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The Role of Remineralizing and Anticaries Agents in Caries Management

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ABSTRACT

The first ICNARA conference (International Conference on Novel Anticaries and Remineralizing Agents) was held in Chile in January, 2008, and the proceedings were published in *Advances in Dental Research* (Volume 21, 2009). That issue of *Advances* summarized the state of the science and set a research agenda for the future for two key components of caries management, namely, antibacterial agents and remineralizing agents. The second conference (ICNARA 2, January 2012) provided an update on science and new directions for research and clinical practice. Over the past decade, renewed efforts have been made across the world to establish proven methods of caries risk assessment and to provide direction for improved methods of caries management based upon risk levels. Evidence-based caries risk assessment tools are now available. The need for improved therapy to reduce the bacterial challenge that initiates the caries process, and to enhance remineralization, is now very clear. Fluoride therapy alone is insufficient to control the caries process in high-risk individuals. New remineralizing and anticaries products and new delivery systems are in development, and ICNARA 2 presents future technology for the management of dental caries.

INTRODUCTION

The first ICNARA conference (International Conference on Novel Anticaries and Remineralizing Agents) was held in Chile in January, 2008. The stated objectives of ICNARA 1 were (a) to summarize the current state of research on antibacterial and remineralizing agents, (b) to critically assess the presentations and the data included therein, and (c) to document a research agenda for the future based upon discussions and presentations at that meeting. The topics covered in ICNARA 1 were biofilm, casein phosphopeptide/ACP, calcium/sodium/phosphosilicate, xylitol, probiotics, antimicrobial peptides, naturally occurring antibacterials, implementation of new remineralizing technologies, and dental erosion. The proceedings were published in *Advances in Dental Research* (Volume 21, 2009; Proceedings of the International Conference on Novel Anti-caries and Remineralizing Agents, Vina del Mar, Chile, January 10-12, 2008). They summarized the state of the science and set a research agenda for the future for two key components of caries management, namely, antibacterial agents and remineralizing agents. Following that conference and the resulting publication, much work was done around the world, some published and some unpublished.

In January 2012, the second conference (ICNARA 2) provided an update on science. It was co-supported by faculty from the School of Dentistry - University of California-San Francisco (USA), the College of Dentistry - New York University (USA), the School of Dentistry - Academic Center for Dentistry Amsterdam (ACTA) (the Netherlands), and the Facultad Odontologîa - Universidad Finis Terrae (Chile). Approximately 29 of the leading international experts in cariology, bacteriology, remineralization, and preventive dentistry were invited, to focus on the state of the field and, from this, to build a multidisciplinary agenda for future research. The conference included researchers from Australia, Brazil, Finland, Israel, the United Kingdom, the Netherlands, Switzerland, and the United States, countries where much of the research on caries prevention and intervention is conducted. The conference was also open to professionals, including scientists, young investigators, and academic faculty, as well as interested corporate representatives and observers. The stated objectives of ICNARA 2 were (a) to explore further the state of knowledge on caries antibacterial (anticaries) and remineralizing agents, (b) to provide a forum for the discussion of new and underutilized technologies and data, and (c) to provide a shared multidisciplinary research agenda for the next decade. The topics presented at ICNARA 2 (this issue) included biofilm management, new remineralizing agents, casein phosphopeptide/ACP, slow-release technologies, nanotechnology, probiotics and targeted antimicrobials, the oral microbiome, lasers and antibacterial action, computational biology, xylitol, polyols, and genomic analyses.

The aims of the present manuscript are: (1) to present the rationale for the ICNARA meetings; (2) to present summaries of recent studies about caries risk assessment and caries management by risk assessment as examples that highlight the need for

Key Words

caries risk assessment, caries management, high caries risk, remineralization, antibacterial agents, dental caries.

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new and improved remineralizing and anticaries agents, and (3) to set the stage for the presentations that followed at the conference and that form the body of the present issue of *Advances in Dental Research*.

Rationale Behind The ICNARA Meetings

The overall rationale for both conferences (ICNARA 1 and 2) was to advance the state of knowledge to the point where improved therapy for the management of dental caries will become available to improve the oral health of people worldwide.

In spite of millions of dollars of research and many improvements in treatment approaches in recent decades, caries is still the predominant disease, both in the general population and in special-needs patients (Evans and Kleinman, 2000; Casamassimo *et al.,* 2009). It has been well-documented that major reductions in the prevalence and incidence of dental caries have been achieved over the past 30 years (Macek *et al.,* 2004; Marthaler, 2004; Beltran-Aguilar *et al.,* 2005; Dye *et al.,* 2007). However, these improvements have plateaued, and 75% of caries occurs in 25% of the population (Kaste *et al*., 1996; Macek *et al.,* 2004). This implies that we need methods of assessing the risk for caries development and progression in populations and individuals, and, most importantly, improved methods of therapy are needed to deal with high-caries-risk individuals or populations (Berg, 2006).

Even though improved therapeutic methods may be known, it takes many years and large sums of money to bring products to the market, especially when approval by regulatory agencies is necessary. Technology without purpose does not improve human health and well-being. As researchers, academicians, and clinicians, we need to continue to change the way in which dentistry is delivered, with more emphasis on prevention and intervention as the forerunner to necessary restorative work (Featherstone, 1999; Elderton, 2003; Fontana and Wolff, 2011). We need to target improved remineralization technology and anticaries agents to those who most need it. Better remineralization and antibacterial agents are essential for effective management of high-caries-risk individuals and for making the shift from the operative to a more conservative approach, thereby inhibiting and reversing lesion progression.

CARIES RISK ASSESSMENT

Effective caries prediction and caries risk assessment have been among the goals of cariologists for decades. Numerous models of caries risk assessment have been developed, and these have formed the basis for much activity in recent years in attempts to validate methods that can be used in practical dentistry (Bader *et al.,* 2003; Featherstone *et al*., 2003, 2007; Bratthall and Hansel Petersson, 2005; Southward *et al.,* 2008; AAPD, 2011-2012; Ditmyer *et al.,* 2011; Morou-Bermudez *et al*., 2011; Macritchie *et al*., 2012). Featherstone proposed the concept of caries balance in 1999 (Featherstone, 1999). The concept is that caries progression or reversal is determined by the balance between pathological factors (that are related to demineralization) and protective factors (that enhance remineralization or reduce the bacterial challenge). Patients in whom pathological factors (*e.g.,* cariogenic bacteria, fermentable carbohydrate frequency, salivary dysfunction, deep pits, and fissures) outweigh protective factors are likely assessed as being at high risk for future caries lesions. The aim of caries disease management is to reduce the bacterial challenge if it is high and, conversely, to increase the remineralizing activity and enhance the natural repair of non-cavitated lesions.

A simple caries risk assessment procedure was proposed in 2003 (Featherstone *et al*., 2003), based upon the above principles and much prior research around the world. A short list of risk factors, pathological factors, and protective factors was included in this proposed risk assessment method. The method was introduced into the pre-doctoral teaching clinics at the University of California-San Francisco School of Dentistry. Outcomes data were assessed after 6 yrs and have recently been published (Doméjean *et al*., 2011). The study showed that the list of items used and the manner in which they were used successfully identified 69% of those at high risk and 88% of those at extreme risk (high risk plus salivary dysfunction) of presenting with new cavities at subsequent follow-up examinations. Further, 76% of those assessed at low risk did not progress to cavities. Please refer to that publication for details and a more extensive literature review. The list of components is shown in the Table. This report validates the caries risk assessment method documented in the above publications as a viable way of successfully assessing risk. Cariogenic bacterial challenge was also assessed as mutans streptococci and lactobacilli by the "dipslide method" (CRT® bacteria; Ivoclar-Vivadent, Schaan, Liechtenstein). High mutans streptococci and high lactobacilli levels were related to cavitation at 90% and 91%, respectively, with a p value less than 0.001 (chi-square test).

The above-mentioned caries risk assessment method can of course be improved and modified, and other procedures are also open to validation. Regardless, these results provide one example that indicates clearly that the use of specific remineralization and antibacterial modalities is essential to control the disease and improve the oral health of the high- and extreme-risk individuals.

CARIES MANAGEMENT BY RISK ASSESSMENT

Clinical Trial

A clinical trial on high-risk adults (18 yrs and older) has been conducted by UCSF researchers to test the hypothesis that altering the caries balance alters the caries risk and thereby the caries outcome. Details are presented elsewhere (Featherstone *et al.,* 2012). This randomized parallel-group clinical trial assessed whether combined antibacterial and fluoride therapy benefits the balance between caries pathological and protective factors over 2 yrs. The participants, each of whom had from 1 to 7 cavitated caries lesions at baseline, were randomly assigned to a control or an intervention group. Salivary mutans streptococci (MS), lactobacilli (LB), and fluoride (F) levels, and resulting caries risk status (low or high) assays were determined at baseline and every 6 mos. After baseline, all cavitated lesions were restored. An examiner masked to a group conducted caries examinations at baseline and 2 yrs after completing restorations. The intervention group used fluoride dentifrice (1,100 ppm F as NaF), 0.12% chlorhexidine

Table. Caries Risk Assessment Components as Validated by Doméjean *et al.* (2011)

Risk Assessment Component	Odds Ratio	95% Confidence Interval
Disease Indicators (Clinical Observations)		
Approximal enamel lesions (detected by radiograph)	8.2	7.4-9.1
White spots on smooth surfaces	2.8	2.5-3.1
Restorations in preceding 3 yrs	1.5	1.4-1.6
Biological Risk Factors (Pathological Factors)		
Heavy plaque on the teeth	2.6	2.4-2.8
Recreational drug use	2.0	1.7-2.3
Deep pits and fissures	1.8	1.6-2
Frequent snacking	1.8	1.6-1.9
Inadequate saliva flow	1.3	1.1-1.4
Exposed tooth roots	1.2	1.1-1.3
Mutans streptococci high	NR*	
Lactobacilli high	NR*	
Protective Factors		
Uses fluoride mouthrinse	0.8	0.7-0.9
Uses fluoride toothpaste	0.8	0.7-0.9
Lives or works in a fluoridated community	0.9	0.8-0.97

Odds ratios are related to cavitation (which is also a disease indicator). Odds ratios greater than 1.0 are positively related. Odds ratios less than 1.0 are negatively related. All components in the Table were statistically significant at $p < 0.01$.

*NR = not reported in the Doméjean *et al.* (2011) publication. Odds ratios were not calculated for these items in that publication. For patients with high MS, 89.7% had cavities, and for high LB, 90.8% had cavities.

gluconate rinse based upon bacterial challenge (MS and LB), and 0.05% sodium fluoride rinse based upon salivary F. The chlorhexidine rinse was used daily for 1 wk every mo.

Results can be summarized as follows:

(1) The mean MS, but not LB, levels in saliva were significantly lower in the intervention group. The MS levels remained lower throughout the two-year period after restorations were complete only in the intervention group. Change in MS bacterial challenge differed significantly between groups (odds ratio = 6.70), but not for LB.
(2) The overall mean bacterial levels of MS and LB in the control group were not significantly lowered by the restorative work. Placement of restorations did not significantly lower the cariogenic bacterial levels in the rest of the mouth.
(3) Higher levels of MS and LB coincided with the presence of cavities.
(4) The intervention group had a statistically significantly 24% lower mean caries increment (change in DMFS) than the control group ($p = 0.02$).
(5) Overall, caries risk was reduced significantly in the intervention compared with the control group over 2 yrs.
(6) Targeted antibacterial and fluoride therapy based on salivary microbial and fluoride levels favorably altered the balance between pathological and protective caries risk factors.

Although the management of caries in this high-risk population was somewhat satisfactory based upon lowering of the bacterial challenge and enhancing remineralization, there are two main conclusions: Although rinsing with chlorhexidine lowered the MS bacterial challenge, the resultant mean MS bacterial levels were still in the region of 10^3 CFU/mL. Further, the chlorhexidine therapy had no significant effect on mean LB levels. Although the study demonstrated in principle that altering the caries balance alters the caries outcome, the results clearly indicate that (a) better antibacterial therapy is needed, and (b) better fluoride and remineralizing therapy is needed to deal with high-caries-risk individuals who have a high bacterial challenge.

Antibacterial Agents

Although numerous caries antibacterial agents have been proposed over the years, there is still nothing on the market that is clinically proven to markedly reduce the cariogenic bacteria levels and reduce the caries increment as a result (Rosin *et al.,* 2002; Smullen *et al*., 2007; Ferrazzano *et al*., 2009, 2011). At the time of writing, clinical trials are in progress with other agents that may be superior to the chlorhexidine results summarized above. The results are not yet available for reporting.

More Effective Fluoride Therapy

Recent publications have highlighted the need for higher concentration fluoride therapy for high-caries-risk individuals. One such study showed a superior preventive effect of a 5,000-ppm dentifrice compared with a 1,450-ppm-F dentifrice in a two-year clinical trial in adolescents (Nordstrom and Birkhed, 2010). Numerous clinical trials have demonstrated the efficacy of a high-concentration fluoride varnish in high-caries-risk individuals, although there is still some debate about whether this vehicle is best for prevention or for repair of non-cavitated lesions (Autio-Gold and Courts, 2001; Bader *et al.,* 2001; Ferreira *et al.,* 2009; Du *et al*., 2011). Even with these higher concentration fluoride systems, there is a long way to go before caries levels are reduced dramatically. Improved remineralizing methods and improved delivery methods for fluoride are essential to progress.

CONCLUSIONS

The conclusions that can be drawn, relevant to ICNARA 2 and the collection of manuscripts in this current issue of *Advances in Dental Research,* are:

(1) Caries risk assessment methods are available that have been validated, but there is still considerable room for refinement and improvement.
(2) Caries management based upon risk assessment will target those who will benefit the most and who need it the most.
(3) Improved remineralizing therapy is needed, including improved delivery systems.
(4) Antibacterial agents are necessary for high-risk individuals, since remineralization alone is insufficient to deal with the

caries challenge. Methods of disrupting the biofilm beneficially are needed for high-caries-risk individuals.

(5) The work presented and reviewed at this conference and in this publication will take us to the next steps to improve the oral health of people worldwide.

(6) Further clinical research is needed – especially practice-based research – to guide treatment planning and decision-making in everyday clinical practice.

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