference between the groups was not significant.[70,96] In the doxycycline trial, the experimental group was significantly different from the placebo group only at weeks 3 and 6; at 12 and 24 weeks, the two groups did not differ significantly, with the 0.6 mm nonsignificant difference at 24 weeks favoring the placebo group.[98] One spiramycin study found significant differences in PD reduction favoring the drug group at 2 weeks into the study; at 24 weeks, the net reduction favoring the group receiving spiramycin was 0.47 mm (P = 0.0075).[97] Another spiramycin study showed greater reductions in PD favoring the experimental group in only the least severe class (probing PD = 3 mm) of 0.42 mm at 24 weeks but the difference was not significant. For the other severity groups, the results favored the placebo groups—0.40 mm in those with PD 4 mm to 6 mm and 0.28 mm in those with PD = 7 mm—and neither was significant.[45] In the azithromycin study, the mean values of subjects' average PDs differed between the azithromycin and the SRP-only groups at baseline; thus, the investigators

used analysis of covariance to render the experimental and control groups equivalent at baseline. The study results showed greater reductions in PD favoring the experimental group in each of three severity classes (probing depths of 1 mm to 3 mm, 4 mm and 5 mm, and 6 mm or greater) at various measurement points. At 22 weeks, the net reductions in PD for patients with the most advanced periodontitis was 0.87 mm ($P < 0.05$) and for these in the intermediate group, 0.52 mm ($P < 0.01$).[99]

Six trials measured CAL.[45,46,70,96-98] The doxycycline trial showed a 1.3 mm gain in CAL at 24 weeks ($P = 0.05$).[98] The three spiramycin studies had mixed results. In one (used with metronidazole), the experimental group exhibited a significantly ($P < 0.05$) greater gain in attachment level than did the control group but provided no data;[96] another reported a nonsignificant 0.29 mm gain in CAL for the experimental group.[97] In the third, at 24 weeks a gain of 0.92 mm favoring the treatment group was not significant (for those with least severity), and results favored control groups (although also not significant) for those with greater severity.[45] The amoxicillin and clavulanic acid trial reported only a nonsignificant difference at the end of the trial,[46] and in the other amoxicillin trial no data or significance test were given.[70]

Two trials performed microbiological examinations on the studies' subjects and found a significant decline in the spirochetes level. In one, the proportion of spirochetes among experimental subjects receiving spiramycin decreased from 28 percent at baseline to 3 percent at 24 weeks; the respective values for the placebo group were 30 percent and 11 percent ($P < 0.05$).[45] In the other, the proportion of spirochetes declined significantly among experimentals relative to controls at 14 days and thereafter; at 6 months, the proportions were 3 percent for experimental subjects and 15 percent for controls ($P < 0.05$).[96]

Most of these studies did not report adverse events or effects of the experimental intervention (or reported that they did not observe any). Adverse reactions mentioned, which occurred infrequently, included nausea, diarrhea, gastrointestinal upset, and abdominal pain.

Local Antibiotics

Two clinical trials of local antibiotics as the adjunctive therapy met the inclusion criteria (Table 14; Evidence Table 6b). One trial used local ofloxacin (a broad-spectrum antibiotic);[100] the other used doxycycline gel.[101] Both were randomized, placebo-controlled studies; one was a multi-center, double-blind trial.[101]

In all, 135 subjects completed the two trials. All subjects in both studies received SRP, and each subject had one site treated with the local antibiotic regimens with SRP and a different site treated with placebo.

These two trials differed in several dimensions. With respect to periodontal disease experience, one study included subjects with chronic periodontitis diagnosed by showing on affected teeth more than 30 percent bone loss by radiographs.[100] The other study included subjects suffering from moderate to severe periodontitis with at least 3 single-rooted teeth either with PD depth of 5 mm and bleeding on probing or with PD of 6 mm or more.[101]

Details of the experimental regimens and SRP procedures regimens also differed. In the doxycycline trial, investigators used a subgingival application of a newly developed, biodegradable 15-percent doxycycline gel (DOXI); subgingival SRP was performed with hand

instruments at all test and respective neighboring teeth under local anesthesia, and then mechanical debridement of one test tooth was limited to 10 minutes.[101] In the other study, investigators used a controlled-release, film-shaped insert of ofloxacin that was applied once a week from baseline through 35 days; supragingival SRP was done for the first 2 weeks and root planning and subgingival scaling for 4 weeks after that.[100]

Only the doxycycline trial reported on clinical measures.[101] At 26 weeks both net PD reduction (0.44 mm, $P = 0.0066$) and CAL gain (0.37 mm, $P = 0.038$) favored the experimental group over the control group.[101] Interim measures were said to show improvement compared to baseline but statistical significance was not reported. The ofloxacin trial analyzed the proportion of spirochetes over a 4-week period.[100] Two weeks after supragingival scaling period, the difference between the experimental and the placebo groups favored the former (9.5 percent versus 20.2 percent, $P < 0.05$); however, as the SRP treatment changed to mechanical subgingival debridement, proportions of spirochetes dropped for all groups, and differences between treatment and placebo groups were no longer statistically significant through the remainder of the study. Only the doxycycline study reported any adverse effects (swelling at one treatment tooth).

Other Antimicrobials

Five clinical trials of adjunctive use of antimicrobials other than antibiotics, published between 1987 and 2001, all used locally, met our inclusion criteria (Table 15 and Evidence Table 7).[85,89,102-104] They included (alone or in various combinations or forms): povidone-iodine solution, tetrapotassium peroxydiphosphate, hydrogen peroxide, triclosan, amine fluoride and stannous fluoride. Three were randomized, placebo-controlled, double-blind trials; one was randomized, placebo-controlled and single-blind; and one was described only as placebo-controlled. The duration of the studies ranged from 2 months to 13 years.

Although experimental regimens were applied subgingivally in all studies, none of these studies used exactly the same antimicrobial agent; the treatment regimens, including the SRP approaches, varied considerably too and included the following:

- irrigation with hydrogen peroxide 3 times a week, with SRP started at week 32 with six visits during a period of, on average, 6 weeks to complete;[85]
- application of 1.25 percent amine fluoride gel on one site (tooth) or application of 4 percent stannous fluoride gel on another site, with both treatments applied three times within 10 minutes and selected pockets subjected at baseline to mechanical debridement with hand or ultrasonic instruments;[89]
- application of supragingival gel and dentifrice, both containing triclosan, twice a day for two time periods, each lasting for 14 days with 1 week of wash-out period between them, as well as subgingival gel application at days 0 and 7 in each time period, with the assigned quadrant anaesthetized and teeth exposed to meticulous SRP until root surfaces were hard and smooth;[102]
- use of 0.1 percent of iodofor solution (a water solution of povidone-iodine) as a cooling liquid for an ultrasonic device to provide nonsurgical therapy, with nonsurgical supra- and subgingival SRP under local anesthesia using ultrasonic device for 1 hour for four to six sessions (intervals between sessions never exceeding 1 week);[104] and,
- subgingival irrigation of a 7-percent solution of tetrapotassium peroxydiphosphate twice a day for 8 weeks before SRP was done; SRP was performed through thorough

subgingival scaling by hand (which took place at week 32 of the study, so week 32 was considered the baseline of the reported clinical results).[103]

Taken together, the trials included 236 subjects and 326 sites (148 sites on antimicrobial regimens with SRP, and 178 sites on control regimens). Subjects in the studies experienced a full spectrum of periodontitis: moderate periodontitis;[102] moderate to severe;[85,103] only severe periodontitis;[89] and advanced destructive periodontitis.[104]

The studies differed markedly in the selection of sites used to characterize a subject's response to therapy, but generally all studies involved patients with PDs in the range of 5 mm to 10 mm. One study based analyses on two pairs of contralateral sites with at least 5 mm PD that bled on probing at baseline.[102] A second study selected for each experimental group one interdental pocket of 7 mm to 9 mm that affected a single-rooted tooth.[89] A third study included subjects with a minimum of eight nonmolar teeth, at least two of which in each dentate quadrant had PDs of 6 mm or more;[104] another study selected two or three interproximal sites in each jaw quadrant on the basis of the presence of PDs of 6 mm or more.[85] Finally, another study included subjects with PDs of 5 mm to 10 mm.[103]

All teams used net reduction in PD as a clinical outcome.[85,89,102-104] The hydrogen peroxide study reported net PD reduction of 0.8 mm at 52 weeks ($P < 0.05$);[85] two other trials reported nonsignificant reductions of 0.65 mm (tetrapotassium peroxydiphosphate solution[103]) and 0.6 mm (povidine-iodine[104]) after 8 weeks among persons at baseline with 4 mm to 7 mm probing depths. In the triclosan study, the 0.1 mm reduction favored the control groups;[102] the fluorides study did not report data but only that the results were not significant but favored the treatment group.[89]

Three trials reported results for CAL – two in terms of actual gains or losses in attachment[85,104] and one in terms of less of a loss of attachment.[103] The hydrogen-peroxide trial reported a CAL gain of 0.1 mm for the treatment group (not significant).[85] It also reported the percentage distribution of sites that demonstrated a gain of more than 1 mm of clinical attachment level at the end of the phase that included both SRP and hydrogen-peroxide treatment; for both hydrogen-peroxide and control groups, 40 percent of sites showed an attachment gain of that magnitude (for no difference between the groups). In the tetrapotassium peroxydiphosphate trial, the net difference in attachment level between test and control groups at the end of 8 weeks was 0.25 mm (a nonsignificant finding).[103] Finally, in the longest study (of povidine-iodine), the control group had a greater attachment *gain* after 13 years of 0.597 mm (significance not reported).[104]

Three trials examined microbiological outcomes including spirochetes.[89,102,103] None of these studies showed that the treatment groups differed significantly from the control or placebo groups at the end of their respective observation periods. In the triclosan trial,[102] the mean percentages dropped by day 14 to about 13 percent for both groups (from 46 percent among test patients and 37 percent among controls). In the tetrapotassium peroxydiphosphate study, the drop in percentage of spirochetes for both treatment and control groups was reported to be statistically significant between baseline and 8 weeks, but the net difference between groups was noted as not significant.[103] Finally, for fluoride gel treatment, the percentages of spirochetes was reported to have dropped significantly for both treatment groups (amine fluoride and stannous fluoride) and placebo between baseline and 36 weeks, but the differences between groups at the end were not significant.[89]

By and large, these trials did not report on adverse events or effects. The tetrapotassium peroxydiphosphate trial noted mucosal irritation.[103]