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MINIREVIEWS

Pierre Robin sequence from orthodontic and surgical perspective

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Abstract

Pierre Robin sequence (PRS) is a triad of micrognathia, glossoptosis, and cleft palate that results in an obstruction of the airway on inspiration and impeding feeding. The tongue of infants with PRS fall back toward the posterior pharyngeal wall (glossoptosis) due to receding chin produced by mandibular micrognathia (small jaw) or retrognathia. This causes a serious condition with potentially severe, life-threatening airway obstruction. If untreated, this problem can lead to exhaustion, cardiac failure, and ultimately death, especially during the early months of life. Actually, in the majority of PRS infants, these symptoms can be managed by placing the infant in the prone position until adequate growth of the jaw occurs. If this type of treatment fails, the infant then should be considered for other conservative therapies or surgical interventions. This paper reviews surgical interventions such as tongue-lip adhesion, mandibular traction, mandibular distraction, tracheotomy and conservative orthodontic approaches, and presents a baby treated successfully with an orthodontic appliance.

Key words: Pierre Robin sequence; Micrognathia; Glossoptosis; Surgical interventions; Orthodontic approaches

Core tip: Pierre Robin sequence is a severe congenital condition characterized by triad of micrognathia, glossoptosis, and cleft palate. Glossoptosis and micrognathia may result in obstruction of the airway on inspiration and impeding feeding. If untreated, this problem can lead to exhaustion, cardiac failure, and ultimately death, especially during the early months of life. This paper give detailed reviews supported with figures for surgical interventions and conservative orthodontic approaches, and also presents a baby treated successfully with an orthodontic appliance. Orthodontic nutrition plate appears to be a viable alternative in treatment of Pierre Robin sequence to surgical treatment modalities that are more aggressive in nature.

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INTRODUCTION

Infants with congenital craniofacial anomalies often display associated severe mandibular hypoplasia causing obstruction of the airway through retro-positioning of the tongue-base into the posterior pharyngeal airway. Pierre Robin[1], a French Stomatologist at French School of Stomatology, defined a new syndrome in 1923 which involves mandibular micrognathia, glossoptosis and respiratory distress. In 1934, Robin[2] revised the characteristics of the syndrome and included cleft palate as an additional factor that could be present. An incomplete

cleft of the palate is associated with the Robin sequence in approximately 50% of these patients. Formerly, it was named Pierre Robin syndrome, anomalad, or complex. Today, it is referred as Pierre Robin sequence because the underdeveloped lower jaw initiates a sequence of events (*i.e.*, the micrognathia resulting in glossoptosis, which prevents the palatal shelves to fuse at intra-uterin growth)[3].

The main clinical problems faced by clinicians include upper airway obstruction and feeding difficulties. The tongue of infants with pierre robin sequence (PRS) fall back toward the posterior pharyngeal wall (glossoptosis) due to receding chin produced by mandibular micrognathia (small jaw) or retrognathia. This results in an obstruction of the airway on inspiration and impeding feeding. If untreated, this problem can lead to exhaustion, cardiac failure, and ultimately death, especially during the early months of life[4].

In normal intra-uterine growth and development, the tongue moves downward and goes away from the roof of the mouth between nine to eleven weeks of gestation. This movement of the tongue allows an accurate space for two palatal shelves to shift towards to the midline and become integrated (palatal closure). In PRS cases, however, micrognathic or retrognathic lower jaw results in failure of the tongue to descend and thus keeps the tongue positioned higher in the mouth than normal, thereby interfering with the normal closure of the palate. As a conclusion, a wide U-shaped cleft occurs in the soft palate, and sometimes it may involve posterior part of hard palate. To varying degrees, glossoptosis contributes to tongue-base obstruction, sleep apnea, and respiratory distress. Additional factors such as tongue prolapse into the cleft area, lack of voluntary control of the tongue musculature, and negative pressure pull of the tongue into hypopharynx may also contribute to dysphagia[5]. Three pathophysiological theories exist to explain the occurrence of micrognathia: mechanical or positional theory, neurological maturation theory, and dysregulation theory. The most widely accepted one is mechanical or positional theory although the etiopathogenesis of mandibular micrognathia itself remains a matter of considerable debate. According to mechanical or positional (compression) theory, mandibular micrognathia is a result of intrauterine molding against sternum, possibly associated with oligohydramnios[6]. If this theory is true, it would appear logical to expect some rebound growth of mandible shortly after birth, reducing facial convexity and perhaps allowing the mandible to "catch up" with maxilla.

TREATMENT APPROACHES

Since the major symptoms included glossoptosis, upper airway obstruction and feeding difficulties are definitely or at least mostly related to micrognathia, clinicians' special interest are focused upon growth of and/or lengthen the mandible in these infants. Actually, in the majority of PRS infants, these symptoms can be managed by placing the infant in a prone position until adequate mandibular growth occurs. This traditional treatment method causes the jaw and tongue to fall forward, opening the airway[7].

If this type of treatment fails, the infant then should be considered for other conservative therapies and/or surgical interventions. Conservative interventions can be performed with different orthodontic methods until adequate mandibular growth occurs. Surgical options include tongue-lip adhesion (a procedure to pull the tongue forward), release of the musculature of mouth floor, mandibular traction, and mandibular distraction or tracheotomy[3].

SURGICAL INTERVENTIONS

Surgical interventions are really more aggressive in nature. Currently there are no undisputed practical guidelines for surgical management of airway obstruction in patients with PRS who fail conservative treatment[8]. The PRS literature is unclear as to which surgical intervention is most effective. According to Mackay[9], it is even unclear if there is a "one surgery fits all" type of approach that is superior to a more adaptable and patient-dependent approach. Each surgical intervention has significant potential complications that must be considered. Other factors such as surgeon's training and experience may also play key roles in decision process[9]. Level and severity of airway obstruction or presence of multiple levels of airway narrowing demonstrated clinically and endoscopically, should guide the intervention[5].

Tracheostomy

Tracheostomy is a surgically created opening through the neck into the trachea (breathing tube) for the purpose of assisting breathing. With the exception of patients who are seen as candidates for a first-line surgical therapy by some surgeons, the traditional approach in the infants with PRS is tracheostomy[10]. Tracheostomy is the definitive and often a reserved procedure for the treatment of airway obstruction of patients with PRS whose condition fails to respond to other measures. It should be applied particularly for the patients with lower airway obstruction who require chronic ventilator support[11].

Tracheostomy may be associated with frequent and serious adverse effects, complications, and even death[12,13]. Up to 60% of the infants undergoing tracheostomy may experience some type of complications such as suprastomal granulation and collapse, tracheal stenosis, tube obstruction, fistulas, accidental decannulation, creation of false passages, cellulitis, neck scarring and loss of airway[12-14]. Recurrence of airway obstruction or feeding difficulties may also occur following tracheostomy.

As stated previously, although tracheostomy is still a first-line surgical therapy for some surgeons and the technique improved over the last 20 years, morbidity and mortality associated with tracheostomy are undeniable. This explains why it has now become a last resort for the treatment of PRS[15].

Mandibular traction by wires

Introduction of this technique to the literature is far away up to approximately 80 years ago[11]. Documentation of

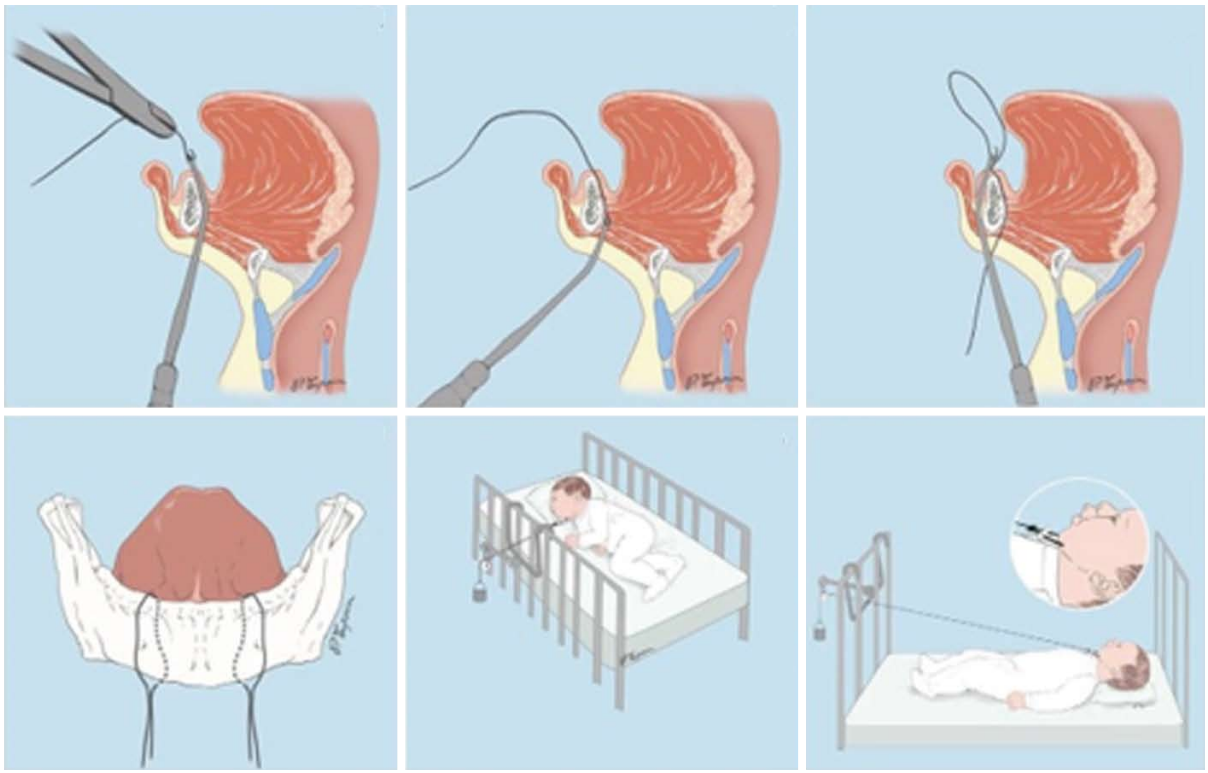

Figure 1 Mandibular traction by wires[18] (with kind permission of publisher).

high incidence of temporomandibular joint ankylosis was the primary reason why the first attempts regarding mandibular traction by wires were abandoned[16]. Although this technique is currently gaining great interest and popularity among surgeons[17,18], it is considerably aggressive in nature and requires an intensive care. Mandibular traction is accomplished by positioning two circum-mandibulary wires on both sides of the symphysis under local anesthesia (Figure 1). Continuous mandibular tractions are performed by using weights ranged from 50 to 200 g, except feeding[17-19]. Duration of the traction therapy has been reported to vary between 26.6[17] and 40[18] d. Position of the infant is changed every 2 h during this period[18].

The data obtained from the results of these studies suggest that mandibular traction with wires may be an effective treatment for upper airway obstruction with no major complication. The procedure immediately alleviates patients' respiratory problems and apnoea[17-19]. The piercing of the skin by traction wires may cause small scars on the chin.

Tongue-lip adhesion

Glossopexy or tongue-lip adhesion can be effective in relieving tongue-base obstruction. In this technique, anterior ventral part of the tongue is anchored to lower lip (mucosa plus or minus muscle), and posterior part to mandible. Main adverse outcomes are dehiscence and need for subsequent procedures[20]. Other complications of tongue-lip adhesion are infection, submaxillary duct obstruction, lip scarring, postoperative obstructive sleep apnea, severe dysphagia, and growth retardation[20,21]. Although some authors have observed weight gain and improved feeding after glossopexy[22], tongue-lip adhesion may result in airway obstruction or feeding difficulties due to altered tongue mobility and swallowing.

Mandibular distraction osteogenesis

Distraction osteogenesis (DO) is the surgical technique in which new bone formation is induced by gradual separation of bony segments after an osteotomy. This technique increases pharyngeal airway size by gradual mandibular lengthening. Distraction osteogenesis generates not only new bone but also new soft tissue in the distraction area. Mandibular distraction osteogenesis is becoming more common in management of the infants with PRS, and overcorrection of mandibular position is currently recommended to maximize the mandibular length and airway size[23].

The first maxillofacial application of DO was carried out by McCarthy[24], in 1992 when he used this method to lengthen a congenitally hypoplastic mandible. It is commonly used in medicine and dentistry for mandibular advancement in very severely affected (syndromic) children. In this regard, now, it gained common use to treat PRS infants. This procedure involves bilateral mandibular osteotomies and the placement of distraction devices (Figure 2)[25].

External or internal devices can be used, but both have pros and cons. External devices are easy to adjust and remove but can be dislodged and are associated with scarring. Internal devices are usually better tolerated but

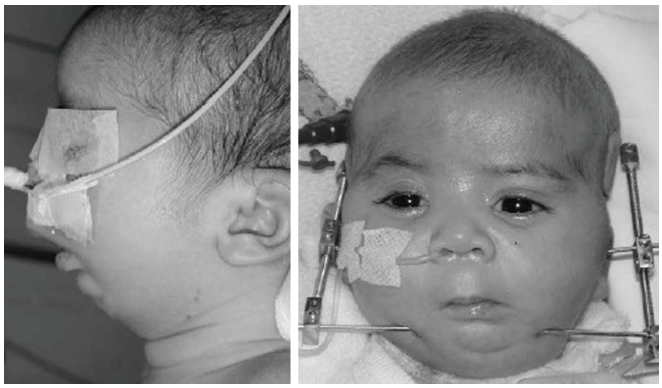

Figure 2 Mandibular distraction osteogenesis applied to one-month-old child with Pierre Robin sequence[25] (with kind permission of publisher).

require repeat dissection for removal under general anesthesia. Activation of the distractor is usually done at a rate of 1 mm per day. However, distraction can be carried out at the rate of 1.5 mm per day in infants because of their fast healing response[26].

The fact that three-dimensional computed-tomography analysis indicates an increased mandibular length and volume after distraction may explain the airway improvement in the children who undergo MDO[27,28]. In a recent paper by Pfaff *et al*[28], the mean increase in the mandibular volume following distraction was measured as 113.3%. Denny *et al*[16] evaluating the effects of mandibular distraction on very young patients (from 3 mo to 8 years of age) with congenital micrognathia showed a normalization in the maxillo-mandibular relationships and 67.5% increase in cross-sectional area of the airway. Rachmiel *et al*[29] evaluated eighteen patients (between 6 mo and 14 years of age) with hypoplastic mandible and glossoptosis and found a mean of 22 mm forward mandibular elongation, an increase in SNB angle and pharyngeal airway after mandibular distraction.

These very short-term reports demonstrated favorable mandibular growth following distraction. Long-term effects of this procedure, however, on mandibular and also facial growth are not subjected to any research and remain unanswered due to being a relatively new procedure in infants and young children. In addition, a lot of severe complications regarding MD have been reported, which include wound infections, facial cellulitis, temporary paresthesia, facial nerve injury, scarring, cheek abscess, open bite deformity, tooth bud injury, jaw deformity, and dentigerous cyst formation[30]. As reported by some authors, the most common complication is loss or malformation of permanent teeth at a rate of 21%[31].

ORTHODONTIC INTERVENTIONS

It is well known that PRS newborns often suffer from serious or even life-threatening airway obstructions in the respiratory tract resulting from anatomic malformations (mandibular micrognathia, glossoptosis and potentially a median cleft palate). Correction of the infant's micrognathia and associated glossoptosis is possible by the previously mentioned interventions. Besides these treatment alternatives, orthodontists use various palatal plates and function-stimulating devices which enable the physicians to refrain from invasive surgery.

Traditionally, pioneer orthodontic plates used in PRS, also called feeding obturators, were used to facilitate feeding because it was assumed that feeding difficulties in these children were related with sucking inability due to the cleft[32]. These plates were designed to obturate the cleft area and close the opening between oral and nasal cavities. They created an artificial non-cleft palate which aided extraction of milk from a nipple. They successfully used to facilitate feeding, reduce nasal regurgitation, and shorten the time required for feeding[32].

Currently, function-stimulating devices have gained popularity among orthodontists and are commonly used for PRS infants. These devices can stabilize the infant's vital parameters and ensure that it can be adequately fed during the appliance is placed. It is assumed that moving the tongue forward by a device that incorporates a tongue retaining and stimulating extension part result in mandibular growth promotion and thus orofacial musculature harmonization[4,33].

This kind of device was firstly introduced by Hotz *et al*[34] in 1982, and this appliance was later modified by Buchenau *et al*[35] in 2007 and called as "Pre-Epiglottic Baton Plate". This palatal plate was made from a compound soft and hard acrylic covering both whole palate including alveolar ridges and velar extension approximately 2 to 3 cm in length, and a wire structure was added to extending acrylic in severe cases. The position of velar extension was endoscopically inspected and adjusted. According to these authors, this appliance reduced apnea indices of PRS infants by 71%[35]. In 2011, Bacher *et al*[36] introduced a new plate with velar extension, which was quite identical to the Pre-Epiglottic Baton Plate. This appliance stimulated mandibular growth and resolved airway obstruction by forward positioning of the tongue and mandible by applying posterior pressure on the root of tongue.

In 2006, "Tübingen soft palate plate" was described in the German literature by Brosch *et al*[37]. This appliance includes three parts: an acrylic palatal plate, an adjustable velar spur connected to the palatal plate with wires, and two frontal wire bows to keep the appliance in stable position with extra-oral fixation by applying adhesive tapes in the cheek and nose area.

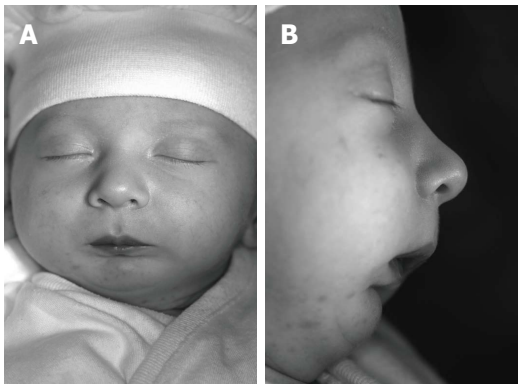

Figure 3 Frontal (A) and lateral (B) facial views before treatment.

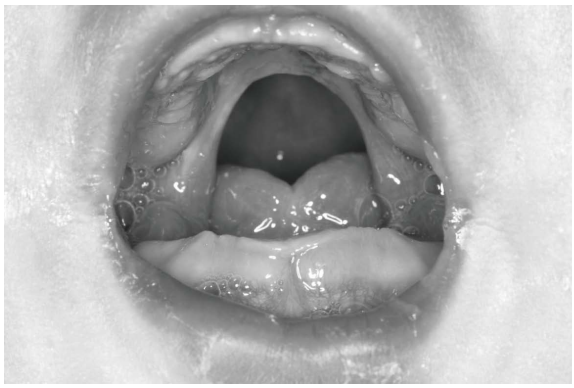

Figure 4 Intraoral view showing the tongue located in oropharynx behind the palatal shelves.

In 2007, Oktay *et al*[4] introduced a modified nutrition plate including palatal plate and adjustable pharyngeal wire extension covered with an acrylic button. The rest of this paper describes this plate and a baby treated with this appliance. The following text and figures reproduced with kind "written permission" of the publisher.

CASE REPORT[4]

A newborn girl with complaints of cleft palate, malnutrition, and respiratory distress was brought to the Pediatric Department at Research Hospital of the Faculty of Medicine in Atatürk University. The patient was diagnosed with Pierre Robin sequence and oxygen was provided to her so that the cyanosis in her legs and arms could be eliminated. In addition, a nasogastric catheter was inserted for nutrition. After the general condition of the patient improved, she was transferred to the Department of Orthodontics at the Faculty of Dentistry in Atatürk University for consultation and fabrication of a nutrition plate.

The mother stated that the baby was her first child. The mother had used some medicine for pharyngitis in the 3rd month of pregnancy and had a traffic accident in the 28th week of pregnancy, when she was slightly injured. It was stated also that there was no similar congenital or genetic anomaly in the grandparents. At another health

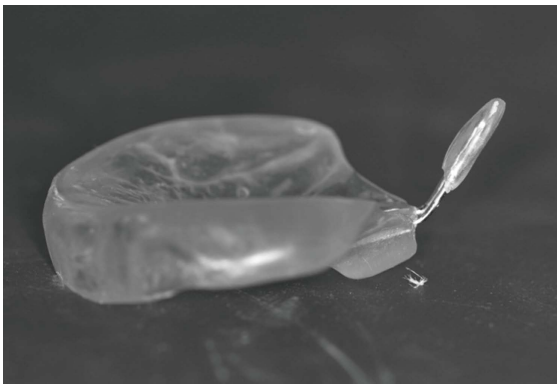

Figure 5 Modified nutrition plate with wire extension.

center, where the parents had gone to get information about the baby's condition, it was recommended that the baby's mandible be brought forward by means of distraction osteogenesis. However, the parents refused this approach.

The baby was brought to our department when she was 13-day-old (Figure 3). Clinical examination showed that the baby had three characteristics of Pierre Robin sequence. Because the mandible was small and the tongue was located in the oropharyngeal area (Figure 4), there were severe difficulties with breathing and nutrition. It was decided that a modified nutrition plate should be applied so that vital functions could be restored and the tongue could be brought to its normal position within the mouth.

Impressions from the baby were taken with a silicone-based material in operating room conditions, and a fine study cast was created with hard plaster. To prevent the tongue from falling back into the oropharynx, a wire extension would be added to the nutrition plate. The slope and length of the wire extending toward the tongue root was determined with clinical experience. The borders of the nutrition plate were determined on the plaster cast, and after the waxing processes in the cleft region, the extension to be added to the rear part of the plate was prepared from 0.9-mm diameter stainless steel wire. The acrylic portions of the plate were prepared using typical methods. To prevent the wire extension from damaging the soft tissues, the end of the extension was covered with an acrylic button (Figure 5).

After construction of the nutrition plate and its extension was completed, the appliance was inserted in the mouth. The wire extension forced the tongue to displace anteriorly, and it returned to its normal position in the oral cavity as soon as the modified nutrition plate was positioned in the mouth (Figure 6). The obstruction caused by the tongue in the oropharynx was eliminated and the patient was able to breathe easily and comfortably. The baby began to feed comfortably with a bottle.

The parents were taught how to insert and to remove the nutrition plate and were informed of the importance of appliance care and cleaning, cleanliness of the cleft area and tongue, nutrition, and preferred sleeping posi-

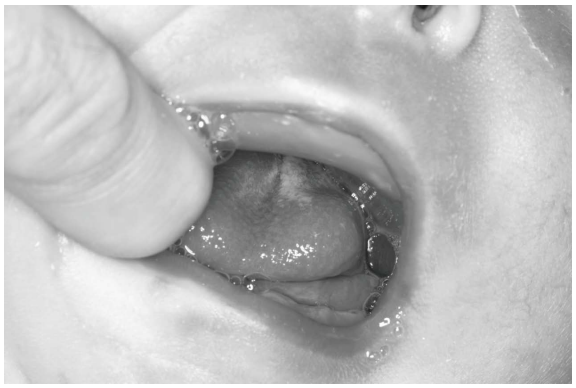

Figure 6 Tongue in the oral cavity just after the modified nutrition plate was inserted.

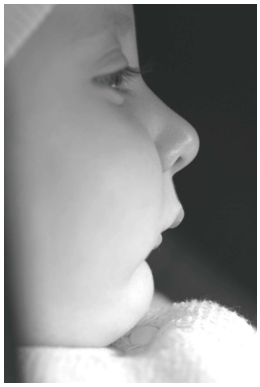

Figure 7 Facial view of the baby after 6 mo.

tions. The baby was examined 1 d later, and no mucosal damage was seen to be caused by the plate and wire extension. However, the parents stated that the baby had felt disturbed initially due to the distal extension pressing on the tongue root anteriorly and that she had vomited a few times. However, they also reported that she got used to its presence in the following hours.

In the visit 1 mo later, the baby's nutrition was observed to be fine. She was gaining weight normally and was breathing comfortably. The baby was seen monthly until the sixth month and her nutrition plate was changed every 2 mo. At the end of the sixth month, there appeared to be a correction in the baby's profile (Figure 7), and the tongue had adapted to its normal position. Intraoral examination revealed that even after the appliance was removed, the tongue did not move back toward the oropharyngeal area (Figure 8). Because of this result, use of the appliance was discontinued. The parents' pretreatment apprehension and concern about their baby's state appeared to have subsided. The surgery was completed at another health center when the baby was 12 mo and 22-day-old.

The facial photographs, taken 18 mo after the modified nutrition plate application, showed that facial growth and development were returned to a normal pattern, and that the mandible had caught up to the maxilla (Figure 9).

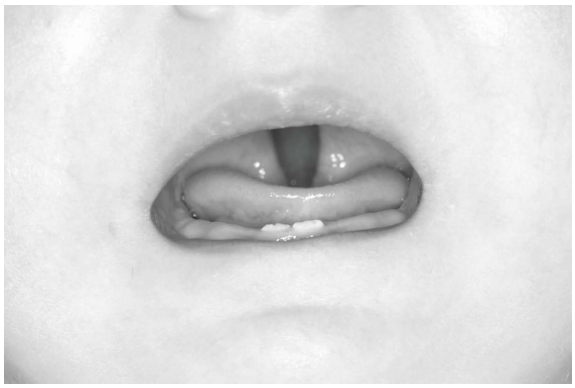

Figure 8 Intraoral view. The tongue in position in the oral cavity without the appliance.

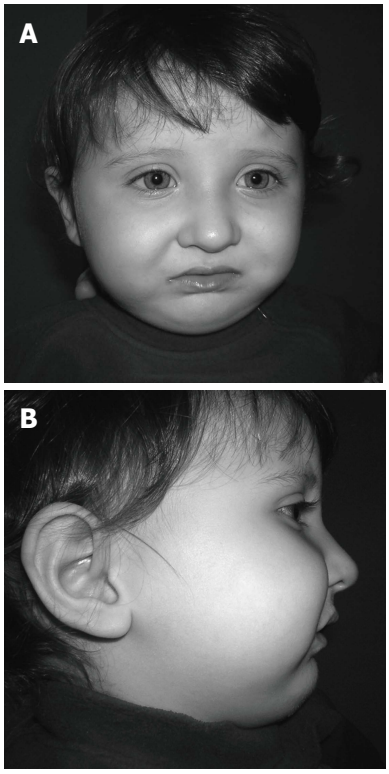

Figure 9 Frontal (A) and lateral (B) facial views of the baby after 18 mo.

In conclusion, the modified nutrition plate appears to be a viable alternative in the treatment of Pierre Robin sequence to surgical treatment modalities that are more aggressive in nature.

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Non-surgical periodontal therapy: An update on current evidence

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Abstract

Periodontal disease is an inflammatory condition that involves a complex interaction between pathogenic bacteria, environmental and acquired factors and host related factors. Till recently periodontal treatment was directed primarily towards reduction of bacterial load by subgingival debridement of root surfaces and modification of environmental risk factors. The current paradigm of periodontal disease stresses greater role of host-mediated inflammatory response in tissue destruction characteristic of periodontal disease. Various therapeutic modalities have been developed adjuvant to mechanical periodontal therapy. The use of laser and photodynamic therapy show great promise but their effectiveness has still not been conclusively proven. Chemotherapeutic agents, either systemic and local antimicrobials or host modulating drugs, played pivotal role in better and more predictable management of periodontal disease. The present review focuses on the best available evidence, for the current management of the chronic periodontal patients, gathered from systematic reviews and meta-analysis of mechanical non surgical periodontal therapy (NSPT) (subgingival debridement, laser therapy and photodynamic therapy) and the adjunctive chemotherapeutic approaches such as systematic and local antibiotics and antiseptics, subgingival pocket irrigation and host modulation therapies. The review also attempts to briefly introduce future developments in some of these modalities. At the end, the review summarizes the analysis of the current evidence that suggests that thorough subgingival debridement remains the mainstay of NSPT and that adjunct use of chemotherapeutic agents may offer better management of clinical parameters in periodontitis patients.

Key words: Systematic reviews; Mechanical nonsurgical periodontal therapy; chemotherapeutic approaches; Host modulation therapy; Laser

Core tip: The present review focuses on the best available evidence, for the current management of the chronic periodontal patients, gathered from systematic reviews and meta-analysis of mechanical non surgical periodontal therapy (NSPT) (subgingival debridement, laser therapy and photodynamic therapy) and the adjunctive chemotherapeutic approaches such as systematic and local antibiotics and antiseptics, subgingival pocket irrigation and host modulation therapies. The review also attempts to briefly introduce future developments in some of these modalities. At the end, the review summarizes the analysis of the current evidence for mechanical and chemotherapeutic approaches of NSPT.

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INTRODUCTION

Periodontal diseases are biofilm-mediated, chronic infec-

tious diseases and are the most common cause of tooth loss in the modern world. According to data from the World Health Organization report gingival bleeding and calculus, which primarily reflects poor oral hygiene, are most prevalent in adults from all regions of the world while advanced disease with deep periodontal pockets (≥ 6 mm) affects approximately 10% to 15% of the adult population[1].

Periodontitis involves a complex interaction between environmental (such as specific bacteria) and host (genetic and immunological) factors that leads to loss of periodontal attachment apparatus. The current paradigm of etiopathogenesis for periodontitis suggests that though periodontal diseases are pathogen and site specific, the host- microbial interactions leading to overproduction of destructive enzymes and pro-inflammatory mediators determine the extent and severity of tissue destruction[2,3]. This shift in paradigm has led to better understanding of the underlying host immune responses and to development of novel treatment strategies that may improve therapeutic outcomes and overall clinical management of periodontitis patients.

Treatment of periodontitis is directed primarily towards the reduction of pathogens embedded in the subgingival biofilm[4]. Non surgical periodontal therapy (NSPT) has been shown to improve probing pocket depths (PPD) and clinical attachment levels (CAL) in mild to moderate periodontitis cases with probing pocket depths of less than 6 mm[5]. In the treatment of deep pockets (> 6 mm) surgical periodontal therapy results in greater PPD reduction and clinical attachment gain[5]. Chronic periodontal disease can be successfully treated by NSPT provided adequate plaque control is maintained throughout the supportive phase of treatment[6].

NSPT includes both mechanical and chemotherapeutic approaches to minimize or eliminate microbial plaque associated with the periodontal tissues, tooth surfaces and within other niches in the oral cavity[4,7], and to alter host immune-inflammatory response in the periodontal tissues. Mechanical therapy refers to both supragingival and subgingival scaling and debridement of the roots by use of hand or power-driven scalers to remove local deposits such as plaque, calculus, endotoxins, and other plaque-retentive local factors[8].

Chemotherapeutic approaches includes antimicrobial therapies that can be used systemically or locally to address changes in the microflora and host modulatory therapy that can be used to address altered host immune response consisting of excessive levels of pro-inflammatory enzymes, cytokines, and prostanoids and excessive osteoclast function that may be related to certain risk factors[9].

Once the active bacterial challenge and host inflammatory reactions are controlled by surgical or nonsurgical therapy, it is imperative for the patient to maintain periodontal health with daily plaque control at home and periodic professional maintenance by the dentist or dental hygienist[10,11].

Systematic reviews include a comprehensive appraisal of research using transparent methods whilst aiming to minimize bias. This present review will cover an evidence based update through recent systematic reviews on NSPT and provide an insight into current advances in both mechanical and chemotherapeutic approaches used adjunctively to treat, manage and prevent periodontal diseases.

ASSESSMENT AND MODIFICATION OF RISK FACTORS

It is a well established fact that periodontal diseases are multifactorial in nature and one or more risk factors are necessary for disease initiation and progression. These risk factors include microbial factors, host related factors and environmental and acquired factors. Presence of poor oral hygiene, poorly controlled diabetes mellitus, persistent stress, habits such as tobacco smoking, genetic susceptibility, extent of alveolar bone loss are just some of the risk factors that may influence long term outcomes periodontal therapy[1,11]. Evaluation of these risk factors is a dynamic process and therapeutic strategies to modify them become an integral part of NSPT.

MECHANICAL NON-SURGICAL PERIODONTAL THERAPY

Mechanical periodontal therapy is usually the first line treatment for most periodontal infections and includes subgingival scaling and root debridement procedures. Previously aggressive root planing was thought to be required to remove bacterial endotoxin bound to the contaminated root surface[12]. Listgarten *et al*[13] in an electron-microscope study observed that the epithelial attachment on calculus that had been treated with chlorhexidine gluconate (CHX) has the same ultrastructure as normal epithelial attachment on various tooth surfaces. Current evidence suggests that bacterial endotoxins are weakly adherent to root surfaces and therefore intentional removal of root substance and contaminated cementum is not required for successful periodontal healing as it occurs even in the presence of calculus, provided that the subgingival bacterial plaque had been meticulously removed[14,15]. Hence the term debridement is now frequently used instead of root planing (Table 1).

Manual vs sonic or ultrasonic instrumentation

Manual instrumentation and sonic or ultrasonic scalers have been shown to be very effective in reducing the risk of tooth loss, slow down the rate of periodontal disease progression, reduce bleeding on probing and probing pocket depths and improve gingival health[6,10]. Use of hand scalers has been referred to as "gold standard" in mechanical periodontal therapy[16] but it is more time consuming, requires more skill, and is tiring for dentist and patients alike. On contrary, ultrasonic instrumentation improves patient compliance and requires less time

Table 1 Summary of the systematic reviews for mechanical non surgical periodontal therapy

Systematic review	No. of studies	Treatment modalities	Tested clinical parameters	Conclusion
Mechanical therapy				
Tunkel *et al*[17]	27	Machine driven *vs* subgingival debridement	Tooth loss, CAL, PPD, BOP	No difference between ultrasonic/sonic and manual debridement in the treatment of chronic periodontitis for single-rooted teeth. Ultrasonic/sonic subgingival debridement requires less time than hand instrumentation
Van der Weijden *et al*[25]	26	Subginigval debridement + supragingival plaque control	BOP, PPD, CAL	Improvement in PPD and CAL by subgingival debridement (with supragingival plaque control)
Slots *et al*[19]	15	Vector® ultrasonic scaler *vs* conventional ultrasonic instruments and/or hand instrumentation	Calculus removal, time of instrumentation, root surface aspects, patients' perception, BOP, PPD, CAL and microbiological effects	Comparable clinical and microbiological effect of all 3 modalities. Vector® ultrasonic system is more time consuming
Laser therapy				
Schwarz *et al*[29]	11	Laser monotherapy *vs* mechanical debidement	Clinical data Laser safety data	Er:YAG laser monotherapy resulted in similar clinical outcomes, both in the short and long term compared with mechanical debridement. Insufficient evidence to support the clinical application of either CO(2), Nd:YAG, Nd:YAP, or different diode lasers
Karlsson *et al*[32]	4	Laser therapy + SRP	BOP, PPD, CAL	No consistent evidence for efficacy of laser as an adjunct to NSPT in adults with chronic periodontitis
Slots *et al*[30]	8	Nd:YAG Laser monotherapy *vs* Laser + SRP	Plaque, BOP, gingivitis, PPD, CAL, and GR	No beneficial effect of a pulsed Nd:YAG laser compared to ultrasonics and/or hand instrumentation in the initial periodontitis
Sgolastra *et al*[31]	5	Er:YAG laser *vs* SRP	CAL, PPD and GR	No evidence of effectiveness of Er:YAG laser compared to SRP
Photodynamic therapy				
Azarpazhooh *et al*[40]	5	Monotherapy or adjunctive PDT	PPD, CAL, GR, Full mouth plaque and bleeding scores	Routine use of PDT for clinical management of periodontitis cannot be recommended
Sgolastra *et al*[39]	4	PDT used alone or adjunctive to scaling root planning	CAL, PPD, GR	PDT adjunctive to conventional treatment provides short-term benefits, but microbiological outcomes are contradictory. No evidence of effectiveness for the use of PDT as alternative to SRP

CA: Clinical attachment level; PPD: Probing pocket depth; BOP: Bleeding on probing; SRP: Scaling and root planing; GR: Gingival recession; PDT: Photodynamic therapy; Er:YAG: Erbium-doped: yttrium-aluminum garnet; Nd:YAG: Neodinium doped: yttrium-aluminum garnet.

for thorough debridement.

A systematic review of efficacy of machine-driven and manual subgingival debridement in chronic periodontitis concluded that ultrasonic/sonic subgingival debridement can be completed in less time compared to hand instruments, though the clinical efficacy remained similar. It further reported no major difference in the frequency and severity of adverse effects following the two treatment modalities[17]. Ultrasonic instrumentation when used on medium power settings has shown comparatively lesser root surface alteration and found to be more effective in furcation areas[18]. A new pain free ultrasonic system, Vector®, has been introduced few years back. It's a linear oscillating device that result in the parallel movement of the instrument tip to the root surface[19]. A systematic review concluded that clinical and microbiological effects of the Vector® system is comparable to power-driven and manual instrumentation in moderately deep pockets. However the system was found to be is less effective in deep pockets and was considerably more time consuming[19].

Several other comparison studies have observed that both manual and ultrasonic instrumentation were equally effective in removal of plaque, calculus and endotoxins[18] and resulted in changes in the composition of the microbial flora in deep periodontal pockets such as reduction of spirochetes and motile rods[20,21] and increase in gram positive rods and cocci[7,22].

A thorough review of nonsurgical periodontal therapy by Cobb *et al*[23] reported mean PPD reductions of 1.29 mm to 2.16 mm and CAL gains of 0.55 mm to 1.19 mm for initial probing depths of 4 mm to 6 mm or more than 6 mm before treatment in chronic periodontitis patients receiving sungingival debridement[23,24]. Another systematic review[25] reported weighted mean of attachment gain of subgingival debridement in deep pockets (≥ 5 mm) was 0.64 mm while PPD reduction was 1.18 mm and clinical attachment gain was 0.74 mm. The author concluded that subgingival debridement in conjunction with supragingival plaque control is an effective treatment in reducing probing pocket depth and improving the clinical attachment level.

Mechanical instrumentation alone has shown limited ability in areas with deeper pockets, underlying bony defects and also found to be ineffective in reducing levels of tissue penetrating bacteria, such as *Aggregatibacter acti-*

nomycetemcomitans (*A. actinomycetemcomitans*)[26,27]. Therefore use of chemotherapeutic agents as adjuncts to mechanical therapy has been strongly suggested along with regular maintenance visits[9].

Laser (Light amplification by stimulated emission of radiation)

The use of lasers has been advocated for past few years within the periodontal pocket for subginigival debridement, reduction of subgingival bacterial loads and scaling and root planing (SRP). But its clinical effectiveness in the treatment of periodontal diseases remains debatable among clinicians and there is dearth of clinical evidence for their benefit over traditional mechanical therapy[28].

Among the different wavelengths of lasers compared with traditional mechanical therapy involving manual and sonic and ultrasonic instrumentation, the erbium-doped: yttrium-aluminum garnet (Er:YAG) laser is reported to be the most effective[29]. However, current evidence suggests that the clinical effectiveness of the Neodinium doped: yttrium-aluminum garnet (Nd:YAG)[30] or Er:YAG[31] laser was comparable to SRP in terms of clinical attachment gain, PPD reduction or change in gingival recession and that there was no added advantage of using lasers as a standalone therapy in treatment of chronic periodontitis[30-32]. Even in terms of reduction in subgingival putative pathogens use of the Nd:YAG or Er:YAG wavelengths was found to be equivalent and not superior to SRP[33].

Photodynamic therapy

Antimicrobial photodynamic therapy (PDT) is a non-invasive therapeutic modality, which relies upon an oxygen-dependent photochemical reaction that occurs upon light mediated activation of a photosensitizing compound bound to the target cell. This reaction leads to the generation of cytotoxic reactive oxygen species, predominantly singlet oxygen[34,35] and hence can be very effective in anaerobic infections like periodontitis. The light source could be a low-power laser[36,37] or light emitting diodes[38].

There are very few systematic reviews and well designed research published on clinical effectiveness of PDT over conventional periodontal therapy. A recent systematic review of seven randomized controlled trials (RCTs)[39] and another with five trials[40] concluded that the use of photodynamic therapy as a standalone therapy does not produce any beneficial clinical effect as compared to SRP. The review further noted that PDT as an adjunctive to SRP provides only short-term benefits. Finally both reviews recommended well-designed, long term RCTs as currently there is an insufficient evidence to suggest that PDT is superior to the conventional periodontal therapy.

CHEMOTHERAPEUTIC APPROACHES IN NON-SURGICAL PERIODONTAL THERAPY

Although mechanical non-surgical and surgical therapy continues to dominate other treatment approaches in the treatment of periodontal disease, its inability to completely eliminate periodontal pathogens from the soft tissues and hard tissue surfaces and within other niches in the oral cavity may cause recolonization of these pathogens leading to reinfection[1,2]. To overcome these deficiencies in traditional periodontal therapy, adjunctive use of chemotherapeutic agents either systemically, locally or topically becomes an indispensible treatment modality[2,8,9].

As the current paradigms in the etiopathogenesis of periodontal disease suggests greater role of host immune reaction to bacterial challenge in the ensuing periodontal tissue destruction, the newer chemotherapeutic approaches are focused on how to effectively modulate these host responses and lessen the degree of tissue destruction as well as help periodontal tissue regenerate and repair to a healthy state[41].

Various chemotherapeutic approaches include use of antimicrobials and antiseptics via topical application, subgingival pocket irrigation, local delivery into the periodontal pocket and systemic administration.

Systemic antibiotic therapy

Systemic antimicrobials therapy as an adjunct to mechanical debridement has been advocated in past few decades, the rationale for their use being the suppression of periodontal pathogens persisting in biofilms in deep pockets, root furcations and concavities or residing within the periodontal tissues or other oral niches where mechanical therapy alone may prove to be ineffective. In particular the periodontal pathogen *A. Actinomycetemcomitans*, *Porphyromonas gingivalis* (*P. gingivalis*), *Prevotella intermedia* (*P. intermedia*), *Bacteroides forsythus* (*B. forsythus*), staphylococci and enteric rods has been reported to be difficult to eradicate with nonsurgical therapy alone[42]. While more than 500 bacterial species may be present in the gingival sulcus[43], it is clear that only a subset of bacterial species are consistently found to be associated with diseased sites[44]. These findings suggest that systemic antimicrobial therapy may prove an indispensible adjunct to mechanical therapy for efficient management of periodontal conditions that cannot be managed with mechanical therapy alone. These conditions may include severe or acute infections, aggressive periodontitis, and recurrent or refractory cases[45], (Table 2).

Common antibiotic regimens for the treatment of periodontitis are included in Table 3. Early approaches to systemic antibiotic therapy for periodontal treatment involved monotherapy with metronidazole, tetracyclines, doxycycline, amoxicillin (with or without clavulanic acid), spiramycin, clindamycin, and azithromycin[45,46].

Since periodontitis is a polymicrobial infection, the heterogeneity of pathogenic bacteria necessitates use of drug combination therapies that can also be effective to overcome drug protective effects of biofilm[47]. Combination therapy should involve drugs with complementary but different mechanisms of action and synergistic or additive effect[45]. *In-vitro* experiments have reported synergistic effect of amoxicillin with metronidazole and

Table 2 Summary of systematic reviews on adjunctive chemothrerapeutic agents

Systematic review	No. of studies	Treatment modalities	Tested clinical parameters	Conclusion
Systemic antimicrobial therapy				
Herrera *et al*[50]	25	SRP + systemic antibiotics *vs* SRP alone or SRP + placebo	PPD, CAL	Systemic antimicrobials in conjunction with SRP can offer an additional benefit over SRP alone in the treatment of periodontitis
Haffajee *et al*[51]	29	SRP + systemic antibiotics *vs* SRP alone or SRP+ placebo	CAL	The use of systemically administered adjunctive antibiotics with and without SRP and/or surgery appeared to provide a greater clinical improvement in CAL
Goodson *et al*[52]	RCT# (187 Patients)	SRP + systemic antibiotics *vs* SRP + local antibiotic therapy and/or periodontal surgery	CAL, PPD	Adjunctive therapies generally exhibited improved CAL gain and/or PPD reduction when compared with SRP alone
Sgolastra *et al*[54]	6	AMX/MET + SRP *vs* full mouth SRP alone	CAL, PPD, secondary outcomes, and adverse events	Significant CAL gain and PPD reduction in favor of full mouth SRP + AMX/MET; no significant risk difference in the occurrence of adverse events
Sgolastra *et al*[55]	4	AMX/MET + SRP *vs* SRP alone	CAL, PPD, secondary outcomes, and adverse events	Significant CAL gain and PPD reduction in favor of SRP + AMX/MET; no significant difference in BOP or suppuration. Supports effectiveness of SRP with AMX/MET in chronic periodontitis
Zandbergen *et al*[53]	28	Adjuvant AMX/MET + SRP	CAL, PPD, plaque index, BOP	AMX/MET as an adjunct to SRP can enhance the clinical benefits of non-surgical periodontal therapy in adults who are otherwise healthy
Keestra *et al*[56]	43	Different systemic antibiotics + SRP *vs* SRP alone	BOP, CAL, PPD	Systemic antibiotics combined with SRP offer additional clinical improvements compared to SRP alone. For initially moderate and deep pockets, MET or MET + AMX, resulted in clinical improvements that were more pronounced over doxycycline or azithromycin. Clinical benefit became smaller over time (1 yr)
Local antimicrobial therapy				
Hanes *et al*[60]	32	Local controlled-release anti-infective drug therapy with or without SRP *vs* SRP alone	PPD, CAL	Local anti-infective agents resulted in significant adjunctive PPD reduction or CAL gain for minocycline gel, microencapsulated minocycline, CHX chip and doxycycline gel during SRP compared to SRP alone. The decision to use local anti-infective adjunctive therapy remains a matter of individual clinical judgment, the phase of treatment, and the patient's status and preferences
Bonito *et al*[61]	3	Local antimicrobials with SRP *vs* SRP alone	CAL, PPD	Only modest improvements in PPD reductions
Matesanz-Pérez *et al*[62]	52	Local antimicrobials with SRP *vs* SRP alone	CAL, PPD, plaque index, BOP	Scientific evidence supports the adjunctive use of local antimicrobials to debridement in deep or recurrent periodontal sites, mostly when using vehicles with proven sustained release of the antimicrobial
Full mouth disinfection				
Eberhard *et al*[78]	7	FMD with or without antiseptics *vs* quadrant scaling	Tooth loss, BOP, PPD, CAL	Only minor differences in treatment effects between the treatment strategies
Eberhard *et al*[79]	7	FMD with or without antiseptics *vs* quadrant scaling	Tooth loss, BOP, PPD, CAL	Slightly more favourable, but modest outcomes were found following FMD in moderately deep pockets. Very limited number of studies available for comparison, thus limiting general conclusions about the clinical benefit of full-mouth disinfection
Lang *et al*[80]	12	FMD with or without antiseptics *vs* conventional staged debridement	BOP, PPD, CAL microbial changes	Despite the significant differences of modest magnitude, FMD with or without antiseptics do not provide clinically relevant advantages over conventional staged debridement. Hence, all three treatment modalities may be recommended for debridement in the initial treatment of chronic periodontitis
Farman *et al*[81]	7	Full mouth debridement *vs* FMD with antiseptics *vs* quadrant scaling	BOP, PPD, CAL	Traditional quadrant approach and full-mouth debridement could be equally effective

CAL: Clinical attachment level; PPD: Probing pocket depth; SRP: Scaling and root planing; BOP: Bleeding on probing; RCT: Randomized controlled clinical trial; AMX/MET: Amoxicillin plus metronidazole; FMD: Full mouth disinfection.

ciprofloxacin with metronidazole against *A. actinomycetemcomitans* and other periodontal pathogens[48,49]. Combina-

Table 3 Recommended systemic antibiotic dosing regimens

Single agent regimen dosage/ duration	
Amoxicillin	500 mg, three times per day × 8 d
Azithromycin	500 mg, once daily × 4-7 d
Ciprofloxacin	500 mg, twice daily × 8 d
Clindamycin	300 mg, three times daily × 10 d
Doxycycline or minocycline	100-200 mg, once daily × 21 d
Metronidazole	500 mg, three times daily × 8 d
Combination therapy	
Metronidazole + amoxicillin	250 mg, of each three times daily × 8 d
Metronidazole + ciprofloxacin	500 mg of each twice daily × 8 d

Adapted from Krayer *et al*[41].

tion therapy of amoxicillin with metronidazole has been the most well documented for adjunctive treatment of chronic and aggressive periodontitis.

Herrera *et al*[50] in a systemic review of 25 studies concluded that systemic antimicrobials in conjunction with SRP, can offer an additional benefit over SRP alone in the treatment of periodontitis, in terms of CAL and PPD change, and reduced risk of additional CAL loss. They further noted that patients with deep pockets, progressive or active disease, or specific microbiological profile, can benefit more from this adjunctive therapy. Haffaji *et al*[51] in a systematic review of 29 studies concluded that systemically administered antimicrobials were uniformly beneficial in providing an improvement in clinical attachment gain when used as adjuncts to scaling and root planing.

In a large multicenter randomized controlled trial, Goodson *et al*[52] reported that adjunctive systemic antimicrobial therapy with amoxicillin and metronidazole resulted in significantly more clinical attachment gain and PPD reduction in deep periodontal pockets (probing depth ⩾ 5 mm) compared to SRP alone in chronic periodontitis patients. The results of recent systematic reviews involving aggressive periodontitis[53,54] and chronic periodontitis[53,55,56] also corroborate earlier findings of significant clinical attachment gain and reduction in PPD when systemic amoxicillin with metronidazole was administered with conventional periodontal therapy. Another recent systematic review of 43 studies utilizing different antibiotic regimens concluded that systemic antibiotics combined with SRP resulted in significant PPD reduction for initially moderate pockets at 3 mo (0.27 ± 0.09 mm), at 6 mo (0.23 ± 0.10 mm) and at 12 mo (0.25 ± 0.27 mm) and deep pockets at 3 mo (0.62 ± 0.17 mm), at 6 mo (0.58 ± 0.16 mm) and at 12 mo (0.74 ± 0.30 mm) though there was a trend that the magnitude of the clinical benefit became smaller over period of time (1 year)[56]. The authors further conclude that clinical effects of metronidazole or metronidazole combined with amoxicillin resulted in clinical improvements that were more pronounced over doxycycline or azithromycin, though the difference was not statistically significant[56].

The best available evidence indicates that systemic antimicrobials used in conjunction with SRP, can offer an additional benefit over SRP alone, in terms of CAL, and PPD change, especially in deep periodontal pockets. However it should be remembered that systemic antibiotics are an adjunct to mechanical periodontal therapy and should not be used as monotherapy. Their use should be restricted in severe or acute infections, aggressive periodontitis, and recurrent or refractory cases that cannot be managed with other therapeutic modalities. The indiscriminate use of systemic antimicrobials can lead to development of antibiotic resistance among human pathogens. To reduce this risk, microbiological analysis and antimicrobial susceptibility testing is suggested for selecting the optimal antimicrobial therapy[47].

Local antimicrobial delivery

Limited indications of systemic antimicrobial therapy and the risk-benefit ratio of their use led to development of local delivery of antimicrobial and antiseptics (LAD) directly in the periodontal pocket. The rationale of using LAD in periodontal disease is to chemically kill or reduce the plaques within the biofilm in the pocket by placing high concentrations of an antibiotic or antiseptic in direct contact with the root surface without noticeable systemic effect, which may not be always possible with systemic antibiotics. Sakellari *et al*[57] reported that gingival crevice fluid concentration of systemically administered antimicrobials tetracyclines was less than that of plasma concentration and vary widely among individuals (between 0 and 8 Lg/mL), with approximately 50% of samples not achieving a level of 1 Lg/mL. This possibly explains variable clinical response to systemic tetracyclines observed in clinical practice.

Various non-resorbable and resorbable intrapocket delivery systems have been developed. The first LAD agent developed for periodontitis was Actisite™, supplied as hollow, non-resorbable fibers filled with tetracycline (12.7 mg/9 inch fiber)[58]. Though very effective, the non-absorbable fibers were tedious to insert in the deep pockets and required a second visit for retrieval from pocket. These deficiencies fuelled the development of absorbable systems for LAD.

Among the first absorbable system to be developed was Atridox™, which is a 10% formulation of doxycycline (50 mg in a bioresorbable gel system).The polymer gel fills and conforms to pocket morphology, then solidifies to a wax-like consistency upon contact with gingival crevicular fluid. Doxycycline is released at effective concentrations over 7 d, and significant reductions (60%) in anaerobic pathogens are sustained for up to 6 mo post treatment[59].

The early success of Atridox™ led to development of other absorbable LAD systems such as minocycline microspheres (Arestin™), chlorhexidine gluconate chips (PerioChip™) and gel (Chlosite™), and metronidazol gel (Elyzol™).

Hanes *et al*[60] in a meta-analysis of 19 studies compared SRP and adjunctive local sustained-release agents

with SRP alone. The authors concluded that local anti-infective agents resulted in significant adjunctive PPD reduction or CAL gain for minocycline gel, microencapsulated minocycline, CHX chip and doxycycline gel during SRP compared to SRP alone.

Bonito *et al*[61] in a subsequent systematic review, reported most positive results for tetracycline, minocycline, metronidazole, and CHX with modest but statistically significant improvements in PPD reductions compared with scaling and root planing alone. The authors did not report any significant changes in clinical attachment gain and questioned the clinical significance of these small improvements though they were statistically significant.

In a recent systematic review of 52 studies, Matesanz-Pérez *et al*[62] observed that subgingival application of tetracycline fibers, sustained released doxycycline and minocycline resulted in statistically significant benefit in PPD reduction (WMD between 0.5 and 0.7 mm) while that for CHX and metronidazole showed a minimal effect (WMD between 0.1 and 0.4 mm) when compared with placebo. The authors concluded that the scientific evidence supports the adjunctive use of local antimicrobials to debridement in deep or recurrent periodontal sites, mostly when using vehicles with proven sustained release of the antimicrobials.

The advent of newer formulations, such as subgingival delivery of statins and azithromycin, have shown promise in improving clinical parameters in chronic periodontitis patients when used along with SRP[63,64].

Current evidence seems to suggest that site-specific delivery of drug can overcome the disadvantages with systemic administration of antimicrobials for periodontitis and may prove to be a viable adjunct to conventional periodontal therapy.

Subgingival pocket irrigation

Sub gingival irrigation of agents such as chlorhexidine digluconate, 10% povidone iodine (PI), and 0.1% sodium hypochlorite has been advocated in periodontal disease as they show excellent antibacterial and antiviral properties and are readily available[65,66]. They are also more effective in flushing out the bacteria and reducing gingivitis scores as it penetrates much deeper in to the pocket when compared to mouth rinses or suprgingival irrigation[67].

Systematic reviews analysing the effect of subgingival irrigation with CHX[51] and PI[68] observed no additional clinical benefit to mechanical debridement for CHX irrigation[51] and a small but statistically significant effect of PI in probing depth reduction[68]. Consensus report of 6th European workshop on periodontal disease also concluded that the use of antiseptic irrigants has not shown any advantage over conventional periodontal therapy in periodontal diseases[69]. Current evidence suggests that subgingival irrigation is never intended to be used as a standalone therapy; rather it is meant to be used as an adjunct to professional debridement, but one that simplifies home-care oral hygiene for the patient[70].

Topical antiseptic application

Topical application of antiseptics such CHX, povidone iodoine, phenolic compounds and sodium hypochlorite, with anti-plaque or anti-gingivitis action, has been suggested as useful oral hygiene aids to complement mechanical periodontal therapy. Though topical application seems to be of limited value, since it does not appreciably penetrate into the gingival crevice, they are useful adjuncts to control gingival inflammation, especially in acute conditions, post-surgically and during periods of interrupted hygiene[71].

A recently published meta-analysis of 50 studies, of atleast 6 mo duration, reported clinically and statistically significant antiplaque and antigingivitis effect of dentrifices containing triclosan/copolymer formulations and mouthrinses with 0.12% CHX and essential oils-containing formulations [menthol (0.042%), thymol (0.064%), methyl salicylate (0.060%), and eucalyptol (0.092%)]. Statistically and clinically significant antigingivitis effect was reported with dentifrices containing stannous fluoride. The author concluded that the meta-analysis provided strong evidence in favor of the use of antimicrobial agents as adjuncts to mechanical plaque control[72].

Certain disadvantages associated with long term use of mouthrinses include staining of teeth, mucositis and reversible epithelial desquamation, alteration of taste, and increased supragingival calculus[73]. Another important aspect of using topical antiseptics is that drugs should be in contact with periodontal pathogens at optimal concentration for optimal time period to exert bactericidal activity. For example, CHX must be in contact with *P. gingivalis* for 10 min at concentrations of 0.5% to 2%[74]. While povidone iodine, active against most bacteria, viruses, fungi and some spores, must be in contact with these pathogens for at least 5 min at concentrations between 0.5% and 10% to reach bactericidal activity[75].

Full mouth disinfection

The full mouth disinfection (FMD) protocol was first proposed by Quirynen *et al*[76] in 1995 as a new therapeutic approach to eradicate or at least suppress all periodontal pathogens in a short time not only from the periodontal pockets but also the entire oropharyngeal cavity so that the recolonization of the pockets by bacteria residing at non-treated pockets and other oral sites is prevented. The purported advantages of the FMD approach include significant additional clinical and microbiological improvements, better outcome of the mechanical debridement, reduced need for surgery and more efficient treatment and time management with less overall chair-side time and less travelling or absence from work for the patient[77].

Full-mouth disinfection involves removal of all plaque and calculus in two visits within 24 h. In addition, at each of these visits, the tongue was brushed with a 1% CHX gel for one minute, CHX spraying on tonsils and the mouth rinsed with a 0.2% CHX solution for two minutes. Furthermore, subgingival CHX (1%) irrigation was performed in all pockets. The recolonization of the pockets was retarded by oral hygiene and 0.2% CHX rinses during two weeks[76].

Two systematic reviews of 7 studies each, comparing full-mouth scaling and root planing within 24 h with antiseptics (FMD) or without (FMS) the adjunctive use of an antiseptic (chlorhexidine) with conventional quadrant scaling and root planning as control, concluded that in patients with chronic periodontitis, only minor differences in reduction in PD and CAL were observed in moderately deep pockets between the treatment strategies[78,79]. The authors further concluded that there were very limited number of studies available for comparison, thus limiting general conclusions about the clinical benefit of full-mouth disinfection[79]. Lang *et al*[80] in a systematic review of 12 trials and Farman and Joshi[81] in a systematic review of 7 trials concluded that FMD or full mouth scaling do not provide clinically relevant advantages over conventional staged debridement and recommended all three treatment modalities for debridement in the initial treatment of patients with chronic periodontitis.

HOST MODULATION THERAPY

As the role of host immune reactions to the bacterial challenges is being established in the etiopathogenesis of periodontal disease, modulation of these reactions provides for very promising and exciting therapeutic options to manage periodontal disease. Host modulation therapy has witnessed rapid advances in recent years and newer therapeutic modalities are being developed to restrain or inhibit release of proteolytic enzymes, pro-inflammatory mediators and osteoclast activity that occur as a result of host-microbial interactions. Different agents currently being investigated as an adjunct to mechanical NSPT are anti-proteinases, anti-inflammatory agents, and anti-resorptive agents (Table 4)[9,41].

Anti proteinase agents

Current research postulates that host cells, when stimulated directly or indirectly by bacterial endotoxins, secrete tissue-destructive enzymes known as the matrix metalloproteinases (MMPs). Although several periodontal pathogens produce MMPs, including collagenase, host derived proteinases are considered to be the major destructive enzymes associated with periodontal disease progression[82]. Golub *et al*[83] first reported that the semisynthetic analogs of tetracyclines, like doxycycline, were more effective in reducing excessive collagenase activity in the gingival crevicular fluid of adult periodontitis patients. This is accomplished through the non-antimicrobial activities of low-dose doxycycline *via* the inhibition of MMP-8 and 13 protease mechanisms[84] and downregulation of key inflammatory cytokines (interleukin-1,6; tumor necrosis factor-α)[85].

Currently doxycycline hyclate (Periostat®) is the only collagenase inhibitor available for use specifically in periodontal disease, the recommended dosage being 20 mg tablet two times daily for a minimum of 3 mo to achieve long-term benefit without a rebound[86]. More recent trials recommend a 6 to 9 mo regime of Subantimicrobial dose doxycycline (SDD) to prevent a rapid rebound in collagen-destructive enzyme activity and to enhance clinical efficacy[87,88]. Since their introduction, the beneficial effects of SDD in improving CAL, reducing PPD, and clinical attachment gain when used as an adjunct to SRP have been established through many systematic reviews[89-92]. A recent meta-analysis[90] of 9 randomized controlled double-blind clinical trials reported that the host modulating agent such as SDD was effective in improving CAL and reducing PPD when administered as an adjuvant in the nonsurgical management of chronic and aggressive periodontitis. Another meta-analysis of 3 trials by Sgolastra *et al*[91] supported the long term effectiveness of the adjunctive SDD treatment. Preshaw *et al*[92] in a meta-analyses of 2 trials reported significant PPD reduction and clinical attachment gain in smokers with chronic periodontitis when SDD was used as an adjunct to SRP.

Anti-inflammatory agents

In periodontal inflammation, significantly high levels of prostaglandin E_2 (PGE2) has been reported in gingival tissues and gingival crevicular fluid (GCF)[93,94]. The tissue damage resulting from host-microbial interactions allows production of free arachidonic acid (AA) from phospholipids in plasma membranes of cells by action by phospholipase A2 *via* the cyclooxygenase (CO) or lipoxygenase (LO) pathways. The final products of the CO pathway include prostaglandins, prostacyclin, and thromboxane, whereas the end results of the LO pathway include leukotrienes and other hydroxyeicosatetraenoic acids.

Non-steroidal anti-inflammatory drugs (NSAIDs) have the ability to block the enzyme CO and reduce prostaglandin synthesis and rate of alveolar bone resorption. A recent systematic review[89] of ten trials compared various NSAIDs such as indomethacin, flurbiprofen, ibuprofen, naproxen, meclofenamic acid, piroxicam and Ketoprofen in periodontal disease treatment. Although the heterogeneity of data did not allow a meta-analysis, limited quantitative analysis suggested a significant benefit related to alveolar bone height maintenance when NSAIDs were combined with mechanical periodontal therapy. Though theses agents are found to be useful in chronic[95] and aggressive periodontitis[96], they require prolonged administration to prevent recurrence of infection and to maintain healthy periodontal status[97]. The adverse effects associated with prolonged systemic administration of non-selective NSAIDs[98] such as gastrointestinal, renal, and hepatic impairment has curtailed their application in management of chronic conditions like periodontitis. To counter these adverse effects of non selective NSAIDs, selective COX-2 inhibitors were developed but they were subsequently withdrawn because of increased incidence of thrombosis and myocardial infarcts associated with their long term administration[98].

Topical application of NSAIDs has been advocated owing to lipophilic properties of these drugs. NSAIDs that have been evaluated for topical administration include ketorolac tromethamine[99], S-ketoprofen[100], and flurbiprofen[101]. Though these trials reported reductions in the

Table 4 Summary of systematic reviews on host modulation therapy

Systematic review	No. of studies	Treatment modalities	Tested clinical parameters	Conclusion
Reddy *et al*[89]	7 (SDD), 10 (NSAIDs), 3 (BPs)	Adjuntive efficacy of anti-proteinases, anti-inflammatory agents, and anti-resorptive	Bone changes, CAL, PPD, plaque index, gingivitis	Use of SDD+ SRP‡ is statistically more effective than SRP alone in reducing PPD and achieving CAL gain Insufficient data for NSAIDs and BPs may have potential adjunctive role in periodontal therapy
Preshaw *et al*[92]	2	SDD + SRP *vs* SRP + placebo	CAL, PPD	Adjunctive SDD enhances therapeutic outcomes compared with SRP alone, resulting in clinical benefit in both smokers and non-smokers with chronic periodontitis
Sgolastra *et al*[91]	3	SDD + SRP *vs* SRP + placebo	CAL, PPD, Plaque Index, Gingival Index, and gingival crevicular fluid levels	Supports long-term effectiveness of adjunctive SDD therapy
Moreno Villagrana *et al*[90]	9	SDD + SRP *vs* SRP + placebo	CAL, PPD	Statistically significant results in patients with aggressive or chronic periodontitis under periodontal treatment

SDD: Subantimicrobial dose doxycycline; NSAID: Non steroidal antiinflammatory drug; BP: Bisphosphonates; CAL: Clinical attachment level; PPD: Probing pocket depth; SRP: Scaling and root planing.

rate of alveolar bone loss, no superior effect was observed for other clinical parameters when topical NSAIDs were used in conjunction with conventional periodontal treatment[97,99,101]. However, currently there is only limited evidence available and further large multi center trials are recommended to determine whether these NSAIDs provide clinically significant improvements when utilized as adjuncts to scaling and root planing[89].

Lipoxins (LX) are endogenous byproduct of AA metabolism through LO pathway and act as proresolving, anti-inflammatory molecules[101] that control the resolution phase of acute inflammation and promote healing of the lesion[102,103]. It has been demonstrated that lipoxins are produced by peripheral blood neutrophils from patients diagnosed with aggressive periodontitis and not from healthy patients[104], suggesting their immunomodulatory role in periodontal disease. LX and their more stable and bioactive form, aspirin triggered lipoxins (ATL) stimulate resolution pathways and restore tissue homeostasis through agonist actions on neutrophils. Experiments in several murine models suggest that in inflammation, stable analogs of LX inhibit *P. gingivalis* elicited neutrophil infiltration, reduce PGE2 levels[104] and also contain vascular permeability changes[105]. These observations suggest a promising role of lipid mediators in the regulation of local acute inflammatory responses in periodontal disease and high potential for the development of novel therapeutic regimens.

Recently, new classes of proresolving lipid mediators such as resolvins (resolution-phase interaction products) and protectin have been identified that are derived from the omega-3 fatty acids, eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) rather than AA[102,103,106]. Resolvins and protectins stimulate anti-inflammatory and proresolving pathways similar to the lipoxins but their binding occurs to distinct sites on inflammatory cells[103]. In a *P. gingivalis*-induced experimental periodontitis, topical application of resolvins demonstrated remarkable efficacy in the reducing alveolar bone loss with complete resolution of inflammation and restoration of soft and hard tissues of periodontium[107,108]. Generation of these potent proresolving molecules may encourage integration of dietary supplementation of omega-3 fatty acids, EPA and DHA in prevention and/or adjunctive management of chronic periodontitis[109,110].

Anti resorptive agents

Bisphosphonates (BPs) are pyrophosphate analogs that suppress osteoclastic activity, prevent dissolution of hydroxyapatite crystals and promote osteoblast differentiation[111]. Mechanism of action of BPs may occur at three levels. At tissue level, they decrease bone turnover by decreasing bone resorption and by reducing the number of new bone multicellular units. At the cellular level, they decrease osteoclast and osteoblast recruitment, decrease osteoclast adhesion, increases osteoblast differentiation and number, and decrease the release of cytokines by macrophages. At molecular level, BPs inhibit mevalonate pathway that induces cell apoptosis[112].

Though use of BPs, either intravenously or orally, in conditions like osteoporosis, osteopenia, and Paget's disease has been established[112], only limited data is available for their application in the management of periodontal diseases. Few well designed human trials have reported significant reduction in alveolar bone loss, reduction in PPD, clinical attachment gain, reduction in bleeding on probing, and gain in alveolar bone height when BPs are used as an adjunctive agent to SRP[89,113-116].

Recently, long term use of high dose intravenous BPs has been reported to be associated with osteonecrosis of the jaw(ONJ)[117] that is essentially exposed bone in the maxilla or mandible that does not heal within 8 wk of identification by health care professionals[118]. A recent report by the American Society for Bone and Mineral Research concluded that with oral bisphosphonate therapy for osteoporosis a risk for ONJ is less than one in 100000 patients while that for IV bisphosphonate therapy in patients with cancer was reported to be in the range of one to 10 per 100 patients[119]. However, scientific community is still divided on whether bisphosphonates indeed cause ONJ. Hence despite the promising therapeutic results, the

data available is insufficient for use of BPs as host modulating agents in periodontal disease management. Further long-term multi center randomized controlled clinical trials are recommended to confirm the benefits of these drugs[89].

CONCLUSION

Non-surgical periodontal therapy continues to evolve and newer therapeutic modalities are being developed to make the outcomes more predictable and last longer. Past two decades have witnessed publication of some excellent systematic reviews on NSPT that has helped formulate novel treatment regimens to combat periodontal infection and restore tissue homeostasis. Current best evidence suggest that: (1) NSPT results in superior clinical outcomes as compared to surgical therapy in periodontitis patients with moderate pocket depth (≤ 5 mm); (2) Thorough mechanical periodontal therapy (manual and ultrasonic debridement) remains a gold standard resulting in significant resolution of periodontal inflammation leading to improvement in the clinical signs and symptoms of active disease. But it may be insufficient for complete elimination of putative pathogens that may cause reinfection; (3) Adjunctive use of lasers or photodynamic therapy in the treatment of periodontitis does not result in superior clinical effects compared to that achieved by conventional mechanical therapy alone; (4) Systemic and local antimicrobials used in conjunction with SRP offer additional benefits in terms of CAL and PPD change, especially in patients with deep periodontal pockets, and aggressive or refractory periodontitis. The clinical effects are modest with LAD; (5) Full mouth disinfection result in clinical benefits comparable to that achieved by full mouth scaling without antiseptics and conventional staged debridement; (6) Host modulation therapy specifically with SDD results in better clinical effects when used as an adjunct to mechanical therapy. Development of newer formulations and novel therapeutic strategies may result in faster resolution of periodontal inflammation and help in regeneration of periodontal attachment apparatus; and (7) Daily oral hygiene maintenance coupled with frequent recall visits by patients is vital for long-term success of NSPT.

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Format

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1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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