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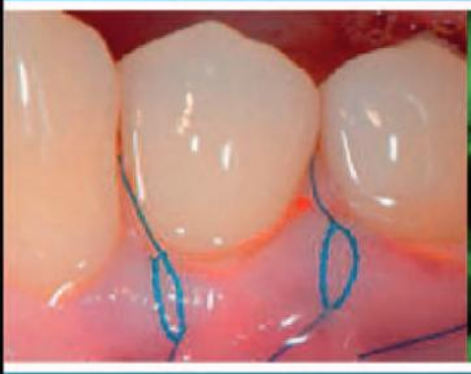
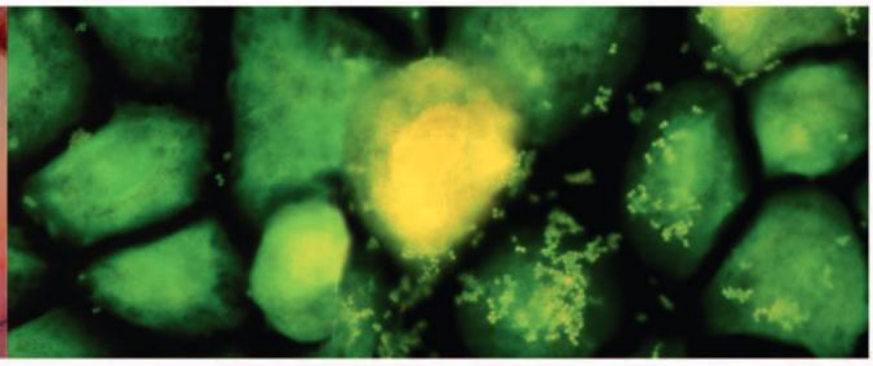
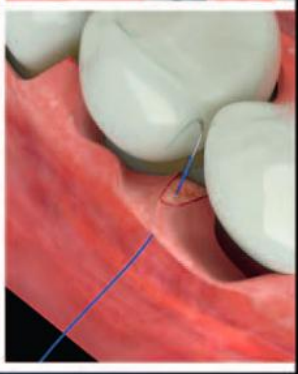

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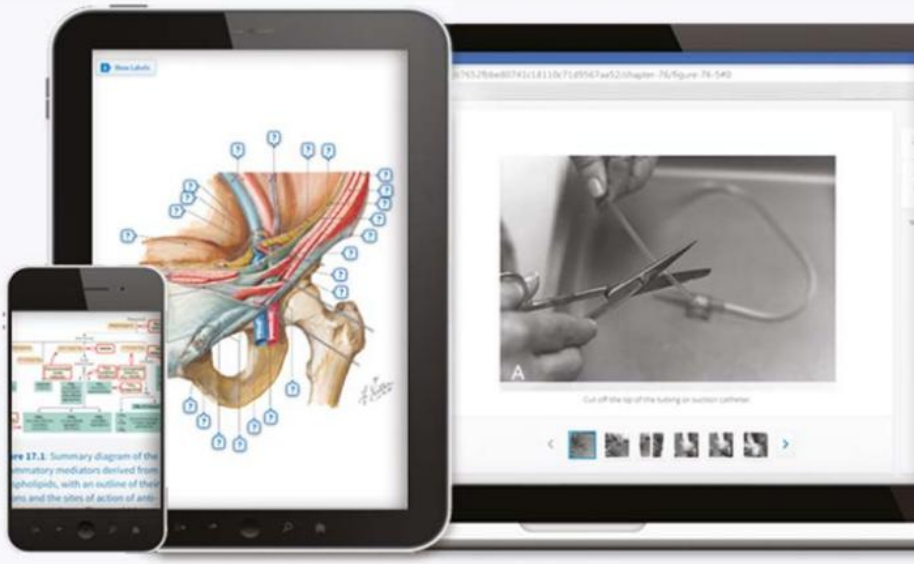

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14TH EDITION

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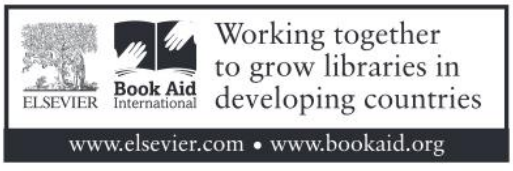

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She has served as a full-time Professor in academia for 25 years at UCSF, University of Michigan, and currently at UCLA. She has held several leadership positions, including the Inaugural Director of Global Initiatives at the University of Michigan School of Dentistry and leadership roles in the American Academy of Periodontology, including the Chair of the Research Submissions Committee. She has served as Chair of Periodontology at UCSF where she concurrently held the R. Earl Robinson Distinguished Professor of Periodontology. She is currently the Associate Dean for Research at the UCLA School of Dentistry.

She is an internationally recognized expert on periodontal disease pathogenesis, oral cancer carcinogenesis, perio-systemic disease relationships with a special focus on oral cancer, host-microbe interactions, the oral microbiome, oral biofilm biology, and antimicrobial-based therapeutics. She has authored over 140 peer-reviewed publications in such journals as *Biochimica et Biophysica Acta Cancer Reviews, Cell Death and Differentiation, Cancer, Molecular Biology of the Cell, Journal of Proteome Research, Journal of Biological Chemistry, Genes and Cancer, PLOS Pathogens, NPJ Biofilms and Microbiomes,* and *Journal of Controlled Release*. She has been continuously funded by the National Institutes of Health (NIH) for over 25 years. She serves on the Editorial Board of the journal *Scientific Reports* and *International Journal of Oral Science*, and as Editor to a Volume of *Periodontology 2000* on Special Populations in 2021.

Her innovative research studies have been recognized with several major research awards: In 1997, she was awarded the prestigious American Association for Dental Research (AADR) Edward H. Hatton Award and the American Academy of Periodontology (AAP) Balint Orban Award; The International Association for Dental Research (IADR) GSK Innovation in Oral Care

PREFACE

To view the following videos, please visit the companion website at eBooks.Health.Elsevier.com.
Overview of the 14th Edition: Perry R. Klokkevold
Introduction to *Clinical Periodontology and Implantology:* Henry H. Takei

With the help of Elsevier's advanced technology and high standards of quality, a recognized team of editors, contributors, and production staff have developed the most comprehensive periodontal resource ever created. This body of work represents the fundamental knowledge base of the profession providing readers an important digitally accessible information resource.

Since publication of the first edition of the parent *Clinical Periodontology* book in 1953, periodontology has made tremendous advancements. Scientific analysis of periodontal tissues and the elucidation of mechanisms and causes of disease have extended far beyond histology and physiology into the realm of cellular and molecular biologic understanding.

Importantly, oral health, especially periodontal health, is now an integral part of overall systemic health. Precision medicine explicitly incorporates periodontal health considerations and the bidirectional influence of periodontal and systemic health.

The patient is the focus of prevention and therapeutic goals and recent advances in patient reported outcomes allows the clinician to assess the patients' feelings and how their functions improve from the rendered treatment. *Newman and Carranza's Clinical Periodontology and Implantology,* 14th edition, is the first textbook in the field that includes background on this important aspect of integrated health care.

Implant dentistry has become a major component of periodontology, and this book offers a wide coverage of important treatment modalities that are relevant to the practice of dentistry. Digital technology is now an integral part of implant treatment, and this edition provides coverage of many essential topics and techniques. Basic and advanced topics are covered with informative illustrations, videos, and insights from leading clinicians.

This new edition is rich with images, animations and videos (marked with ▶ throughout the text), question sets, case reports, PowerPoint slides, audio slides, a virtual microscope, multidisciplinary case scenarios, and more. No other resource offers such a comprehensive approach to providing high-quality content for dental students and clinicians alike. The addition of images and video from PerioPixel company throughout the resource has been an important contribution to learning. With the interactive glossary, the readers can learn terminologies and definitions as they go through the text.

New therapeutic goals and clinical techniques, based on an improved understanding of disease and healing, have facilitated better outcomes and brought us closer to achieving the ultimate goal of optimal periodontal health and function. Today, reconstruction and regeneration of lost periodontal structures, replacement of compromised teeth with implants, and creation of esthetic results are integral parts of clinical practice.

The multifaceted, complex task of producing a major resource required the collaboration of numerous experts from various fields, and their contributions are invaluable. We know that this edition will be an essential part of the continuous progress of our profession.

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CHAPTER 1

Clinical Periodontology and Implantology in the Era of Precision Medicine

Satheesh Elangovan | Chun-Teh Lee | Georgios A. Kotsakis | Irina F. Dragan | Michael G. Newman

CHAPTER OUTLINE

Periodontology and Its Contemporary Practice

Periodontology is a field of dentistry that focuses on the prevention, diagnosis, and treatment of periodontal diseases (and conditions) and on the placement of dental implants to treat edentulism. In this chapter, we will present some of the recent developments and concepts that will change the way periodontics will be practiced in the near future. Periodontal diseases and conditions are pathologic processes affecting the tooth-supporting apparatus called "periodontium" (see Chapter 5). Of these diseases and conditions, gingivitis and periodontitis are highly prevalent across the globe, with gingivitis being the inflammation of gingiva without loss of periodontal attachment, whereas in periodontitis, there will be loss of periodontal attachment, making the latter condition irreversible.

Periodontitis is one of the most prevalent diseases in the world, with an estimated 538 million people affected by its severe form.[19,29] Periodontitis is initiated by specific bacteria in the dental biofilm, but the signs and symptoms of the disease are a result of the host immune response (inflammation) to the bacteria and its by-products (Fig. 1.1). When uncontrolled, the inflammatory mediators that are supposed to be protective attack the host tissues of the periodontium, leading to its loss (see Chapter 8). There is emerging evidence that inflammation can also drive the microbial shift from a nonpathogenic to a pathogenic dental biofilm (see Chapters 8 and 10). The clinical signs of periodontitis include pocket formation and increase in tooth mobility. The typical symptoms patients with periodontitis present with include pain or discomfort, bad breath, bleeding while brushing, or a mobile tooth or teeth. It is important to remember that periodontitis is a noncommunicable chronic condition (NCCC) that shares several of the social and other risk factors of other NCCCs that will be discussed later.[69] There is also a large body of evidence to suggest associations between periodontitis and systemic conditions such as diabetes or cardiovascular conditions, with inflammation being the bridge between the two disease entities.

As mentioned earlier, placement and maintenance of dental implants are an integral part of periodontology, and it is an understatement to say that implants revolutionized the way dentistry is currently practiced and that it has positively impacted countless patients by improving their quality of life (Fig. 1.2). Dental implants, like natural dentition, are prone to pathologic conditions, with periimplant mucositis and periimplantitis being the implant counterpart of gingivitis and periodontitis of natural dentition, respectively. Periodontists, specialists in periodontology and implant dentistry, have extensive additional training beyond dental school and often partner with referring dentists to maximize the overall treatment of the patient. The subsequent chapters of this book will go in depth into all aspects of periodontology and oral implantology.

Fig. 1.3 provides an overview of the currently used workflow in the management of patients with periodontal diseases and conditions. Currently, when patients present to clinic for a periodontal evaluation, most of the time, they already have periodontal or periimplant disease or conditions, with or without symptoms. Often these patients are self-referred or referred by another oral health care provider for treatment. Clinicians with conventional training perform the clinical exam, which is composed of extraoral and intraoral examinations. Clinical periodontal examination involves both visual and tactile examination in the form of periodontal probing to assess probing depths, clinical attachment levels, and several other measures (see Chapter 38). Radiographic examination then follows, which typically involves interpretation of radiographic images of the dentition or implant and its relationship to the alveolar bone. Findings from both the clinical and radiographic assessments are then taken into account to come up with a diagnosis. Then prognosis

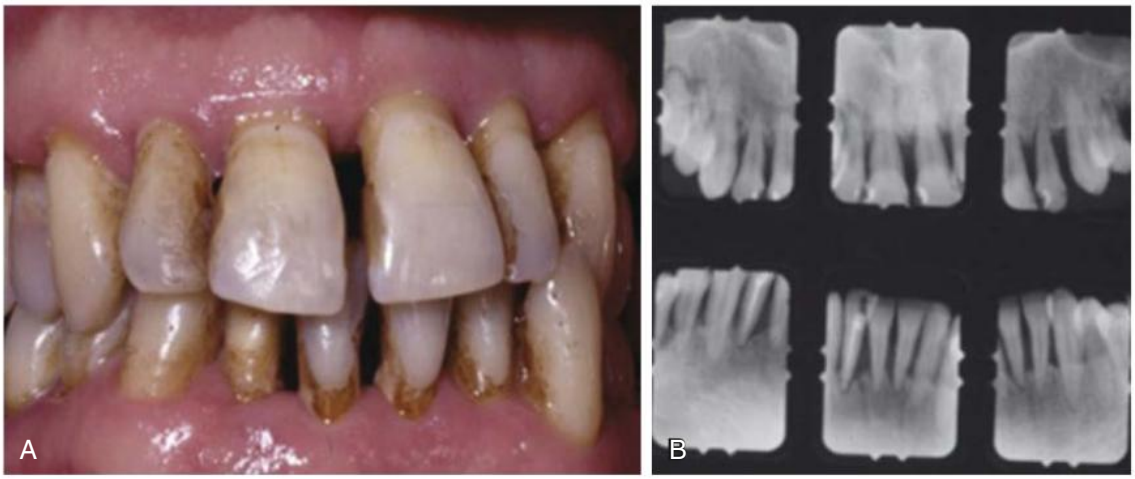

Fig. 1.1 Clinical (A) and radiographic (B) images of a patient suffering from periodontitis showing the classical clinical signs of the disease. The clinical signs include signs of inflammation of the gingiva, deepening of periodontal sulcus (becoming a pocket), and the presence of deposits. Radiographically, bone loss is characteristic of periodontitis, and in the example shown (B) there is bone loss all the way up to the apical third of the root of the anterior dentition.

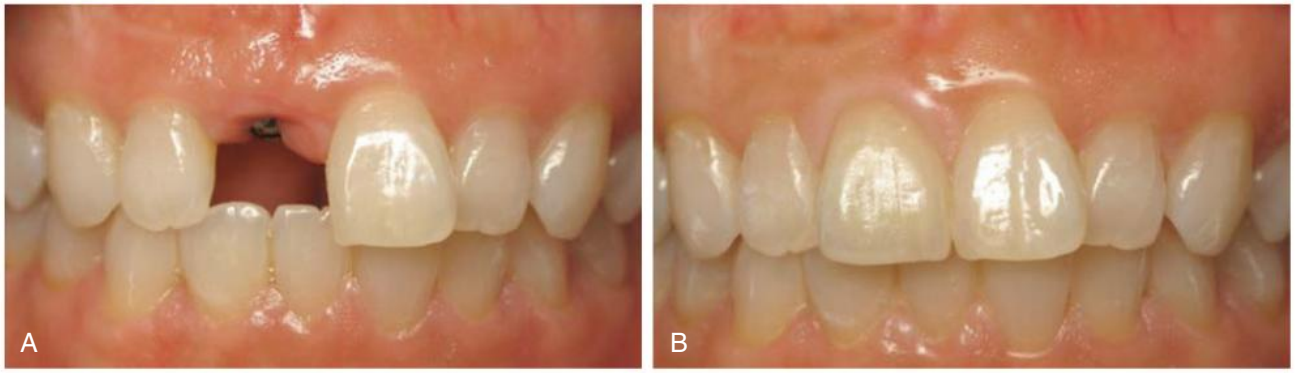

Fig. 1.2 Restoration of an edentulous site (#8) (A) with an implant supported single crown (B). Note the significant improvement in esthetics for this patient following an implant-based fixed restorative solution.

will be assigned for each tooth or implant and for the overall dentition, and subsequently, a treatment plan is devised.

Using the treatment plan as a roadmap, patients typically start with nonsurgical therapy (NST) (see Chapter 51), which will be followed by periodontal reevaluation, to assess outcomes of NST (see Fig. 1.3). Depending on the clinical presentation at the time of reevaluation, the need for additional therapy such as surgery will be assessed. If a patient does not require additional therapy or is not a candidate for surgical therapy, the patient will be placed on a maintenance program (or supportive periodontal therapy) that involves periodic exams and professional cleanings (see Chapter 70).

Contemporary Practice of Medicine

Currently there is a greater emphasis given to patients' well-being and how *they* feel and function, versus the mere presence or absence of disease that can be detected and measured using clinical tests and other diagnostic tools. Yet, still, health care primarily focuses on the physical signs or **surrogate measures** of disease and addresses those using interventions, giving less regard to the patient's mental and social well-being and how they perceive the disease. In addition, the outcomes used to assess the effectiveness of those interventions both in clinical studies and in practice often does not correlate with patients' perception or well-being.[72] Moreover, the health care system traditionally has been very good at being reactive to

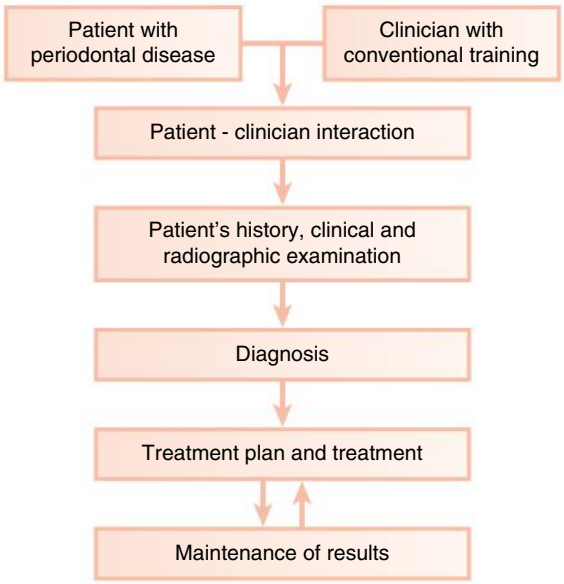

Fig. 1.3 Flowchart depicting the current clinical workflow in the management of patients with periodontal diseases and conditions. To an extent this is a one-size-fits-all approach, and it is more of a reactive approach to disease that already exists than preventative.

an already existing disease rather than being preventive.[70] With the advancements in systems medicine—big-data and digital technologies including **machine learning (ML)**—modern medicine is going through a rapid transformation.

The aforementioned advances allow for a more thorough risk assessment that takes several factors into consideration, that were not available or accessible earlier. These will also facilitate the provision of preventive care and a treatment that is highly customized to the patient rather than taking a "one-size-fits-all" approach. The problem with the latter approach is that it works with the assumption that all the patients will respond to a particular intervention in a similar manner, which is not the case. A good example is the way an individual patient metabolizes a given pharmacologic agent. Using genetics to guide drug prescribing decisions ("pharmacogenetics") now allows the clinician to select a drug based on the genetic makeup of the patient to maximize its safety and efficacy (see Chapter 9). This is a good example of what precision medicine can offer.

Precision Health Care

Clinicians must always strive to come up with the best possible treatment available for a given clinical situation. In precision medicine, the treatment plan generated will be customized to the patient, based on personal history, medical history, and clinical factors, supplemented with environmental factors and biologic information. Therefore the aim of precision treatment is to tailor health care for individuals using their own unique characteristics to enhance treatment outcomes and minimize adverse effects.

KEY FACT

Although the terms precision medicine and personalized medicine are used interchangeably, it is important to note that there is a distinction between the two. Precision medicine encompasses personalized medicine, and it harnesses clinical and biologic information to stratify patients and to guide clinical decision-making.

With the assistance of advanced and novel technology, information derived from biologic specimens such as blood or saliva can now be effectively and rapidly analyzed by computers through informatics. In addition, **artificial intelligence** (AI) has improved the accuracy of diagnostic interpretation of clinical and radiographic images, and the patient's behavioral information can be collected through wearable electronic devices. The other major advancement is the widespread use of **electronic health records** (EHRs) in clinics, which is an ideal platform to connect and integrate all of the aforementioned advancements to aid the clinician chairside in developing a personalized treatment plan that incorporates all of the aforementioned factors.

Emerging Practice Model in Periodontology

The contemporary clinical protocol that uses just surrogate outcomes of periodontitis such as **probing depths** is geared toward detecting periodontal diseases that have already occurred and therefore does not offer any guidance for *preventive* strategies. The current workflow (see Fig. 1.3) also lacks the ability to *predict* the degree of responsiveness to a proposed therapy. In addition, the existing workflow is set up in a way that is not conducive for patients to *participate* and be engaged in their health management process.

The alternative model of care shown in Fig. 1.4 allows the care to be *predictive, preventive, personalized,* and *participatory* (the cornerstones of "precision health care" and often referred to as the 4Ps).[73] With this approach, the expectation is that the patients will see the health care provider before the initiation of disease *(preventive),* and this is feasible by knowing the patient's risk profile (for the disease), based on the biologic makeup of the individual. When information, such as a patient's biologic makeup, is routinely integrated into the clinical assessment and with effective amalgamation of digital innovations such as AI and ML in the EHRs, clinicians will be able to assemble a more accurate diagnosis and prognosis. This allows for the development of a more personalized treatment plan *(personalized)* for the patient that is far more predictable *(predictive)*. Oral hygiene aids such as brushes or intraoral appliances, when fitted with biosensors, can detect plaque levels or biomarker analytes in saliva and can provide real time notifications to patients regarding their oral and systemic health *(participatory)*.[2,31] Equally important to provide personalized care is the availability and application of scientific evidence with dental patient-reported outcome (dPRO) measures in the clinical decision-making process.[54]

Components of Precision Periodontics

This section is focused on introducing some of the key components associated with precision and patient-centered periodontics (see Fig. 1.4).

Biologic Information

Microbiologic and Host Response Information

Maintaining the host-microorganism balance and homeostasis is a prerequisite for maintaining periodontal health. Comprehensively deciphering the host response and microbiome, at the patient level, will be critical to stratify patients for precise diagnosis and effective treatment. Periodontitis is an inflammatory disease initiated by microorganisms, primarily bacteria (see Fig. 1.1). However, tissue damage in periodontitis is primarily mediated by the host response, with a smaller contribution by bacteria. In other words, the presence of periodontal pathogens is required but not sufficient for disease initiation. Therefore understanding the host response in periodontitis patients is critical to assess patients' periodontal conditions and risk for future progression. Analysis of genetic polymorphisms, evaluating cytokine levels in saliva, gingival crevicular fluid (GCF) or serum, and measuring blood immune cell counts are some of the ways clinicians can assess the patient's host response.

Historically, several bacterial species, such as *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Treponema denticola*, and *Tanerella forsythia* were known to be the major periodontal pathogens. Keystone pathogens, such as *P. gingivalis*, with a relatively low abundance in dental plaque, can cause dysbiosis, which can instigate periodontal inflammation[38] (see Chapter 10). Recently, more and more bacterial species and other members of the microbial world, such as viruses, bacteriophages, and fungi are being identified (through novel technologies, such as 16S sequencing, shotgun sequencing, and metagenomics) to be associated with periodontitis. In general, excessive putative and opportunistic pathogens induce inflammation, but specific bacterial species are more important for pathogenesis than others. Analyzing oral plaque samples can provide information on microbial composition and abundance that may help clinicians to assess periodontal disease risk at the individual patient level. For detailed information on periodontal microbiology and the role of host response in the pathogenesis of periodontal diseases, refer to Chapters 10 and 11.

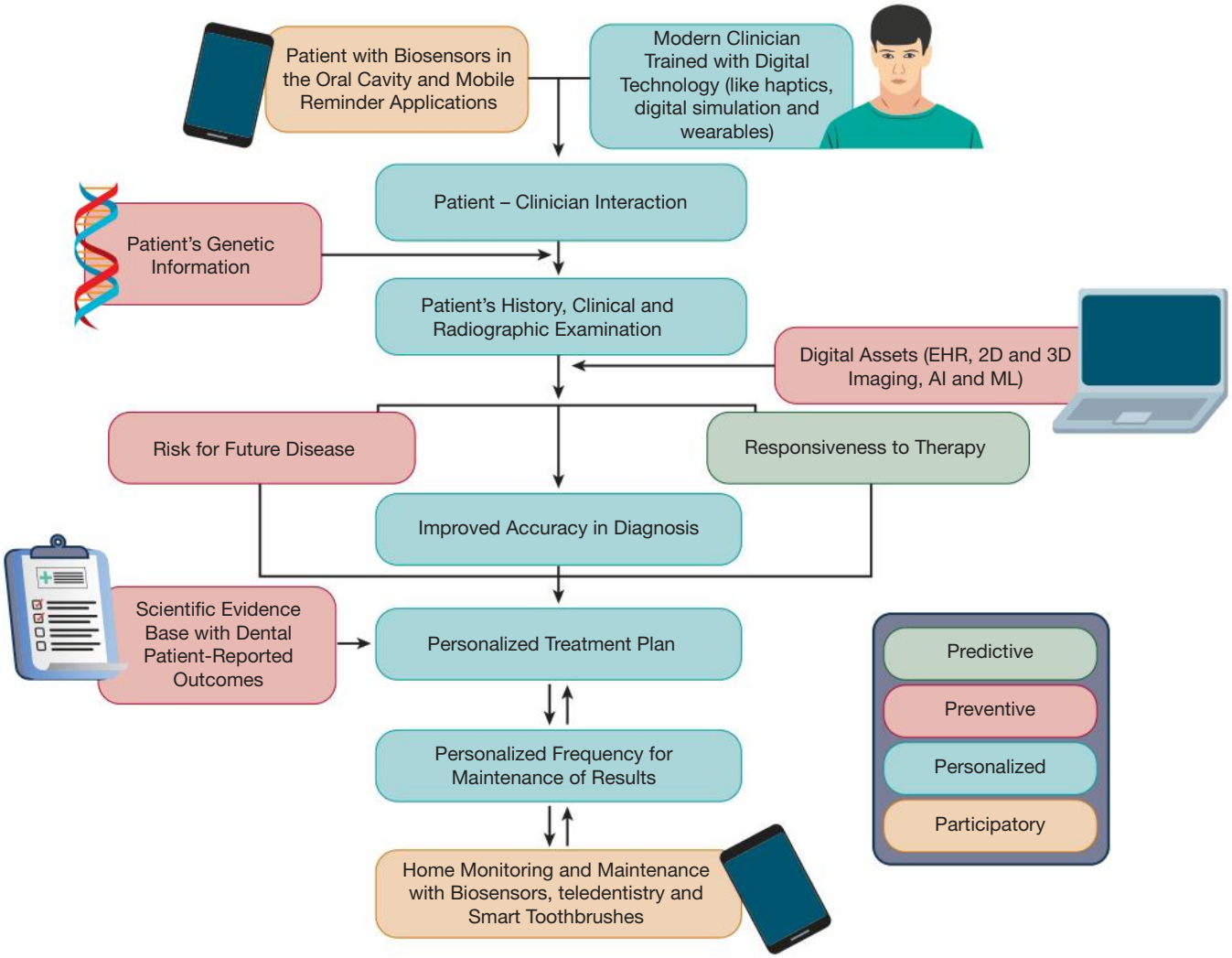

Fig. 1.4 Periodontology and implant dentistry as an integral part of overall connected health and personalized care. At the center is the digital home that maintains the electronic dental record and information from other dentists, practice guidelines, physicians, family, patient-reported outcomes, medication history, pharmacy, and more. Artificial intelligence, virtual reality, teledentistry, sensors, connected devices, and wearables are linked to provide clinical decision support, training, and remote connectivity between the provider and the patient. Biological information such as the microbiome, genetic, environmental, immune status and other info in one central location where algorithms assist the dental professional to provide optimum treatment and prevention guidance. (*Figure by Dr. Ryutaro Kuraji.*)

Genetic Information

It is well known that specific genetic mutations are associated with disorders and diseases (see Chapter 9). Due to the complexity of associations and interactions between a large number of genes and disorders, the single gene–single disorder ("candidate gene") approach to study the impact of genetic factors on diseases is no longer effective. By using advanced informatics technology, a conceptual framework can now be developed to systematically link all genetic disorders (disease phenome) with all of the disease-associated genes (disease genome), resulting in a global view or "diseasome" that comprises of comprehensive known disorder/disease gene associations.[20]

Biomarkers in Periodontitis

A biomarker, or "biologic marker," is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or responses to a therapeutic intervention or a hazard.[6,74] This section is focused on providing a brief overview of biomarkers (molecules) that can be measured in biologic samples that correlate with the severity and progression of periodontal inflammation.

GCF is a physiologic fluid and an inflammatory exudate originating from the gingival vascular plexus and exists in the gingival sulcus.[5] GCF is composed of a mixture of molecules that originate from the blood, host tissues, and bacteria, including, electrolytes, metabolites, cytokines, antibodies, bacterial antigens, and enzymes. GCF can be easily collected from both healthy and diseased sites using special paper strips (Fig. 1.5) or micropipette, and its volume increases when periodontal tissues are inflamed. The concentration of specific molecules (biomarkers) from GCF can be assessed by techniques such as enzyme-linked immunosorbent assay (ELISA), proteomics, or metabolomics, depending on the purpose and characteristics of the molecules of interest.

Omics Technologies

Omics technologies help analyze the characteristics of a large number of biologic molecules in samples in a cost-effective and high-throughput

or diabetes presenting with at least one of the risk factors associated with hyperglycemia.[35,36] By setting up these thresholds in the EHR system, a clinician can be notified of the potential risk of the patient for diabetes, based on the findings from dental examination and personal information. Once these potential diabetic patients are identified, dentists can refer the patients to physicians for further testing and management.[37] In addition, several risk-assessment tools, such as Periodontal Risk Assessment (PRA),[39] and Periodontal Management by Risk Assessment (PEMBRA),[49,53] that are available to assess the risk for periodontal disease progression can be integrated into the EHR (see Chapter 40). This allows for chairside risk determination that can be used for treatment planning and patient education purposes.

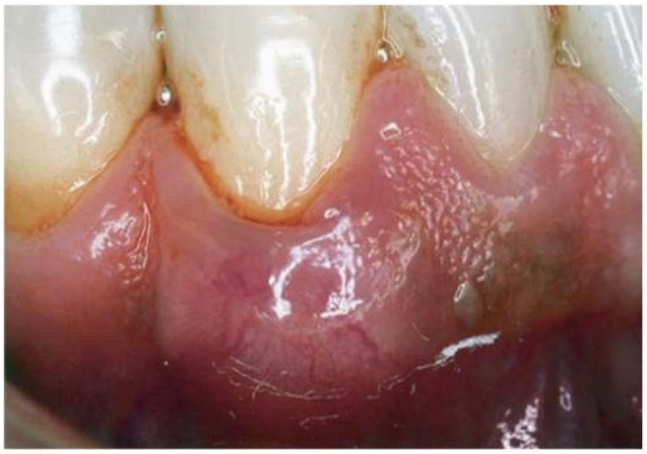

Fig. 1.7 Localized periodontal abscess of a mandibular right canine in a poorly controlled diabetic patient. Diabetes, when uncontrolled, predisposes a patient to periodontal abscess formation.

Artificial Intelligence–Assisted Clinical Data and Radiographic Image Analyses

Artificial intelligence refers to the ability to build machines with the capability of performing tasks that are performed normally by humans.[60] The utilization of AI to assist and supplement clinicians to improve the overall accuracy of diagnosis is called augmented intelligence.[61] In contrast, ML is a subset of AI applications that refers to the ability of self-learning by the machine itself with the capability to detect patterns and make predictions.[25,60] Deep learning (DL) is a subset of ML applications that teaches itself to perform a specific task with increasingly greater accuracy as compared with ML.[25] (ML or DL models have been extensively applied to perform complex data analysis, to identify anatomic structures and pathologic findings on radiographs, and for disease detection; Fig. 1.8.) A research group using ML, recently demonstrated that a well-designed combination of salivary bacteria can distinguish periodontally healthy from the disease group.[30] In separate studies, a DL-based computer-aided diagnosis (CAD) tool was shown to assist in making periodontal diagnosis by measuring alveolar bone levels on oral radiographic images.[8,34] *Very recently, authors applied ML algorithms to a large national database and identified predictors of tooth loss.*[16]

Wearable/Portable Electronic Devices

Many wearable or portable electronic devices, such as a smart phone and a smart watch, that are used in day to day lives can collect and transfer data effectively. These devices are developed based on the concept called the "Internet of Things" (IoT), which is about connecting and exchanging data between a variety of devices and systems over the Internet. The Internet of Medical Things (IoMT) is a cloud network–based advanced technology which is basically IoT that is applied to the medical field. It allows for collection and active monitoring of patients' health status information for disease prevention (Fig. 1.9). The same concept can be applied in dentistry

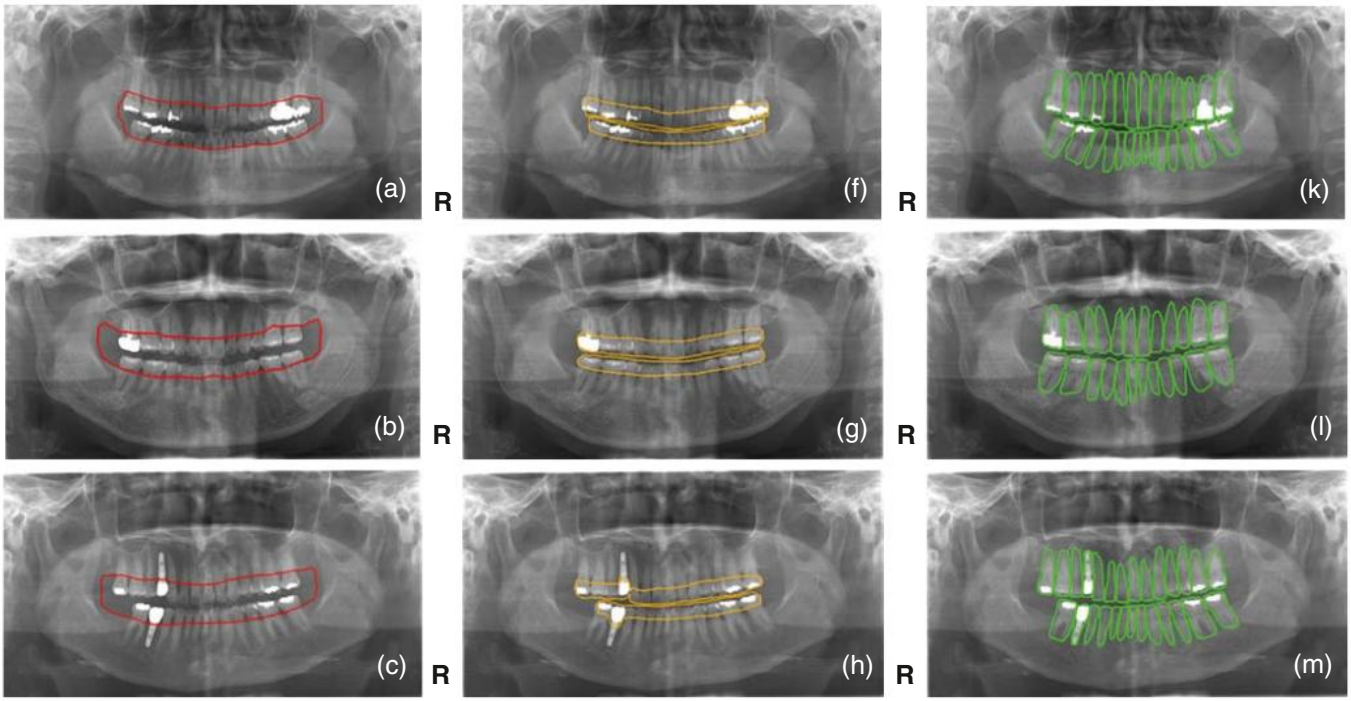

Fig. 1.8 Use of deep learning (DL) program to diagnose periodontal disease. DL program was used to detect bone levels (a, b, and c), cementoenamel junctions (f, g, and h), and tooth/implant morphology (k, l, and m) in three different patients. (*From Chang HJ, Lee SJ, Yong TH, et al. Deep learning hybrid method to automatically diagnose periodontal bone loss and stage periodontitis.* Sci Rep. *2020 May 5;10[1]:7531. doi: 10.1038/s41598-020-64509-z. PMID: 32372049; PMCID: PMC7200807.*)

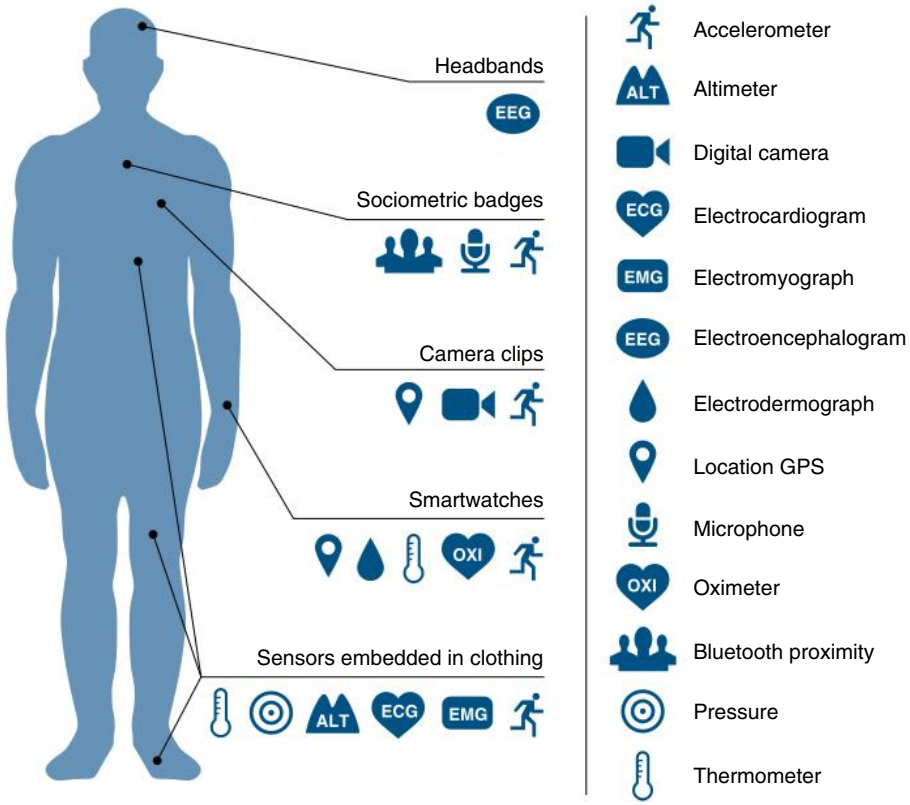

Fig. 1.9 Examples of consumer wearables to monitor health. (*From Piwek L, Ellis DA, Andrews S, et al. The rise of consumer health wearables: promises and barriers.* PLoS Med. *2016 Feb 2;13[2]:e1001953. doi: 10.1371/journal.pmed.1001953. PMID: 26836780; PMCID: PMC4737495.*)

as the Internet of Dental Things (IoDT).[59] For example, a Bluetooth-incorporated smart toothbrush can detect dental plaque, monitor real-time brushing location, sense brushing pressure, and document brushing behavior. These connected devices can then transfer this information to the dental EHR to aid clinicians in improving their patient's home care by customized behavioral modifications.

Teledentistry

Teledentistry is an effective way to remotely interact with patients by videoconferencing to provide dental consultations and instructions. With the increased availability and access to broadband internet services, teledentistry is gaining popularity. It can be a good medium to reach patients who would otherwise not have access to dental care (e.g., in rural areas, patients in nursing facilities, or during a pandemic). Although a large majority of dental treatments can be only provided in person, teledentistry offers an alternative approach to screen for oral diseases and potentially help patients to manage oral diseases when immediate dental care is unavailable. The coronavirus disease 2019 (COVID-19) pandemic has brought to light the importance and usefulness of teledentistry, which would potentially pave way for its regular future use even in nonpandemic situations.[66]

Patient-Reported Outcomes and Clinical Research

Periodontal practice has made tremendous progress toward evidence-based treatment over the past decade, but in some aspects, it is still trailing behind medical practice. This important progress can be further accelerated with the availability of patient-perceived outcomes of periodontal and implant interventions. One critical aspect of personalized medicine is that each person perceives disease burden differently.[51] Disease-related morbidity has an experiential component that cannot be captured by clinical disease measures. In periodontal practice, treatment effects are routinely based on clinician measured surrogate outcomes, such as probing depth and attachment levels, which are not easily communicated to or perceived by dental patients. The fact that in most cases these physical measures are not readily perceived by patients generates a communication gap in the dentist-patient relationship that ultimately affects care. For instance, a clinician would be concerned with a 6-mm probing depth on an anterior central incisor, whereas this would mean very little to a patient without a dental background. Therefore proper diagnosis and communication is key to devising tailored treatment plans that meets patient preferences and expectations.

Tailored treatment plans go beyond precision dentistry, which considers individual host inflammatory characteristics, to encompass behavioral characteristics and individually perceived treatment needs. A periodontal patient who strongly prioritizes function and pain over esthetics or over social interactions and appearance may not be necessarily amenable to undergoing a surgical procedure to retain a tooth and maintain esthetics. To address the communication gap and to include patient-specific quality of life considerations in treatment planning, dPROs, which are true outcomes of disease, have gained significant momentum in dental and medical research to better capture disease burden and treatment effects.[54]

KEY FACT

Examples of dental patient-reported outcome measures (PROMs) include how a patient feels and functions and the overall *patient-reported* satisfaction, phonetics, chewing comfort, stability, cleanability, and esthetics.[50] PROMs must be reported directly by the patient without interpretation by anyone else, including the dentist.

As dPROs gain momentum in dental practice, our understanding of the true outcome of dental therapies will vastly increase. One key question that the utilization of dPROs is poised to address is, "To what extent does periodontal disease contribute to an individual's burden of disease?" *As mentioned earlier, the Global Burden of Diseases study has consistently revealed that periodontitis is one of the most prevalent noncommunicable diseases in adults worldwide.[29] The global epidemiology of population health has fundamentally changed during the past decades. Since 2000, the burden of NCCC has become the leading cause affecting population health worldwide, with communicable diseases negatively impacting population health, only in limited developing regions, or areas affected by war.[15] Therefore new health metrics are being developed, such as years lived with disability and proportion of years spent in ill health, to capture the extent of diseases on nonfatal health loss. Nonetheless, although periodontitis is highly prevalent, its contribution to nonfatal yet negative impact on health is consistently underappreciated, in comparison with medical conditions, such as diabetes mellitus, because the patient-perceived burden of periodontitis is not adequately captured in dental practice and research settings.[29] Despite the understanding that periodontal diseases affect a person's well-being and oral health–related quality of life (OHRQoL), in most cases, physical measures of diseases are solely captured to track an individual's oral health status.* [54]

In clinic, treatment interventions seem to lead to varying levels of patient-perceived improvements; however, these effects are not routinely captured by clinicians. As a result, the individual patient perspective is not adequately influencing clinical decisions. To implement a real world change in the practice of periodontics and implantology by centering clinical practice on dPROs and complementing them with disease-relevant clinically measured outcomes, a clinically relevant and valid instrument for assessing OHRQoL becomes necessary. *Previous efforts to incorporate psychosocial measures in clinical practice have focused on the assessment of OHRQoL. The most frequently used OHRQoL instruments have been modeled after a seven-dimensional theoretical model of OHRQoL, based on Locker's conceptual model of oral health,[41] leading to the development of lengthy instruments that may be too burdensome to be used in real life situations. For example, the most commonly used measuring instrument for OHRQoL in dental research has been the Oral Health Impact Profile (OHIP), which in its original version included seven self-report items for each of the seven dimensions of OHRQoL.[64] Therefore the OHIP-49 requires considerable time and dedication by dental patients to complete, making it impractical for routine use at each dental visit. The use of lengthy measurement instruments and the practical limitations that they impose in clinical care settings and in large-scale research studies have remained the main impediment in the incorporation of the assessment of OHRQoL as a standard outcome in periodontology and implant dentistry.[26]*

Future Clinical Trials

In addition to the inclusion of dPROs in clinical trials, it is extremely important to rethink the way clinical trials are conducted. Due to inherent variations between patients, there will be responders and nonresponders to any given treatment intervention. Based on the response to prior intervention and patient characteristics at any given point in therapy, the next decision in treatment sequence is made, and this is the principle behind the concept of dynamic treatment regimens (DTRs). Traditional clinical trials in periodontics will not allow researchers to identify DTRs or validate interventions that have to be adapted based on patient responses called "adaptive interventions." Sequential Multiple Assignment Randomized Trial (SMART) clinical trials with the help of advanced statistical techniques will allow researchers to identify DTRs and adaptive treatment interventions in a given patient population.[3,40] *Multiple nodes of key clinical decision-making steps along with specific outcomes embedded within the SMART designs make it an ideal design to identify and validate DTRs. Therefore, in the near future, clinical trials embedded with SMART design will have an important place in the development of dynamic treatment protocols in periodontics.*

Periodontal Education to Support Future Clinical Practice

With the forthcoming changes in the landscape of clinical practice, educators will be required to adapt and update the curriculum accordingly to prepare clinicians for the future. The Commission on Dental Accreditation, the accreditation body of dental education in the United States, requires academic institutions to integrate technologies in a meaningful way in the training offered for both dental students and postgraduate residents.[9] Significant efforts have been made by different institutions to offer consistent programs able to inform faculty members on the best pedagogic practices in their teaching activities.[27] Framing these activities using validated educational models can positively impact not only the students (Logic Model) but also the patients (Kirkpatrick Model).[17] The release of the new Integrated National Board Dental Examination in the United States in August 2020, with a focus on case-based assessment, is consistent with the ongoing shift in clinical practice to a more person-centered approach.[28] Most chapters in this book will have a case-based learning exercise. Students are now required to apply fundamentals in basic and clinical sciences in a specific clinical scenario.[14] *To expand on the scope of the American Academy of Periodontology's In-Service examination offered to all postgraduate residents in the United States, a case-based component has been piloted in 2021. This initiative might be able to leverage on the benefits of case-based assessment for different clinical scenarios, testing key concepts in diagnosis, etiology, prognosis, treatment plan options, and maintenance.*

Surgical Education

Multiple studies in various health care professions have shown the key role of simulators in surgical education, but there is only sparse evidence in the field of dentistry.[67] The pedagogic principles that support this type of technology are cognitive task analysis (CTA) and constructivism.[68,69] Applying the CTA framework, clinicians will be able to divide a complex task into its cognitive phases, enabling their decision-making process.[68] When applying such a process into the teaching activity, an educator can assess whether the students were able to comprehend a complex task step by step (Fig. 1.10). Furthermore, one can modify the complex procedure by adding intraoperative complications and assess the situational awareness of the student.

Virtual reality (VR) is an advanced computer-generated technology that offers realistic experience by three-dimensional visual rendering of the background or surroundings. The students or clinicians can wear a special electronic device (e.g., VR headset) to interact with virtual patients or perform virtual procedures to gain experience and practice clinical procedures in a simulated environment. These VR devices can also help patients as a tool to reduce their dental anxiety.[45] VR is becoming an important part of medical education, and dental education is not too far from this.[57] With more and more dental schools investing in virtual simulators in the fields of operative dentistry, prosthodontics, and endodontics, the use of VR will soon be a standard in periodontal education as well.[13] As these technologies make their way into clinical education, it is prudent to evaluate their impact not only on the students' attitudes, behaviors, and learning but also on other key stakeholders (faculty, staff, and patients).[47]

Augmented reality (AR) is simulation of the real world environment, where the real objects are enhanced by computer-generated perceptual information to provide interactive experience (Fig. 1.11). By

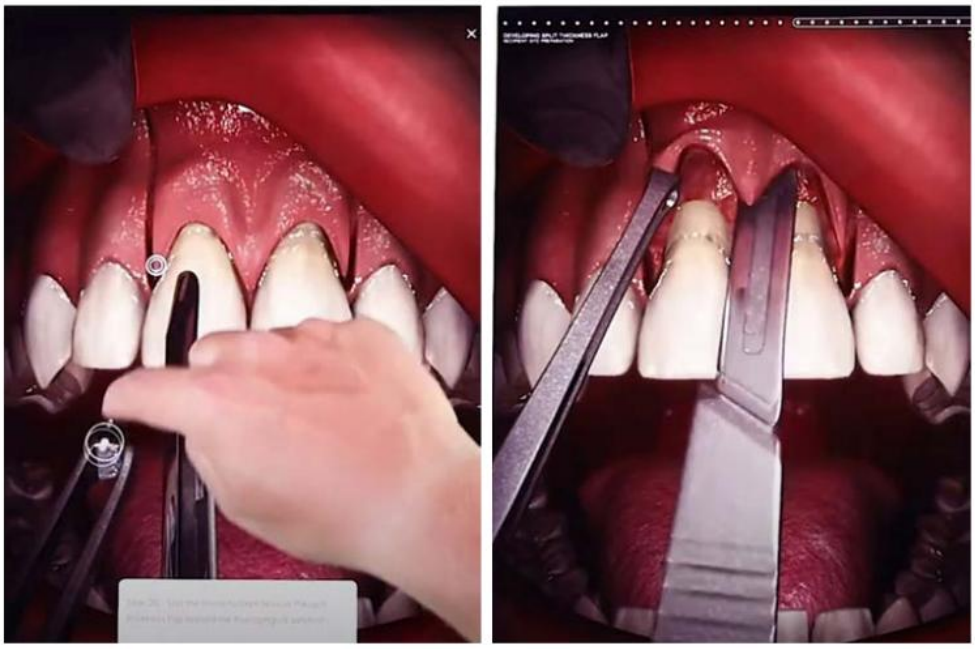

Fig. 1.10 Screenshots showing an interactive learning experience using a surgical simulation program (*Touch Surgery, Medtronic* https://www.youtube.com/watch?v=pL-amyBgu6Q)

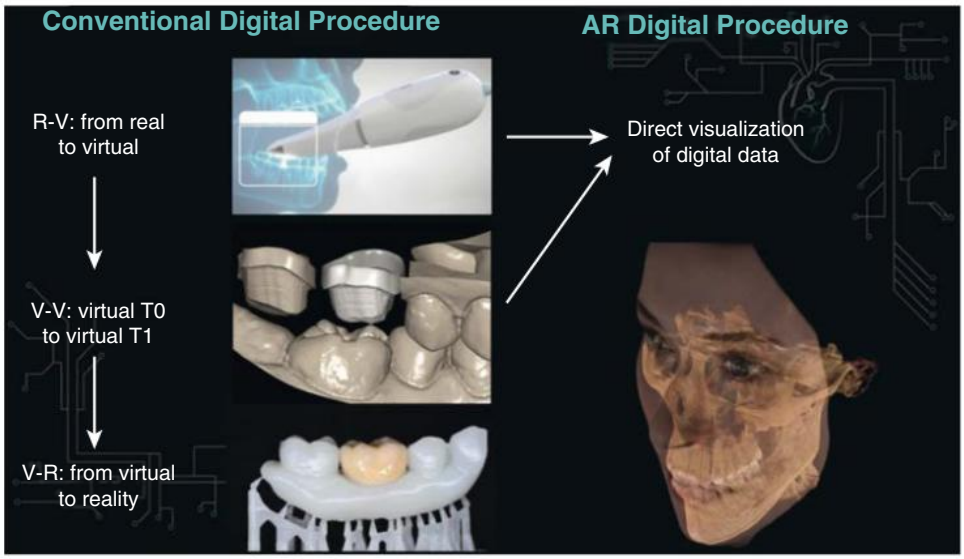

Fig. 1.11 Illustration showing how augmented reality can enhance the current digital dentistry workflow. *(From Farronato M, Maspero C, Lanteri V, et al. Current state of the art in the use of augmented reality in dentistry: a systematic review of the literature.* BMC Oral Health. *2019 Jul 8;19[1]:135. doi: 10.1186/s12903-019-0808-3. PMID: 31286904; PMCID: PMC6613250.)*

wearing a specific device (e.g., AR glasses), the user can see virtual objects seamlessly integrated with the real environment. The key difference between VR and AR is that VR attempts to create an artificial environment in which the user interacts through the senses, whereas AR also provides an interactive experience by supplementing the real environment rather than creating a new artificial environment.[48] In addition to their potential uses in dental education, emerging evidence points to the application of AR-based technologies in the clinics.[48] An example would be an AR-based implant navigation system developed to increase the accuracy of implant placement.[56]

Conclusion

Recent biologic and technologic innovations are rapidly changing the health care landscape, and dentistry is no exception. Periodontists, despite tailoring treatment based on patient needs, still follows a one-size-fits-all approach when it comes to providing periodontal care. Now with the availability of biologic information from innovative technologies, continuously monitorable real world data from biosensors, all well integrated into an EHR that is powered by AI and ML, periodontics now enters into a precision care model that allows the treatment to be predictive, preventive, personalized, and participatory. These changes in clinical care should be supplemented by changes in the dental education curriculum to adequately prepare clinicians for this model and by rethinking how clinical trials should be conducted and by giving greater emphasis to dPROs in those trials.

References for this chapter are found on the companion website eBooks.Health.Elsevier.com.

CHAPTER 2

Evidence-Based Decision Making

Satheesh Elangovan | Jane L. Forrest | Syrene A. Miller | Greg W. Miller | Michael G. Newman

CHAPTER OUTLINE

Dental care professionals make decisions about clinical care on a daily basis. It is important that these decisions incorporate the best available scientific evidence to maximize the potential for successful patient care outcomes. It is also important for readers of this book to have the background and skills necessary to evaluate information they read and hear about. These evaluative skills are as important as learning facts and clinical procedures. *The ability to find, discriminate, evaluate, and use information is the most important skill that can be learned as a professional and lifelong learner.* Honing this skill will provide a rewarding and fulfilling professional career.

Background and Definition

Using evidence from the medical literature to answer questions, direct clinical action, and guide practice was pioneered at McMaster University, Ontario, Canada, in the 1980s. As clinical research and the publication of findings increased, so did the need to use the medical literature to guide practice. The traditional clinical problem-solving model based on individual experience or the use of information gained by consulting authorities (colleagues or textbooks) gave way to a new methodology for practice and restructured the way in which more effective clinical problem solving should be conducted. This new methodology was termed *evidence-based medicine* (EBM).[14]

KEY DEFINITIONS

Evidence: Evidence is considered the synthesis of all valid research that answers a specific question and that, in most cases, distinguishes it from a single research study.[2]

Evidence-based medicine: The integration of the best research evidence with our clinical expertise and our patient's unique values and circumstances.[36]

Evidence-based dentistry: An approach to oral health care that requires the judicious integration of systematic assessments of clinically relevant scientific evidence, relating to the patient's oral and medical condition and history, with the dentist's clinical expertise and the patient's treatment needs and preferences.[4]

The use of evidence to help guide clinical decisions is not new. However, the following aspects of EBM are relatively new:

- The methods of generating high-quality evidence, such as **randomized controlled trials** (RCTs) and other well-designed methods
- The statistical tools for synthesizing and analyzing the evidence (**systematic reviews** [SRs] and **meta-analysis** [MA])
- The ways for accessing the evidence (electronic databases) and applying it (**evidence-based decision making** [EBDM] and practice guidelines)[11,12]

These changes have evolved along with the understanding of what constitutes the evidence and how to minimize sources of bias, quantify the magnitude of benefits and risks, and incorporate patient values.[9,15] "In other words, evidence-based practice is not just a new term for an old concept and as a result of advances, practitioners need (1) more efficient and effective online searching skills to find relevant evidence and (2) critical appraisal skills to rapidly evaluate and sort out what is valid and useful and what is not."[33]

EBDM is the formalized process and structure for learning and using the skills for identifying, searching for, and interpreting the results of the best scientific evidence, which is considered in conjunction with the clinician's experience and judgment, the patient's preferences and values, and the clinical and patient circumstances when making patient care decisions. Translating the EBDM process into action is based on the abilities and skills identified in Box 2.1.[36]

Principles of Evidence-Based Decision Making

The use of current best evidence does not replace clinical expertise or input from the patient but rather provides another dimension to the decision-making process,[13,19,22] which is also placed in context with the patient's clinical circumstances (Fig. 2.1). It is this decision-making process that we refer to as "evidence-based decision making" and is not unique to medicine or any specific health discipline; it represents a concise way of referring to the application of evidence to clinical decision making.

BOX 2.1 Skills and Abilities Needed to Apply an Evidence-Based Decision-Making Process

1. Convert information needs and problems into clinical questions so that they can be answered.
2. Conduct a computerized search with maximum efficiency for finding the best external evidence with which to answer the question.
3. Critically appraise the evidence for its validity and usefulness (clinical applicability).
4. Apply the results of the appraisal, or evidence, in clinical practice.
5. Evaluate the process and your performance.

National Library of Medicine: MEDLINE, PubMed, and PMC (PubMed Central). How are they different? https://www.nlm.nih.gov/bsd/difference.html.

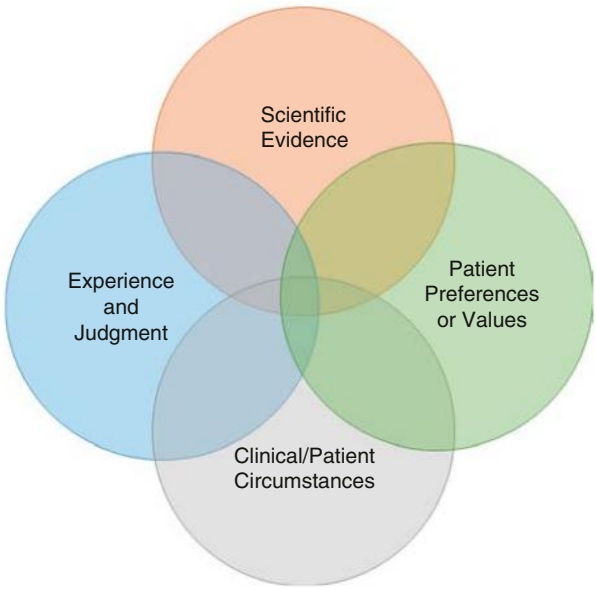

Fig. 2.1 Evidence-based decision making. (*Adapted from Image Copyright Jane L. Forrest, reprinted with permission.*)

EBDM focuses on solving clinical problems and involves two fundamental principles, as follows[15]:

1. Evidence alone is never sufficient to make a clinical decision.
2. Hierarchies of quality and applicability of evidence exist to guide clinical decision making.

EBDM is a structured process that incorporates a formal set of rules for interpreting the results of clinical research and places a lower value on authority or custom. In contrast to EBDM, traditional decision making relies more on intuition, unsystematic clinical experience, and pathophysiologic (biologic) rationale.[15]

Evidence-Based Dentistry

Since the 1990s, the evidence-based movement has continued to advance and is widely accepted among the health care professions, with some refining the definition to make it more specific to their area of health care. The American Dental Association (ADA) has defined evidence-based dentistry (EBD) as "an approach to oral health care that requires the judicious integration of systematic assessments of clinically relevant scientific evidence, relating to the patient's oral and medical condition and history, with the dentist's clinical expertise and the patient's treatment needs and preferences."[4] They have also established the ADA Center for Evidence-Based Dentistry (ebd.ada.org) to facilitate the integration of EBD into clinical practice.

The ADA's definition is now incorporated in the Accreditation Standards for Dental Education Programs.[3] Dental schools are expected to develop specific core competencies that focus on the need for graduates to become critical thinkers, problem solvers, and consumers of current research findings to enable them to become lifelong learners. The accreditation standards require learning EBDM skills so that graduates are competent in being able to find, evaluate, and incorporate current evidence into their decision making.[3]

KEY FACT

PICO

The first step in evidence-based decision making is asking the right question. The key is to frame a question that is simple and at the same time highly specific to the clinical scenario. Dissecting the question you want to ask into its components—problem or population (P), intervention (I), comparison group (C), and outcomes (O)—and then combining them will facilitate a thorough and precise evidence search.[36] In some cases, the time duration that it takes to demonstrate a measurable clinical outcome or the observation period (T) is also included in the research question.

Evidence-Based Decision-Making Process and Skills

The growth of evidence-based practice has been made possible through the development of online scientific databases, such as MEDLINE (PubMed) and internet-based software, along with the use of computers and mobile devices (e.g., smartphones) that enable users to quickly access relevant clinical evidence from almost anywhere. This combination of *technology* and *good evidence* allows health care professionals to readily apply the benefits from clinical research to patient care.[34] EBDM recognizes that clinicians can never be completely current with all conditions, medications, materials, or available products, and it provides a mechanism for assimilating current research findings into everyday practice to answer questions and to stay current with innovations in dentistry. A critical thinking skillset is an important prerequisite in EBDM. Fig. 2.2 depicts the traits that overlap between critical thinking and EBDM processes and how they are interconnected to tackle everyday clinical problems. Translating the EBDM process into action is based on the abilities and skills identified in Box 2.1.[36] This is illustrated clearly in a real patient case scenario (management of a patient with trauma-related avulsion and luxation of teeth) that is introduced in Case Scenario 2.1 (Figs. 2.3 and 2.4) and used throughout the chapter.

Asking Good Questions: The PICO Process

Converting information needs and problems into clinical questions is a difficult skill to learn, but it is fundamental to evidence-based practice. The EBDM process almost always begins with a patient question or problem. A "well-built" question should include four parts that identify the patient problem or population *(P)*, intervention *(I)*, comparison *(C)*, and outcome(s) *(O)*, referred to as PICO.[36] Once these four components are clearly and succinctly identified, the following format can be used to structure the question:

"For a patient with _____ (P), will _____ (I) as compared with _____ (C) increase/decrease/provide better/in doing _____ (O)?"

The formality of using PICO to frame the question serves two key purposes, as follows:

TABLE 2.1 Type of Question Related to Type of Methodology and Levels of Evidence

Type of Question	Methodology of Choice[32]	Question Focus[25]
Therapy, prevention	MA or SR of randomized controlled trials SR of cohort studies	Study effect of therapy or test on real patients; allows for comparison between intervention and control groups; largest volume of evidence-based literature
Diagnosis	MA or SR of controlled trials (prospective cohort study) *Controlled trial* (Prospective: compare tests with a reference or "gold standard" test)	Measures reliability of a particular diagnostic measure for a disease against the "gold standard" diagnostic measure for the same disease
Etiology, causation, harm	MA or SR of cohort studies *Cohort study* (Prospective data collection with formal control group)	Compares a group exposed to a particular agent with an unexposed group; important for understanding prevention and control of disease
Prognosis	MA or SR of inception cohort studies *Inception cohort study* (All have disease but free of the outcome of interest) *Retrospective cohort*	Follows progression of a group with a particular disease and compares with a group without the disease

MA, Meta-analysis; *SR,* systematic review.

Sources of Evidence

The two types of evidence-based sources are primary and secondary, as follows:

- *Primary sources* are original research studies and publications that have not been filtered or synthesized, such as an RCT or a cohort study.
- *Secondary sources* are synthesized studies and publications of the already conducted primary research. These include **clinical practice guidelines** (CPGs), SRs, MAs, and evidence-based article reviews and protocols. This terminology is often confusing to individuals new to the EBDM approach because, although SRs are *secondary* sources of evidence, they are considered a higher level of evidence than a *primary* source, such as an individual RCT.

Both primary and secondary sources can be found by conducting a search using such biomedical databases as MEDLINE (accessed through PubMed), Embase, and Database of Abstracts of Review of Effectiveness (DARE). Other sources of secondary evidence, such as CPGs, clinical recommendations, parameters of care, position papers, academy statements, and critical summaries related to dental practice, can be found on the websites of professional organizations and journals, as listed in Table 2.2. Additional EBDM resources for clinicians are available online in eTable 2.1.

Levels of Evidence

As previously mentioned, one principle of EBDM is that hierarchies of evidence exist to guide decision making. At the top of the hierarchy for therapy are CPGs (Fig. 2.5). These are systematically developed statements to assist clinicians and patients about appropriate health care for specific clinical circumstances.[10] CPGs should be based on the best available scientific evidence, typically from MAs and SRs, which put together all that is known about a topic in an objective manner. The level and quality of the evidence are then analyzed by a panel of experts who formulate the CPGs. Thus guidelines are intended to translate the research into practical application.

Guidelines also will change over time as the evidence evolves, thereby underscoring the importance of keeping current with the scientific literature. One example of this is the change in the American Heart Association guidelines for the prevention of infective endocarditis related to the need for premedication before dental and dental hygiene procedures.[5] Before the 2007 guidelines, the last update was in 1997, and before then, eight updates were added to the primary regimens for dental procedures since the original guideline was first published in 1955. In the 2007 update, the rationale for revising the 1997 document was provided, notably that the prior guidelines were largely based on expert opinion and a few case-controlled studies. With more research conducted, the ability now existed to synthesize those findings to provide a more objective body of evidence on which to base recommendations.[5]

If a CPG does not exist, other sources of preappraised evidence (critical summaries, critically appraised topics [CATs], SRs, MAs, or reviews of individual research studies) are available to help stay current. MAs and SRs have strict protocols to reduce bias and the synthesis of research from more than one study. These reviews provide a summary of multiple research studies that have investigated the same specific question. SRs use explicit criteria for retrieval, assessment, and synthesis of evidence from individual RCTs and other well-controlled methods. SRs facilitate decision making by providing a clear summary of the current state of the existing evidence on a specific topic. SRs provide a way of managing large quantities of information,[28] thus making it easier to keep current with new research.

MA is a statistical process used when the data from the individual studies in the SR can be combined into one analysis. When data from these studies are pooled, the sample size and power usually increase. As a result, the combined effect can increase the precision of estimates of treatment effects and exposure risks.[28]

SRs and MAs are followed respectively by individual RCT studies, cohort studies, case-control studies, and then studies not involving human subjects.[32] In the absence of scientific evidence, the consensus opinion of experts in appropriate fields of research and clinical practice is used (see Fig. 2.5). This hierarchy of evidence is based on the concept of causation and the need to control bias.[24,25] Although each level may contribute to the total body of knowledge, "not all levels are equally useful for making patient care decisions."[25] In progressing up the hierarchy, the number of studies and, correspondingly, the amount of available literature decrease, while at the same time their relevance to answering clinical questions increases.

Evidence is judged on its rigor of methodology, and the level of evidence is directly related to the type of question asked, such as those derived from issues of therapy or prevention, diagnosis, etiology, and prognosis (see Table 2.1). For example, the highest level of evidence associated with questions about therapy or prevention is from CPGs based on MAs and/or SRs of RCT studies. However, the highest level of evidence associated with questions about prognosis

TABLE 2.3 Search Terms for Each PICO Question

PICO Question 1 Search Terms		PICO Question 2 Search Terms
Tooth avulsion (MeSH)[26] OR Tooth replantation (MeSH)[26]	**P**	Tooth avulsion (MeSH)[26] OR Tooth replantation (MeSH)[26]
Pulp extirpation OR Root canal therapy (MeSH)[26]	**I**	Splints (MeSH)[26]
(Same intervention as above; however, timing is the real comparison so that is the factor in the final article selection.)	**C**	(Same intervention as above; however, timing is the real comparison so that is the factor in the final article selection.)
Tooth integration OR Functional periodontal healing OR Root resorption (MeSH)[26] OR Tooth ankylosis (MeSH)[26]	**O** These terms were used as inclusion criteria and were not used when searching PubMed because only a few systematic reviews and guidelines were found using just the P, I, and C terms	Tooth integration OR Functional periodontal healing OR Root resorption (MeSH)[26] OR Tooth ankylosis (MeSH)[26]

MeSH, Medical Subject Heading (database); *PICO,* patient problem or population, intervention, comparison, and outcome(s).

maximize searching efficiency. For example, by typing "avulsed tooth" into the MeSH database, a term from the case scenario, it is learned that the MeSH term is "tooth avulsion." It is defined as partial or complete displacement of a tooth from its alveolar support. It is commonly the result of trauma. It is also learned that "tooth luxation" links to the MeSH term "tooth avulsion." This informs the searcher that "tooth avulsion" is the best term to use for the search because it encompasses both avulsed and luxated teeth.[26]

Using PubMed's Clinical Queries feature, one can quickly pinpoint a set of citations that will potentially provide an answer to the question being posed. Although online databases provide quicker access to the literature, knowing how databases filter information and having an understanding of how to use search terms and database features allow a more efficient search to be conducted.

Because two focused clinical (PICO) questions were generated from the clinical case, two separate searches were conducted, one for each PICO question. In addition to PubMed, several other databases were used to find high levels of evidence. These included the Database of Abstracts of Reviews of Effects (https://www.crd.york.ac.uk/CRDWeb/), Scopus (https://www.scopus.com/), Web of Science (https://apps.webofknowledge.com/), the National Guideline Clearinghouse (http://www.guideline.gov), the ADA Center for Evidence-Based Dentistry website (http://ebd.ada.org), the American Academy of Pediatric Dentistry website (www.aapd.org), and the American Association of Endodontists (www.aae.org), resulting in several relevant references. In addition, clinicians can subscribe to portals such as PracticeUpdate-Clinical Dentistry channel (https://www.practiceupdate.com/explore/channel/clinical-dentistry/sp23) that allow them to stay updated on recent advances in clinical dentistry. The subscribers of this ADA-Elsevier joint initiative receive daily updates of recently published relevant articles with brief take-home messages with or without additional expert commentaries.

When searching for evidence, the PICO question guides the search (Table 2.3).[4,6] By using key terms identified in the PICO question and combining them using the Boolean operators "OR" and "AND," relevant articles can be narrowed to a manageable number.

The first search used the terms "(tooth avulsion OR tooth replantation) AND (pulp extirpation OR root canal therapy)." This resulted in 590 papers. Studies were limited to practice guidelines, MAs, and SRs by using each of these three filters separately so that each of these types of studies could be identified. The findings included four practice guidelines, including those of the American Association of Endodontists and the International Association of Dental Traumatology, one critical summary of an SR, and one SR. The second search used the terms "(tooth avulsion OR tooth replantation) AND splints." This resulted in 340 papers. Again, studies were limited to practice guidelines, MAs, and SRs by using the filter for each publication type separately. Relevant results included four practice guidelines from the International Association of Dental Traumatology and Pediatric Dentistry, one MA, and one SR. Fig. 2.3 provides a detailed review of the decision-making steps in this case and the outcomes.[27]

The articles that were selected as relevant research included each aspect of the PICO question. Inclusion criteria were the following: The patient population studied had to have replanted avulsed or luxated teeth; the research studied the intervention for each of the two PICO questions, pulp extirpation and splint duration, respectively; and the research measured at least one of the outcomes of tooth integration, functional periodontal healing, or the levels of resorption or ankylosis. To reduce the requirement of critical appraisal, the search also looked for critical summaries of the SRs that were found.

KEY FACT

Critical Summary

A critical summary is a brief article that effectively summarizes and critically appraises an already published systematic review (SR). Because it includes a critical appraisal component, it makes it easier for clinicians to apply the results to a given clinical situation without having to read the entire SR. Several critical summaries can be found at the ADA Center for Evidence-Based Dentistry website (https://ebd.ada.org/en/evidence).

Appraising the Evidence

After identifying the evidence gathered to answer a question, it is important to have the skills to understand the evidence found. In all cases, it is necessary to review the evidence, whether it is a CPG, an MA, an SR, or an original study, to determine whether the methods were conducted rigorously and appropriately. International evidence-based groups have made this easier by developing appraisal forms and checklists that guide the user through a structured series of "YES/NO" questions to determine the validity of the individual study or SR. Table 2.4 provides the names and websites of three different guides that can be used for critical analysis.

TABLE 2.4 Examples of Critical Analysis Guides

Guide	Purpose
CONSORT (Consolidated Standards of Reporting Trials) statement[3] http://www.consort-statement.org	To improve the reporting and review of RCTs
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) http://www.prisma-statement.org	To improve the reporting and review of SRs
CASP (Critical Appraisal Skills Program)[11] http://www.casp-uk.net	To review RCTs, SRs, and several other types of studies

RCTs, Randomized controlled trials; *SRs*, systematic reviews.

Common Ways Used to Report Results

Once the results are determined to be valid, the next step is to determine whether the results and potential benefits (or harms) are important. Straus and colleagues[36] identified the clinically useful measures for each type of study. For example, in determining the magnitude of therapy results, we would expect articles to report the control event rate (CER), the experimental event rate (EER), the absolute and relative risk reduction (ARR or RRR), and number needed to treat (NNT). The NNT provides the number of patients (e.g., surfaces, periodontal pockets) who would need to be treated with the experimental treatment or intervention to achieve one additional patient (surfaces, **periodontal pockets**) who has a favorable response. Another way of assessing evidence is presented in Chapter 3, which introduces 12 tools that may be useful in assessing causality in clinical sciences.

In appraising the evidence found for the case scenario, the first research study retrieved that answered the first PICO question was a well-conducted SR published in *Dental Traumatology* in 2009.[20] Results indicated an association between pulp extirpations performed after 14 days following replantation and the development of inflammatory resorption. A corresponding critical summary was also found.[35] This evidence was consistent with the 2007 clinical guidelines from the International Association of Dental Traumatology for pulp extirpation within 10 to 14 days of replantation.[16]

The Practice Guideline on the Management of Acute Dental Trauma from the American Academy of Pediatric Dentistry answered the second PICO question. It recommended a "flexible splint for 1 week" for avulsed teeth. However, for lateral luxation, an additional 2 to 4 weeks may be needed when there is breakdown of marginal bone.[2] In addition, a well-conducted SR about splinting duration reported inconclusive evidence of an association between short-term splinting and an increased likelihood of functional periodontal healing, acceptable healing, or decreased development of replacement resorption.[21] The study found no evidence to contraindicate the current guidelines and suggested that the likelihood of successful periodontal healing after replantation was unaffected by splinting duration. Although this SR excluded studies of luxated teeth, this SR is still applicable to the patient. It concluded that dentists should continue to use the currently recommended splinting periods when replanting avulsed permanent teeth, pending future research to the contrary.[21] Consistent with previous reviews, another SR on splinting luxated, avulsed, and root-fractured teeth reported that "the types of splint and the fixation period are generally not significant variables when related to healing outcomes."[23] These two SRs were appraised using the Critical Appraisal Skills Program (CASP) form for appraising reviews (see Table 2.4).

Applying the Evidence: Evidence-Based Dentistry in Action

Throughout this chapter, the EBDM process has illustrated the application of evidence in clinical decision making. The clinician used the EBDM process to answer two clinical questions. Several relevant resources were incorporated into the decision-making process and the treatment of the patient. The clinician performed pulp extirpations on the avulsed and luxated teeth within the recommended time period of 10 to 14 days (Fig. 2.6A). Healing at 2 weeks post trauma is seen in Fig. 2.6B. The clinician also removed the splint within the recommended time frame for luxated teeth of 2 to 4 weeks. The evidence, in combination with clinical experience, helped provide care for this patient that resulted in the best possible prognosis given the extent of the patient's dental trauma. It also allowed the patient to keep her own teeth, which incorporated the patient preferences aspect of the EBDM process. Fig. 2.6C shows the healing at 4 weeks post trauma; Fig. 2.6D shows the healing at 12 weeks; and Fig. 2.6E shows the patient 2 years post trauma.

Evaluating the Outcomes

The final steps in the EBDM process are to evaluate the effectiveness of the intervention and clinical outcomes and to determine how effectively the EBDM process was applied. For example, one question to ask in evaluating the effectiveness of the intervention is, "Did the selected intervention or treatment achieve the desired result?" In this specific case, the answer is yes.

EBDM is a valuable tool that guides practice decisions to achieve optimal results. In the case of tooth avulsion, the key PICO questions were established to identify research that studied the outcomes of reducing the risk of root resorption and tooth ankylosis and increasing periodontal healing. In using the EBDM process, providers can be confident that they have the most current and relevant evidence available on which to base treatment decisions to provide the best treatment to improve the possibility of a successful outcome.

Using an EBDM approach requires understanding new concepts and developing new skills. In addition to evaluating patient care outcomes, another aspect of evaluation is in using the EBDM process. Questions that parallel each step in the EBDM process can be asked in evaluating self-performance. For example, "How well was the search conducted to find appropriate and relevant evidence to answer the question?" As with most learning, time and practice are essential to mastering new techniques.

Real World Clinical Evidence

It is important to note that RCTs are typically conducted in a well-controlled environment so that the investigators are able to clearly discern the true effects of the intervention. The study participants in RCTs are typically selected based on a predetermined set of inclusion and exclusion criteria. This means that certain patients with uncontrolled diabetes or current smokers at the time of study recruitment were potentially excluded from the trial. Therefore it is important for the clinician reading the published RCTs to know the differences between the characteristics of study participants and the patients they would typically encounter in their clinical practice. It is equally important to be cognizant of the differences between the clinical expertise of the authors conducting the trial and the clinician consuming the evidence. Being aware of these differences while reading RCTs will allow the clinician to accurately extrapolate the results of the study and apply the findings to their patient situations in a judicious manner to get predictable treatment outcomes. To improve the translatability of clinical research findings and to overcome some of the aforementioned barriers, the National Dental Practice-Based Research Network

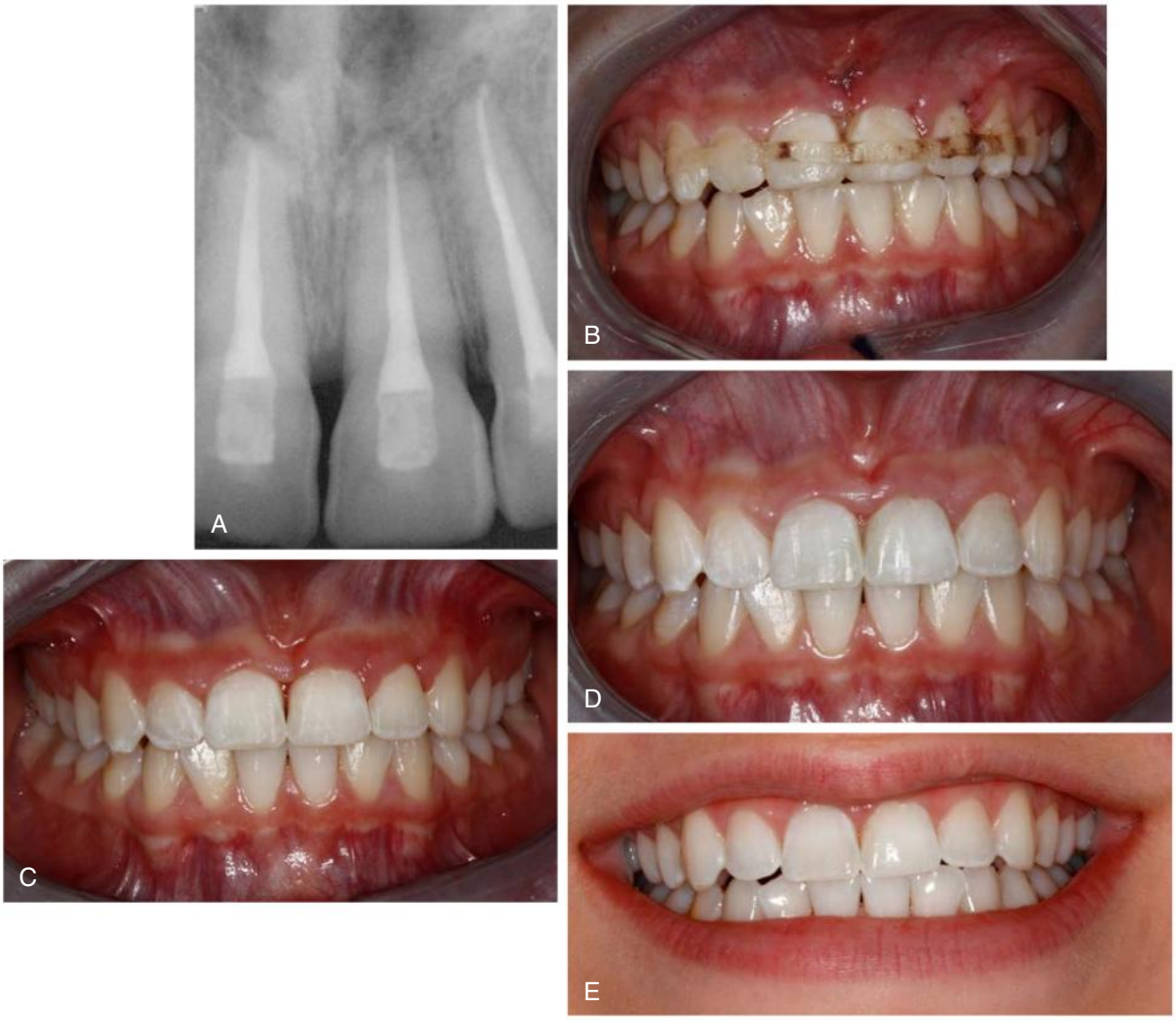

Fig. 2.6 (A) Periapical radiograph following pulp extirpations. (B) Healing at 2 weeks post trauma. (C) Healing at 4 weeks post trauma. (D) Healing at 12 weeks post trauma. (E) Patient 2 years post trauma (*Copyright Greg W. Miller, DDS, reprinted with permission.*)

was created with funding from the National Institutes of Health.[30] The network is a consortium of dental practices across the United States that allows the research to be conducted in the real world of clinical practice by clinicians with varying levels of clinical experience. This effort has led to several publications addressing important clinically applicable questions.[30]

Clinical Decision Support System

Computerized clinical decision support systems (CDSSs), either integrated within the electronic health records (EHR) or as stand-alone systems, are being developed to provide point-of-care patient-specific alerts and guidance to clinicians to aid in informed clinical decision making, be it for prevention, diagnosis, or treatment.[17] A good example is drug interactions alerts provided by CDSSs, prior to prescribing a medication or suggestion alerts for diagnosis based on all the available information. The primary goals of CDSSs are to reduce harm for the patients, improve clinical outcomes, and minimize cost. The available scientific evidence on several health conditions and medications is constantly being fed as data source into CDSSs to keep the system as updated and relevant as it can be. CDSSs are broadly classified into two types: knowledge based and non–knowledge based. In the knowledge-based CDSSs, specific algorithms (IF-THEN) are created (from available scientific evidence) within the system that for a given clinical situation provide an output or actionable item. In the non–knowledge-based CDSSs, data source is still required but the system harnesses the power of artificial intelligence and machine learning to provide patient-specific alerts and clinical recommendations for a given clinical situation.[37] Therefore it is clear that CDSSs have the potential to aid in point-of-care EBDM and SRs confirm their clinical utility and effectiveness.[7,8]

CHAPTER HIGHLIGHTS

- Evidence-based decision making (EBDM) provides clinicians the skills to find, efficiently filter, interpret, and apply research findings so that what is known is reflected in the care provided.
- EBDM takes time and practice to learn to use.
- When mastered, EBDM is an efficient way for clinicians to stay current, and it maximizes the potential for successful patient care outcomes

Conclusion

An EBDM approach closes the gap between clinical research and the realities of practice by providing dental practitioners with the

4. Finally, the possibility needs to be considered that no magic bullets exist against certain **noxious** aspects of civilized lifestyles. It was a popular idea in the 20th century that the harmful effects of smoking could be prevented by prescription (e.g., vitamin A), and not proscription (e.g., quit smoking). The experiences so far with finding prescriptions as protection against harmful lifestyles have been largely disastrous.

These factors may all be at play in periodontics, thus suggesting that skepticism is required in the evaluation of scientific evidence. First, the large number of "effective" periodontal treatments may be a telltale sign of a challenging chronic disease. Before 1917, hundreds of **pneumonia** treatments were available, none of which worked. Before the advent of **antibiotics** in the 1940s, the wealth of available **tuberculosis** treatments was misleading in the sense that none really worked. The current "therapeutic wealth" for periodontal diseases may well mean poverty—an indication of the absence of truly effective treatments—and a suggestion that we are dealing with a challenging chronic disease. Second, many no longer regard periodontal diseases as the simple, plaque-related diseases they were thought to be in the mid-20th century but, rather, as complex diseases. Complex diseases are challenging to diagnose, treat, and investigate. Third, the scientific quality of periodontal studies has been rated as low.[4] Major landmark trials were analyzed using wrong statistics,[36,48] most randomized studies were not properly randomized,[55] and the primary drivers of the periodontitis epidemic may have been misunderstood because of the definition of periodontal diseases as an **infectious** disease without properly controlled **epidemiologic studies**.[30,31,49] The chance that periodontal research somehow managed to escape the scientific challenges and hurdles that were present in research in medicine appears slim. The opposite appears more likely.

Do Not Trust Biologic Plausibility

Born but to die, and reasoning but to err.

—Alexander Pope

If an irregular heartbeat increases mortality risk, and if encainide can turn an irregular heartbeat into a normal heartbeat, then encainide should improve survival.[66] If high serum lipid levels increase myocardial infarction risk, and if clofibrate can successfully decrease lipid levels, clofibrate should improve survival.[69] If *Streptococcus mutans* causes dental decay, and if chlorhexidine can eradicate *S. mutans,* then chlorhexidine can wipe out dental decay. Such "causal chain thinking" (A causes B, B causes C, and, therefore, A causes C) is common and dangerous. These examples of treatment rationales, although seemingly reasonable and biologically plausible, turned out not to help but to harm patients. Causal chain thinking is sometimes referred to as "deductive inference," "deductive reasoning," or a "logical system."

In mathematics, "once the Greeks had developed the deductive method, they were correct in what they did, correct for all time."[5] In medicine or dentistry, decisions based on deductive reasoning have not been "correct for all time" and are certainly not universal. Because of an incomplete understanding of biology, the use of deductive reasoning for clinical decisions may be dangerous. For thousands of years, deductive reasoning largely failed to lead to medical breakthroughs. In evidence-based medicine, evidence that is based on deductive inference is classified as level 5, which is the lowest level of evidence available.

CLINICAL CORRELATION

The Dietary Guidelines for Americans dropped their recommendation to floss because of the lack of scientific evidence. Dental floss has been recommended by oral hygiene companies and the dental profession based on the following biologic plausibility argument: dental **plaque** causes dental **caries**; floss removes dental plaque. Therefore, flossing will lower the risk of dental caries. Such reasoning is no longer accepted as evidence for effectiveness in the 21st century.

Unfortunately, much of our knowledge on how to prevent, manage, and treat periodontitis depends largely on deductive reasoning. Small, short-term changes in **pocket** depth or **attachment levels** have been assumed to translate into tangible, long-term benefits to patients, but minimal evidence to support this deductive inference leap is available. In one small study without statistical hypothesis testing, dental plaque was related to the transition from an unnatural, inflammation-free condition referred to as "Aarhus superhealthy **gingiva**" to experimental **gingivitis** (which is different from clinical gingivitis).[50] Such studies do not offer proof that dental plaque **bacteria** cause destructive **periodontal disease**. It is even unclear whether experimental gingivitis and plaque are correlated at a site-specific level above and beyond what would be expected by chance alone. One subsequent study at the same university, using a similar population, and using a similar experimental design, failed to identify an association between plaque and gingivitis.[50] Evidence that personal plaque control affects the most common forms of periodontal diseases is still weak and largely based on "biologic plausibility" arguments.[33] A move toward a higher level of evidence (higher than biologic plausibility) is needed to put periodontics on a firmer scientific footing.

KEY FACT

Biologic plausibility will increasingly become an unacceptable rationale to recommend dental treatments.

What Level of Controlled Evidence Is Available?

Development of Western science is based on two great achievements: the invention of a formal logical system (in Euclidean geometry) by the Greek philosophers, and the discovery of the possibility to find out causal relationships by systematic experiment (during the Renaissance).

—Albert Einstein

Rational thought requires reliance on either deductive reasoning (biologic plausibility) or systematic experiments (sometimes referred to as inductive reasoning). Galileo is typically credited with the start of systematic experimentation in physics. Puzzlingly, it took until the latter half of the 20th century before systematic experiments became part of clinical research. Three systematic experiments are now routine in clinical research: the case-control study, the cohort study, and the RCT. In the following brief descriptions of these three systematic experimental designs, the term ***exposure*** refers to a suspected etiologic factor or an intervention, such as a treatment or a diagnostic test, and the term ***endpoint*** refers to the outcome of disease, quality-of-life measures, or any type of condition that may be of interest in clinical studies.

1. ***RCT***. Individuals or clusters of individuals are randomly assigned to different exposures and monitored longitudinally for the endpoint of interest. An association between the exposure and the endpoint is present when frequency of the endpoint occurrence differs among the exposure groups. The RCT is the "gold standard" design in clinical research. In evidence-based medicine, RCTs, when properly executed, are referred to as level 1 evidence and the highest (best) level of evidence available.
2. ***Cohort study***. Exposed individuals are compared with nonexposed individuals and monitored longitudinally for the occurrence of the primary endpoint of interest. An association between the exposure and endpoint is present when the frequency of endpoint occurrences differs between exposed and nonexposed individuals. A cohort study is often considered the optimal study design in nonexperimental clinical research (i.e., for those study designs where randomization may not be feasible). In evidence-based medicine, cohort studies, when properly executed, are referred to as level 2 evidence.
3. ***Case-control study***. Cases (individuals with the endpoint of interest) are compared with controls (individuals without the endpoint of interest) with respect to the prevalence of the exposure. If the prevalence of exposure differs between cases and controls, an association between the exposure and the endpoint is present. In a case-control study, it is challenging to select cases and controls in an unbiased manner and to obtain reliable information on possible causes of disease that occurred in the past. The case-control study is the most challenging study design to use for obtaining reliable evidence. As a result, in evidence-based medicine, case-control studies, when properly executed, are considered the lowest level of evidence.

All three study designs permit us to study the association between the exposure and the endpoint. This association can be represented schematically as follows:

Exposure → Endpoint

An important challenge in the assessment of controlled evidence is determining whether the association identified (→) is causal. Criteria used to assess causality include factors, such as the assessment of temporality, the presence of a pretrial hypothesis, and the size or strength of the reported association. Unlike deductive reasoning, in which associations are either true or false, such absolute truths cannot be achieved with systematic experiments. Conclusions based on controlled study designs are always surrounded by a degree of uncertainty, a frustrating limitation to real-world clinicians who have to make yes/no decisions.

Did the Cause Precede the Effect?

You can't change the laws of physics, Captain.

—"Scotty" in Star Trek

In 2001, a study published in the *British Medical Journal* suggested that retroactive prayer shortened hospital stays in patients with bloodstream **infection**.[47] The only problem was that patients were already dismissed from the hospital when the nonspecified prayer to the nonspecified deity was made. To most scientists, findings in which the effect (shorter hospital stay) precedes the cause (the prayer) are impossible, and this provides an unequivocal example of a violation of correct temporality; the effect preceded the hypothesized cause. In chronic disease research, it is often challenging to disentangle temporality, and fundamental questions regarding temporality often remain disputed. For example, in Alzheimer disease research the amyloid in the senile plaques in the brain is often considered to be the cause of Alzheimer disease, but some researchers suggested that amyloid may be the result, rather than the cause, of Alzheimer disease and that the amyloid may be protective.[46] Or, it is widely believed that obesity is caused by overeating and insufficient physical activity. Yet, increasing evidence points to the opposite—that obesity is a disease induced by carbohydrates that leads to internal starvation and consequent overeating and physical inactivity.[78] Vigorous investigation of temporality is a key aspect in scientific investigation.

Temporality is the only criterion that needs to be satisfied for claiming causality; the cause needs to precede the effect. In periodontal research, almost all studies relating plaque or specific infections to periodontal diseases suffer from unclear temporality.[49] Are observed **microbial** profiles the result or the cause of periodontitis? No cohort studies in adults have established that an infectious cause precedes the onset of periodontitis.[49] Unequivocal establishment of temporality is an essential element of causality and can be surprisingly difficult to establish for chronic diseases, including periodontal diseases.

No Betting on the Horse After the Race Is Over

Predictions are difficult, especially about the future.

—Niels Bohr

One of the most pervasive cancers in clinical research is the inability of researchers to stick to a hypothesis. Science is about formulating a specific hypothesis, testing it in a clinical experiment, and accepting the findings for what they are. Not only does this rarely happen, but also powerful forces sometimes actively try to prevent regulations that would enforce such scientific behavior.

An **acquired immunodeficiency syndrome (AIDS)** researcher at an international AIDS conference was jeered when she claimed that AIDS therapy provided a significant benefit for a subgroup of trial participants.[60] A study published in the *New England Journal of Medicine*[51] was taken as a textbook example of poor science[20] when it claimed that coffee drinking was responsible for more than 50% of the pancreatic cancers in the United States. Results of a large collaborative study demonstrating that aspirin use after myocardial infarction increased mortality risk in patients born under Gemini or Libra provided a comical example of an important scientific principle: data-generated ideas are unreliable.

An essential characteristic of science is that hypotheses or ideas predict observations, not that hypotheses or ideas can be fitted to observations. This essential characteristic of scientific enterprise—prediction—is often lost in medical and dental research when poorly defined prestudy hypotheses result in convoluted data-generated ideas or hypotheses that fit the observed data. It has been reported that, even for well-organized studies with carefully written protocols, investigators often do not remember which hypotheses were defined in advance, which hypotheses were data derived, which hypotheses were "a priori" considered plausible, and which were unlikely.[89] A wealth of data-generated ideas can be created by exploring patient subgroups, exposures, and endpoints, as shown by the following:

1. Modifying study sample definition. A commonly observed posttrial modification of a hypothesis is to evaluate improper or proper subgroups of the original study sample. Improper subgroups are based on patients' characteristics that may have been influenced by the exposure. For example, one may evaluate tumor size only in those patients who survived or pocket depths only in those teeth that were not lost during maintenance. Results of improper

subgroup analyses are almost always meaningless when establishing causality. Proper subgroups are based on patients' characteristics that cannot be influenced by the exposure, such as sex, race, or age. A review of trials in the area of cardiovascular disease suggested that even the results of proper subgroup analyses turn out to be misleading in a majority of cases.[89] In the **human immunodeficiency virus (HIV)** area, one proper subgroup analysis (based on racial characteristics) drew an investor lawsuit on the basis that company officials "deceived" investors with a "fraudulent scheme."[15]

2. Modifying exposure definition. After or during the conduct of a study, the exposure definition can be changed, or the number of exposures under study can be modified. In a controversial trial on the use of antibiotics for middle ear infections, the placebo treatment was replaced with a boutique antibiotic, thus causing a potentially misleading perception of the antibiotics' effectiveness.[16,17,52] In another example of "betting on the horse after the race was over," a negative finding for cigarette smoking (the primary exposure) as a cause of pancreatic cancer reportedly led to the data-generated hypothesis that coffee drinking increased pancreatic cancer risk.[51] When this study was repeated in the same hospital, using the same protocol, but now with the pretrial hypothesis to evaluate coffee drinking, the results of the prior study could not be duplicated.
3. Modifying endpoint definition. Almost all pivotal trials specify one primary endpoint in the pretrial hypothesis. In periodontal research the absence of a specific pretrial defined endpoint is common and permits effortless changing of the endpoint definition. The typical periodontal trial has six endpoints and does not specify which endpoint is primary, and it is not always clear what is a good or a bad outcome.[20] Similarly, the definition of adverse pregnancy outcomes is flexible and susceptible to post hoc manipulations to squeeze out statistical significance. Statistical trickery to reach desired conclusions under such circumstances may be child's play. These problems have remained rampant in clinical research, despite all efforts at preventing them. Two surveys of RCTs published in 2015 reported that 18% to 31% of the trials still changed primary endpoints, and 64% of the trials still changed secondary endpoints.[22,41]

Deviating from the pretrial hypothesis is often compared to data torturing.[56] Detecting the presence of data torturing in a published article is often challenging; just as the talented torturer leaves no scars on the victim's body, the talented data torturer leaves no marks on the published study. Long-term efforts at registering all trials (e.g., see www.alltrials.net) have still not solved this problem.[11] Opportunistic data torturing refers to exploring data without the goal of "proving" a particular point of view. Opportunistic data torturing is an essential aspect of scientific activity and hypothesis generation. Procrustean data torturing refers to exploring data with the goal of proving a particular point of view. Just as the Greek mortal Procrustes fitted guests perfectly to his guest bed either through bodily stretching or through chopping of the legs to ensure correspondence between body height and bed length, so can data be fitted to the pretrial hypothesis by Procrustean means.

What Is a Clinically Relevant Pretrial Hypothesis?

Clinically relevant questions are designed to have an impact on improving patients' outcomes. Usually, clinically relevant questions share four important characteristics of the pretrial hypothesis: (1) a clinically relevant endpoint (referred to as the Outcome in the PICO question), (2) relevant exposure comparisons (referred to as the Intervention and the Control in the PICO question), (3) a study sample representative of real-world clinical patients (should be representative of the patient defined in the PICO question), and (4) small error rates.

Clinically Relevant Endpoint

An endpoint is a measurement related to a disease process or a condition and is used to assess the exposure effect. Two different types of endpoints are recognized. True endpoints are tangible outcomes that directly measure how a patient feels, functions, or survives[80]; examples include tooth loss, death, and pain. Surrogate endpoints are intangible outcomes used as a substitute for true endpoints[23]; examples include blood pressure and probing depths of **periodontal pockets**. Treatment effects on surrogates do not necessarily translate into real clinical benefit (Table 3.1). Reliance on surrogate endpoints in clinical trials has led to widespread use of deadly medications, and such disasters have prompted minor changes in the drug approval process.[67] Most major causes of human disease (e.g., cigarette smoking) were identified through studies using true endpoints. A first requirement for a clinically relevant study is the pretrial specification of a true endpoint.

Common and Relevant Comparisons

The more prevalent a studied exposure is, the more relevant is the clinical question. A clinically relevant comparison implies the absence of comparator bias, which is defined as the presence of contrived or unethical control groups.[53] Providing the control subjects with less than the standard dose of the standard treatment and providing a control therapy that avoids the real clinical questions are examples of clinically irrelevant research. Similarly, the presence of a placebo treatment, instead of "no" treatment, in clinical trials can be critical given the large therapeutic effects that can be obtained by proper attention and care in medical settings. For instance, the absence of placebo controls in fluoride varnish trials for primary teeth raises serious doubts whether or not fluoride varnish has an effect above and beyond what would be observed with only a placebo. In case-control or cohort studies, the measurement and characterization of exposures (e.g., mercury, fluoride, chewing tobacco) can be difficult and imprecise, thus making answers to the questions almost unavoidably imprecise.

Representative Study Sample

The larger the discrepancy between the typical subjects enrolled in clinical studies and the patient you seek to treat, the more questionable the applicability of the study's conclusions becomes. When cholesterol-lowering drugs provided a small benefit in middle-aged men with abnormally high cholesterol levels, it was concluded that those benefits "could and should be extended" to other age groups and women with "more modest elevations" of cholesterol levels.[82] Findings on blood lipids and heart disease that were derived mostly from Polish immigrants in the Framingham Study were generalized to a much more diverse population. An antidepressant that was approved for use in adults was widely prescribed for children, with unexpected, serious consequences.[1]

Ideally, clinical trials should use simple entry criteria in which the enrolled patients reflect the real-world clinical practice situation as closely as possible. Legislation has been enacted to reach this goal. In 1993, US policy ensured the recruitment of women and minority groups in clinical trials.[10] A US policy for the inclusion of children in clinical studies was then set into law in 1998. Experiments with long lists of inclusion and exclusion criteria can be expensive recipes for failure because they can lead to study subjects who are unrepresentative of most real-world clinical patients.

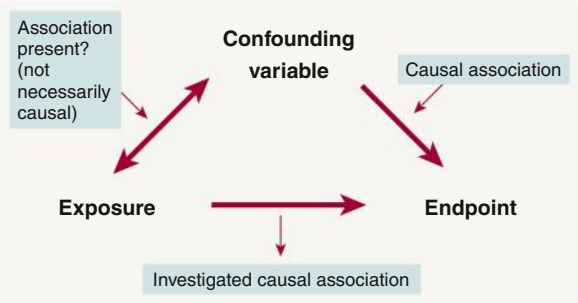

Fig. 3.1 Schematic representation of the two necessary criteria for a variable to induce spurious associations (i.e., to be a confounding variable). The confounding variable has to be associated with the exposure and causally linked to the outcome. When both criteria are satisfied, confounding is said to be present.

explored. More efforts may have been expended toward proving associations by ignoring common causal factors, rather than disproving associations. The highest goal of a scientist is the attempt to refute, disprove, and vigorously explore factors and alternative hypotheses that may "explain away" the observed association.[12] The efforts at refuting smoking and nutrition as potential confounders in periodontics have been minimal and may have led to a significant waste of clinical research resources.

FLASH BACK

Epidemiologic studies are by nature unreliable. It has been estimated that 80% of the epidemiologic studies report false-positive findings. Two large pivotal trials on periodontal treatments and adverse pregnancy outcomes funded by the National Institutes of Health,[21,75] as well as subsequent epidemiologic studies,[88] failed to confirm the dramatic claims of previously published epidemiologic studies.

For a factor (i.e., a potential confounder) to explain away an observed association, two criteria need to be fulfilled. First, the factor must be related to the exposure, but not necessarily in a causal way. Second, the factor must be causally related to the outcome and must not be in the causal pathway. If both criteria are satisfied, the factor is referred to as a confounder, and confounding is said to be present. For example, smoking satisfied the criteria for a confounder in the β-carotene–lung cancer association because (1) cigarette smokers consumed less β-carotene than nonsmokers, and (2) smoking caused lung cancer. Confounding is often represented schematically (Fig. 3.1).

In randomized studies, confounding is typically not an issue because randomization balances known and unknown confounders across the compared groups with a high degree of certainty. In epidemiologic studies, in which no randomization is present, three questions related to confounding need to be considered in the assessment of the causality, as addressed next.

First, were all important confounders identified? Complex diseases have multiple risk factors, which may act as confounders in the reported association. The multiple confounders need to be included in the statistical analyses. An association unadjusted for any potential confounders is sometimes referred to as the *crude association*. When this crude association is adjusted for potential confounders, it is referred to as an *adjusted association*. Typically, crude and adjusted odds ratios are both presented so that readers can evaluate the direction of the bias.

KEY FACT

Single epidemiologic studies reporting large odds ratios are unreliable.

Second, how accurately were confounders measured? Some potential confounders, such as age, sex, and race, can be measured relatively accurately. Other potential confounders, such as smoking or lifestyle factors, such as nutrition, are notoriously more difficult to measure. A discrepancy between what is measured and what is the truth will result in the incomplete removal of bias and lead to spurious associations. The remaining bias is sometimes referred to as *residual confounding*. Residual confounding is common in epidemiology and is one of the reasons that case-control and cohort studies are less effective research tools than randomized trials in identifying small effects. For instance, an accurate summary of smoking history over a person's lifetime may be impossible.

Third, was the statistical modeling of the confounders appropriate? Any mis-specification of the functional relationships causes bias. For example, assuming a linear relationship between a confounder and an endpoint, whereas, in truth, the relationship is quadratic, causes bias.

Evaluating the impact of confounding can be a challenge. The goal of an epidemiologist is to come up with the best possible defense for why an identified association is spurious. All possible efforts should be spent identifying known confounders, obtaining accurate measurements of the confounders, and exploring different analytic approaches to refute the observed association. Smoking, a potential confounder in many studies, has been found to be such a strong confounder that several leading epidemiologists have suggested that restriction to those who have never been smokers is required to eliminate the potential for residual confounding by smoking. Control for confounding is the major methodologic challenge in epidemiology, and randomization is the only tool available to eliminate confounding reliably.

CLINICAL CORRELATION

Epidemiologic evidence has suggested that periodontal patients who comply with periodontal maintenance procedures lose fewer teeth.[35]

Was the Study Properly Randomized?

It is often taken for granted that randomization is properly performed in RCTs. This is, unfortunately, not the case. Attempts by physicians to circumvent randomization are not isolated events; they used to be part of an endemic problem stemming from ignorance.[60]

Randomization can be a counterintuitive process because it (1) creates heterogeneity, (2) takes control over treatment assignment away from the physician, and (3) leads to apparently illogical situations in which patients randomly assigned to a treatment but refusing compliance still are analyzed as if they received the treatment. Although randomization was a radical innovation introduced for agriculture, some have suggested that it is doubtful whether it would have ever been widely introduced into medicine (and subsequently dentistry) if not for a confluence of factors surrounding the end of World War II in Great Britain. Because of the revolutionary nature of randomization, fundamental misunderstandings of this process remained prevalent until recently. In 1994, about one-third of the clinical trials published in elite medical journals apparently did not ensure that patients are assigned to different treatments by