The paediatric dentistry-restorative dentistry interface

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Key points

Highlights contemporary clinical challenges for both paediatric dentistry and restorative dentistry specialties.

Stresses the need for foresight in the treatment planning and management of the child and adolescent.

Features conditions where optimal management in the adolescent has positive repercussions for the adult dentition.

Abstract

This paper examines the various contemporary clinical interfaces between paediatric dentistry and restorative dentistry for patients with both acquired and congenital abnormalities presenting to primary and secondary care. Dental trauma of the child or adolescent has long-standing implications on future oral health due to conditions such as ankylosis, pulp necrosis, coronal tissue loss or tooth loss, all of which provide significant challenges into adulthood. Similarly, congenital conditions, such as hypodontia and structural deficiencies or malformations, such as amelogenesis and dentinogenesis imperfecta, result in the need for collaborative, multi-speciality decision-making from a young age, creating a pathway for longitudinal multi-disciplinary team treatment planning.

Introduction

Modern multidisciplinary treatment planning for complex acquired or developmental anomalies should be delivered through a continuum of care with defined phases and individuals carrying specific roles or responsibilities. Essentially, a team of individuals should manage conditions jointly as the patient grows and develops, with clinicians spanning primary and secondary care providing treatment during certain periods as per an agreed plan.1 Contemporary treatment provision up until the point of dental maturity and adulthood should not be provided in isolation. Where care is provided independently, the outcome into adulthood can be severely compromised due to decisions made without the requisite awareness of their future implications

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(Fig. 1).² A recent publication in the *British Dental Journal* highlighted the lack of transitional care pathways for dental trauma patients where injuries suffered in childhood and adolescence required further treatment or follow-up into adulthood.³ This paper will examine various aspects of the management of the paediatric dentistry patient and highlights the interface with colleagues in restorative dentistry.



Managing patient and parent/ guardian expectations

There are a wide range of dental conditions that require long-term management in the growing patient. As the permanent dentition begins to erupt at age six years, through to the established full arches, the aims of dental treatment should be to provide comfort, aesthetics, function



Fig. 1 This patient presented having previously avulsed her 21 and laterally luxated her 11. a) She was provided with root canal treatment of the 11 and progression to fixed orthodontic treatment. b) Due to iatrogenic apical root resorption, persistent endodontic disease and the absence of an overarching plan the orthodontic treatment was cessated and restorative dentistry treatment provision commenced. This involved root canal retreatment and the provision of an implant



Fig. 2 This patient presented with hypodontia in her late teens, subsequent to which she was provided with an implant. She presented 15 years later, in her early thirties, with late failure of this unit despite the absence of risk factors, such as smoking or systemic disease

and to minimise the risk of compromising the patient's future dental health. Initial treatment planning at the outset must be comprehensive and consider the patient and parents' wishes, any other anomalies that may be present, underlying malocclusion, stage of both dental and general development and dental disease risk.

Setting treatment goals that are achievable and realistic is key to a successful outcome. A large part of this will include managing parental expectations. For many of the dental conditions that are diagnosed in the early mixed dentition stage in childhood, the 'definitive' care is unlikely to be achieved until at least late adolescence or early adulthood and it is crucial that this is communicated effectively with the family. The realistic time commitments, treatment phases, financial implications and maintenance costs of treatment should be discussed early on to avoid compliance burnout or disappointment.

Treatment can often involve several visits and the child's ability to comply with these typically prolonged appointments should be considered. An awareness of the child's changing aesthetic and functional needs is also important. The impact of negative comments from peers and social media on a child or adolescents' psychosocial development cannot be overlooked and adds another dimension to managing these cases with sensitivity.⁵

In a secondary care setting, treatment for children or adolescent patients is often managed within the specialty of paediatric dentistry with input from other specialties; most commonly, restorative dentistry and orthodontics. This ensures that a comprehensive approach is taken



Fig. 3 This patient avulsed the 12, 11 and 22 with 21 having been laterally luxated. The avulsed units could not be repositioned. The 21 required root canal treatment. Note the significant buccal bone resorption in the avulsion sites which also coincided with vertical defects

to the care provided and creates a 'roadmap' for the initial treatment journey. The short and medium end points for treatment can be identified and a plan formulated. The care provided in this phase facilitates and shapes long-term care that can only be achieved once growth has ceased.

Parents may commonly query the nature of the 'permanent' or 'perfect' solution for their child's condition.6 Parents should be forgiven for their keenness in this respect and their motivation to be their child's advocate. Commonly, where teeth are absent or malformed, parents may be under the wrong impression that a dental implant is 'indicated', 'indestructible' and the 'best' option.7 In reality, there are multiple options available at any one time for a prospective edentate space. The key for both paediatric and restorative dentistry specialties is to recognise that depending on the age of the patient, their dental health profile and various factors related to soft and hard tissues, an implant may actually be the worst long-term option (Fig. 2). Within the multi-disciplinary team (MDT) environment, the expectation of the definitive treatment modality for tooth replacement should be communicated early to the patient and the parent and documented in the patient's records to reduce the likelihood of future confusion, misunderstanding or miscommunication.

We present some of the conditions which require comprehensive planning of care between the specialties of restorative dentistry and paediatric dentistry. The clinical presentations are by no means exhaustive but demonstrates a number of both physiological and pathological complexities and challenges faced in managing a number of clinical conditions that present a

during the treatment pathway.

Dental trauma

A significant proportion of cases managed by secondary care MDTs include dental trauma. The *Child Dental Health Survey 2013* reported that 12% of 12-year-olds and 10% of 15-year-olds in England, Wales and Northern Ireland had sustained a traumatic injury to permanent incisors, with boys being more likely to have sustained a dental injury than girls.⁸ Dental trauma has been shown to be associated with several factors, including increased overjet, social deprivation and bullying.^{9,10,11}

Injuries involving the periodontal ligament result in movement of the tooth within the alveolar bone and include luxation, extrusion, intrusion and avulsion injuries, with the latter two being highly associated with loss of vitality. In severe injuries, we may see root resorption and ankylosis occurring.

Avulsion injuries and the implications of tooth loss

Where a traumatic dental injury results in tooth avulsion or luxation in the paediatric patient, the treating clinician should aim to assess the ability to maintain the tooth, as best as possible, through this period. Depending on the presentation, time and location, the most suitably skilled and trained clinician may or may not be able to manage the acute situation. Whenever trauma presents, the clinician may be forgiven to apportion a bleak prognosis to the tooth units depending on the severity of the injury and the child's ability to tolerate treatment. Foresight is needed in these situations as a hasty decision to extract or fail







Fig. 4 a, b, c) This patient presented at 12 years of age subsequent to trauma, resulting in an oblique crown-root fracture. Note the sub-gingival margin palatally

to replant is irreversible, as are the physiologic and psychological changes caused by it (Fig. 3). The process of bone resorption post extraction begins as soon as the tooth is removed and its extent is time-related.12 Practically speaking, a central incisor removed in a six-year-old will result in greater volumetric bone loss in adulthood than that of a 16-year-old if the tooth is eventually extracted. At this juncture, both specialties should engage in the decision-making process with the aim of maintaining an infectionfree tooth for as long as possible. This may even be the aim where coronal tooth structure is severely compromised, making the unit 'unrestorable'. The potentially counterintuitive goal in these circumstances is the maintenance of bone for as long as possible, rather than the maintenance of a 'predictably' restored tooth unit or the creation of an edentate space that will resorb over time (Fig. 4).

Crown fractures

Enamel fractures, enamel-dentine fractures and enamel-dentine-pulp fractures result in loss of extra-coronal tooth structure. In some cases, vertical and oblique fracture lines will propagate sub-gingivally and involve the root surface and cementum, which then presents a management challenge in a growing child (Fig. 5). Difficulties can arise when the entire incisal edge is involved or there is an underlying malocclusion which results in repeated failure of the restoration. In keeping with the need to use as minimally invasive techniques as possible, all restorations should be conservative of tooth structure. Any need for tooth preparation in children should be avoided, within reason. Following failure of a restoration, parents may be keen for a more 'permanent' solution and so expectations around the provision of full coverage crowns and veneers needs to be managed. In a vital

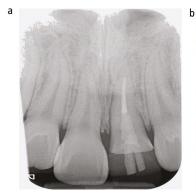




Fig. 5 a, b) Despite the sub-gingival margin, the tooth was restored through a combination of gingivectomy, root canal treatment, fibre post provision and direct composite restoration. The tooth was successfully maintained throughout adolescence, avoiding extraction and retaining alveolar bone





Fig. 6 This patient presented with amelogenesis imperfecta during her teenage years with a history of bullying at school. a) She was provided with direct composite restorations to mask the surface irregularities and discolouration. b) She was subsequently provided with replacement restorations in her late thirties

tooth, the large pulp size means that attempts to prepare a tooth for an indirect restoration could result in loss of vitality.⁶ In addition to this, the gingival maturity and general occlusal stability has not yet been achieved in adolescent patients and so indirect restorations, if absolutely necessary or indicated, need to be deferred for as long as possible (Fig. 6).

Most fractures can be managed with adhesive additive techniques. Cellulose crown formers

are extremely helpful for several reasons; they reduce the amount of time spent restoring the tooth, which is particularly important in younger children who will struggle with mouth-opening. The use of rubber dam is ideal for moisture control but may not always be achievable due to compliance. The life span of a composite restoration should be communicated and the need for maintenance of these restorations, like indirect restorations, should be made clear from



Fig. 7 Cessation of pulpal bleeding during the Cvek pulpotomy procedure. The exposed pulp tissue was subsequently covered with a bioceramic material and the tooth restored with resin composite. Reproduced with permission from Dr Nitesh Tewari

the outset.¹³ A very acceptable aesthetic result can be achieved by using composite alone and therefore this should be considered a definitive restoration for the majority of cases.

Crown-root fractures

Crown-root fractures, with or without pulp involvement, in a growing child can be challenging. Injuries involving the pulp require consideration of the stage of root development. Where possible, pulp exposures in a tooth with an open apex should be managed by Cvek pulpotomy initially (Fig. 7). ¹⁴ This will aim to preserve pulp vitality and support continued root development. The second stage of the treatment will then be to successfully restore the tooth. Taking into consideration the sub-gingival fracture lines, either gingival surgery or surgical or orthodontic extrusion can be considered (Fig. 5). Ability to comply with these treatment modalities in a young child may present behaviour management



Fig. 8 This 14-year-old patient presented with crown root fractures approximately a month after the injury. A conscious decision to leave root remnants and monitor shows the deposition of bone over these fragments at their one-year review

challenges. Various factors will need to be taken into consideration, including, the remaining amount of supra-gingival tooth structure, ability to achieve moisture control and coronal seal for an adhesive restoration, as well as patient and parent wishes and commitment to a potentially lengthy treatment plan.

In cases where adhesive restoration is impossible due to lack of remaining supragingival tooth structure, then the apical portion of the tooth should be left *in situ* following coronectomy (root burial or root submergence) (Fig. 8). In young patients, early loss of a permanent tooth leads to loss of alveolar bone, especially the bucco-palatal width (Fig. 3).



Fig. 9 This patient presented delayed with an avulsed 21. The tooth was repositioned. Over time this unit developed ankylosis resulting in significant aesthetic and functional challenges

Maintaining the width of the alveolar ridge allows optimal positioning of an implant and aesthetic shaping of the crown. ¹⁵ Early extraction of a permanent incisor in a growing patient not only results in a reduction in alveolar bone volume but can also lead to space loss if a removable appliance is not worn. This can complicate the restorative challenge in adulthood further and may necessitate the need for orthodontic treatment. Similarly, even in cases where implants are not being considered, the soft tissue discrepancy due to early tooth loss can lead to poor aesthetics and soft tissue contour around a bridge or denture pontic.

Ankylosis

Ankylosis occurs as a result of damage to the periodontal ligament which leads to fusion of the alveolar bone with all or some of the root surface.¹² The highest risk of this happening is in intrusion and avulsion injuries. Clinically, signs of ankylosis include a high percussion sound, a reduction in mobility and an increasing infraposition in growing individuals (Fig. 9).16 This will cause both a gingival margin and incisal edge discrepancy in comparison to adjacent, uninjured teeth. Over time, if the condition progresses, the root will be replaced by bone, leading to potential tooth loss. The aim of treatment in the younger patient is to retain the tooth for as long as possible in order to retain bone and aid later prosthetic replacement. In cases where there is a significant infraocclusion, decoronation and root burial can be carried out. Without this step, the gingival tissues will migrate apically, adjacent teeth will tilt and as growth continues around the injured tooth, aesthetics will become increasingly poor.¹⁷ When signs of ankylosis are identified, multidisciplinary management is required to identify the interim and long-term plan for the site.18 Malmgren described the following guideline to identify the timing at which decoronation should take place:

- In the early mixed dentition, aged 7–10 years, then decoronation is indicated within two years
- In the late mixed dentition, age 10–12 years and the patient has reached the pubertal growth spurt, a rapid rate of infraposition can be expected and decoronation is indicated as soon as infraocclusion is identified
- In the early permanent dentition, decoronation may not be necessary as the rate infraocclusion may be slow.¹⁵ In these cases, infraocclusion may be managed by composite addition at the incisal edge of the injured tooth to mask the discrepancy with

the adjacent teeth, if other factors, such as a low smile line, favour this.

Where decoronation has been indicated, a resin-bonded bridge can be used to replace the tooth. Once early adulthood has been reached, the remaining root structure within the alveolar bone will have retained the arch integrity, making implant placement and aesthetic outcome much more favourable.

Discolouration

Non-vital teeth discolour due to a variety of physiological and pathological processes. Endodontic treatment for an older child with closed apices is straightforward, but for those underdeveloped units with open apices, the canal system and the apex presents challenges for preparation and subsequent obturation (Fig. 10). Commonly, this is achieved by use of a bioceramic material, often mineral trioxide aggregate (MTA) or Biodentine. MTA is associated with discolouration due to the bismuth oxide component and contact with sodium hypochlorite or due to contact with blood components within the canal. 19,20 Solitary single tooth discolouration can be unsightly, particularly in a young child and with current restrictions on the use of dental whitening products for children under 18 years old, management of these cases can be challenging (Fig. 11).

Hypodontia

The congenital absence of one or more permanent teeth is another common scenario managed by multidisciplinary teams.21 The prevalence of hypodontia varies with geographical location, with Africa having the highest (13.4%), followed by Europe (7%), Asia (6.3%) and Australia (6.3%), with North America the lowest (5%).22 The primary aims of care will be to maintain the existing dentition, provide improved aesthetics, improve function and improve speech. Severe hypodontia can have a huge impact on the psychological wellbeing of a young person and each member of the dental team has a role in helping them to cope with issues of appearance during these formative years.23 The condition may present as part of a syndrome, or in a nonsyndromic form. Syndromes or conditions associated with hypodontia include Down syndrome, ectodermal dysplasia and Ehlers-Danlos syndrome.24

Varying numbers of teeth can be congenitally absent. The reported prevalence of hypodontia shows high variation between studies reported between 0.3–36.5%, with a higher prevalence in





Fig. 10 a) This patient presented with a complicated crown fracture of the 11. b) The apex was subsequently obturated with a combination of MTA and gutta percha and restored with composite



Fig. 11 This patient presented with a high smile line and a history of trauma. The 11 had previously been obturated with MTA subsequent to loss of vitality. In comparison, the 21 lost vitality more progressively over a longer period. Note the difference in type and intensity of discolouration between the two units

women.²² With the exclusion of third permanent molars, the most commonly absent tooth is the mandibular second premolar (2.8%), followed by the maxillary lateral incisors (1.6%), maxillary second premolars and mandibular incisors (0.23–0.08%).²⁵ In any case, the location of the missing tooth may or may not cause aesthetic or functional difficulties and each case presents its own challenge.

Hypodontia is associated with a number of other dental anomalies which can add to the complex management challenges, including: reduced crown and root size of other teeth, enamel hypoplasia, delayed eruption, impaction of maxillary canines, lack of alveolar bone and infraocclusion of primary teeth.

Treatment approaches for the management of hypodontia, broadly speaking, either aim to close the spaces or open them up to allow for prosthetic replacement of missing units. This is more straightforward to manage in cases of one or two missing teeth in a crowded arch. However, the greater the number of missing units, the greater the restorative challenge and subsequent treatment burden.

Space closure

Space closure reduces the long-term restorative burden but does not eliminate it completely. For example, a common scenario will include a case of bilateral missing upper lateral incisors or a unilateral missing incisor presenting with a contralateral peg-shaped lateral incisor. Following multi-disciplinary treatment planning, space closure by orthodontic treatment to bring the canines into the absent lateral incisors position will depend on the patient's malocclusion, smile line and colour, size and contour of the canines in comparison to the central incisors. It will also depend on the patient's willingness to commit





Fig. 12 a, b) This patient with mild hypodontia had orthodontic optimisation of spacing for the 12 site and positioning of the 22 to facilitate further remedial treatment. She also suffered a Class IV fracture of the 21. She was provided with a resin-bonded bridge 12, composite augmentation of the 22 and a replacement restoration for the 21









Fig. 13 a, b) This patient presented with progressive over-eruption of the 24 opposing an infraoccluded 75. c, d) In an effort to maintain occlusal stability, the tooth was restored with an indirect composite onlay restoration

d





Fig. 14 a) This patient presented with severe hypodontia resulting in a number of retained deciduous units. b) Due to the patients age composite resin augmentation was provided to improve aesthetics and maintain occlusal stability during dental development

to orthodontic treatment and of course, their suitability for treatment. Restorative input is then required to then disguise the canines or microdont units as lateral incisors (Fig. 12). This may involve simple composite bonding to recreate the incisal edge. In other cases, gingival margins may need to be re-contoured

in addition to tooth whitening to reduce the natural 'darkness' of canines.

Space opening

In situations where the underlying malocclusion means that the provision of prosthetic replacements of missing units will result in a better aesthetic outcome, then space opening may be the more appropriate treatment option. Often, some degree of orthodontic input will be required but in a few cases, the ideal space requirements for prosthetic replacement may already exist, such as when a primary tooth has been retained and has acted as a space maintainer. However, the vast majority of cases will require orthodontic treatment. To reiterate, planning via a multi-disciplinary clinic will provide a roadmap for treatment and interim plans to replace missing teeth during and immediately after treatment. During growth, missing units will be replaced with a partial denture. Following orthodontic treatment and an adequate period of retention, the spaces created by orthodontic tooth movement may be restored with resin-bonded bridges, as long as a suitable abutment tooth has been identified (Fig. 12). These prostheses should be viewed as definitive long-term option with a view to a fresh option appraisal of further treatment if failure arises.

Challenges associated with hypodontia Infraocclusion of primary molars

Infraocclusion of the primary molars is associated with congenital absence of the permanent successor. Dependent on the extent of infraocclusion, these teeth can be maintained in the arch to preserve alveolar bone in the region of the missing permanent successor (Fig. 13). This will also depend on the rate at which the primary molar is submerging. For a relatively stable primary molar with moderate infraocclusion, elevation of the occlusal surface through a restoration will achieve occlusal contact with the aim of maintaining the primary tooth in place. Case selection is important and factors such as caries risk and ability to maintain good plaque control in the area will be crucial for success.

As a result of infraocclusion, over-eruption of the opposing permanent tooth can occur, having an impact on the overall occlusal table and the creation of occlusal interferences. It is therefore important to identify the potential for over-eruption and to provide opposing occlusal contacts to prevent this from happening as a preemptive approach.

Composite augmentation of primary teeth

In cases where space closure is not possible, maintenance of the primary tooth may be preferred to help maintain aesthetics, function and alveolar bone. Provided that a primary tooth has good root morphology, it can be maintained in the arch in the long term with good oral hygiene and maintenance (Fig. 14).

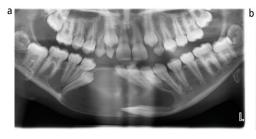






Fig. 15 This patient presented in the mixed dentition to his general dental practitioner complaining of tooth mobility and swelling in the lower jaw. a) Subsequent investigations revealed the presence of an ameloblastoma. b) This was managed by colleagues in maxillofacial surgery. c) Post resection he presented with severe soft and hard tissue defects in the edentate sites. An optimal partial denture was provided. The patient and parents were aware of the long-term implications of his condition and the relative lifelong treatment burden into adulthood



Fig. 16 A hypomineralised molar requiring restoration in a 12-year-old. Due to the poor quality and volume of tooth tissue remaining, an opinion from restorative dentistry was sought prior to definitive treatment





Fig. 17 a) This patient presented with swelling and suppuration from the 12 during orthodontic treatment. The tooth later revealed itself as having an undiagnosed dens invaginatus. b) Orthodontics was cessated and root canal treatment was instigated involving removal of the invaginated portion and obturation with bioceramic material prior to inside-outside bleaching

b

This will depend on several factors, including caries risk, rate of infra-occlusion, tooth wear, root resorption and periodontal condition.²⁶ In some cases, primary units with healthy intact roots can be augmented with composite to mimic a missing lateral incisor. Similarly, in the lower arch, composite augmentation of lower primary central incisors can improve the appearance where permanent successors are missing.

Replacement of multiple adjacent units

The replacement of multiple missing units can present with some difficulties to the paediatric dentist in a growing patient. This situation can arise either congenitally (oligodontia in association with syndromes), through pathology (lesions of the bone) or through trauma resulting in loss of several teeth (Fig. 15).

Management, more often than not, requires early multi-disciplinary input. Discussions around implant-retained prostheses are more likely to happen once growth is completed and is essential to aid the restoration of function and aesthetics.

The prosthodontic challenges of these cases include poor retention and tolerance of removable appliances, particularly in the lower arch. Further to this, with continued growth, they may require numerous replacement appliances. Overdentures have their place in allowing roots or primary teeth to be kept in place to maintain alveolar bone until the time that implants can be considered. Loss of occlusal vertical dimension can be severely reduced where there are several missing teeth and all efforts should be made to maintain this.

Dental anomalies of form and shape

Developmental defects of enamel, dentine and pulp morphology provides a significant proportion of the remit provided by paediatric dentists. Developmental conditions such as amelogenesis imperfecta (AI) and dentinogenesis imperfecta (DI) often require an early start to management due to early-arising symptoms, aesthetic concerns and the effect on function (Fig. 6). The prevalence of AI varies from 1:700 to 1:14,000 depending on the populations studied.²⁷ In comparison, DI type II is thought to have a prevalence of 0.0022% in a Swedish study.²⁸

Localised defects of enamel hypoplasia or hypomineralisation of the incisors, such as those seen in molar-incisor hypomineralisation, can often have a profound impact on self-esteem and often need to be managed at the age when teasing and comments from peers become an issue, which can be as early as late primary school age (Fig. 16). The prevalence of this condition has a wide variation from 2.4-44%, depending on the population studied.29 Generalised defects of enamel, such as chronological hypoplasia associated with vitamin D deficiency, is becoming increasingly more apparent in the population. This can present as a chronological banding or can affect the whole tooth.30 This

can cause issues with sensitivity of teeth but also a noticeable deviation from an acceptable shade of whiteness of the teeth, as well as 'roughness' of the enamel. Fluorosis, although much rarer in the UK, when it does present, can also present with a similar appearance.

Resin infiltration systems, such as ICON, have increased in popularity and can successfully be used in isolation to treat white spot lesions seen in enamel hypomineralisation patches and provide an alternative option to tooth whitening. However, more resistant forms of discolouration may require masking with composite. The advantages of the use of composite include the minimally invasive approach to its use and in a growing child, composite can be added chairside as gingival margins mature. Modern composite resin can provide a suitable definitive long-term option but despite this, patients may still seek treatment involving subtractive indirect treatment (Fig. 6). Full mouth rehabilitation for managing these cases may be required in severe disease, such as severely hypocalcified AI.

With regards to the posterior dentition, preformed metal crowns provide an ideal short-to-medium-term solution to maintain first permanent molars in the arch until adolescence has been reached and when further restorations can be considered. Early input from multi-disciplinary teams is essential in these cases so that treatment plans consider the timing of extraction of poor prognosis teeth.

Dental anomalies of pulpal morphology, such as dens invaginatus and dens evaginatus, can present in the young patient without any signs or symptoms but with established periapical disease (Fig. 17).^{31,32} There is a significant degree of increased prevalence in certain ethnic groups.²⁷ While every effort to maintain teeth should be made, either by endodontic treatment and subsequent techniques to improve aesthetics, a decision with regard to long-term prognosis should be made early on so that teeth with poor prognosis are included as part of an extraction pattern, together with orthodontic treatment as and when necessary.

Conclusion

Childhood and early adolescence represent a period of intense growth and development of orofacial tissues, along with psychosocial development. As the permanent dentition begins to erupt, a number of acquired and congenital dental conditions may be diagnosed and these may force a commitment to a long and complex journey of dental treatment. Comprehensive multi-disciplinary care planning in the secondary care setting with the requisite input and ongoing maintenance in primary care are essential in achieving acceptable aesthetics, function, speech and self-confidence for the patient.

Ethics declaration

The authors declare that there are no conflicts of interest

Author contributions

Both Mona Agel and Aws Alani discussed, planned and contributed to the final manuscript.

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