REVIEW Management of deep caries and the exposed pulp

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Abstract

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Caries prevalence remains high throughout the world. with the burden of disease increasingly affecting older and socially disadvantaged groups in Western cultures. If left untreated, caries will advance through dentine stimulating pulpitis and eventually pulp infection and necrosis; however, if conservatively managed, pulpal recovery occurs even in deep carious lesions. Traditionally, deep caries management was destructive with nonselective (complete) removal of all carious dentine; however, the promotion of minimally invasive biologically based treatment strategies has been advocated for selective (partial) caries removal and a reduced risk of pulp exposure. Selective caries removal strategies can be one-visit as indirect pulp treatment or two-visit using a stepwise approach. Management strategies for the treatment of the cariously exposed pulp are also shifting with avoidance of pulpectomy and the re-emergence of vital pulp treatment (VPT) techniques such as partial and complete pulpotomy. These changes stem from an improved understanding of the pulp-dentine complex's defensive and reparative response to irritation, with harnessing the release of bioactive dentine matrix components and careful handling of the damaged tissue considered critical. Notably, the development of new pulp capping materials such as mineral trioxide aggregate, which although not an ideal material, has resulted in more predictable treatments from both a histological and a clinical perspective. Unfortunately, the changes in management are only supported by relatively weak evidence with case series, cohort studies and preliminary studies containing low patient numbers forming the bulk of the evidence. As a result, critical questions related to the superiority of one caries removal technique over another, the best pulp capping biomaterial or whether pulp exposure is a negative prognostic factor remain unanswered. There is an urgent need to promote minimally invasive treatment strategies in Operative Dentistry and Endodontology; however, the development of accurate diagnostic tools, evidence-based management strategies and education in management of the exposed pulp are critical in the future.

Keywords: dental caries, pulp capping, pulp exposure, selective caries removal, stepwise excavation, tertiary dentinogenesis.

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Introduction

Dental caries is a common, but preventable disease (World Health Organization 2017). Recent epidemiological data highlight that global prevalence has remained high over the last 25 years; however, the burden of untreated caries has shifted from children to adults (Bernabé & Sheiham 2014, Kassebaum *et al.*

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2015). Caries is the most common noncommunicable disease with a greater prevalence in patients from disadvantaged social groups (Whelton *et al.* 2007, Sengupta *et al.* 2017, World Health Organization 2017) and is costly to manage consuming an average of 5% of the overall health expenditure in industrialized and nonindustrialized countries (Petersen 2008, Listl *et al.* 2015).

Caries is a microbial biofilm-induced disease, which is promoted and maintained by a dietary supply of fermentable carbohydrates (Nyvad et al. 2013). In areas of stagnation, the carious potential of the biofilm rises with acidogenic by-products of bacterial metabolism initiating enamel demineralization and stimulating defensive reactions in the dentine and pulp, such as increased intra-tubular dentine and initial inflammation. If the demineralization of enamel continues to progress, dentine will be exposed to bacterial invasion, which leads to further demineralization and eventual cavitation (Bjørndal 2018). A consensus document recently defined deep caries as radiographic evidence of caries reaching the inner third or inner quarter of dentine with a risk of pulp exposure (Innes et al. 2016). Clinically, the depth of caries and residual dentine thickness (Stanley et al. 1975, Whitworth et al. 2005) are difficult to assess. Recent research on deep carious tissue management supports less invasive strategies, highlighting that complete removal of soft dentine to leave a thin barrier of residual dentine may not be necessary or desirable (Innes et al. 2016). In this context, a radiographic threshold to create an 'endpoint' for less invasive strategies aimed at avoiding carious pulp exposure is welcome. To aid management, deep caries can be further subdivided into deep and extremely deep caries lesions (Fig. 1) with extremely deep caries defined as radiographic evidence of caries penetrating the entire thickness of the dentine with certain pulp exposure. In extremely deep lesions, the demineralized process extends the entire thickness of the dentine, which perhaps excludes these cases from selective caries removal and a strategy based on avoiding pulp exposure. Taken together, the awareness of carious lesion penetration depths should be considered with strategies that focus on pulpal symptoms (Wolters et al. 2017); however, strong evidence is still lacking to support the relative importance of individual factors to a favourable treatment outcome.

In health, a mineralized shell of enamel and dentine naturally protects the pulp; however, untreated caries may progress into extremely deep lesions, inducing inflammatory pulpal reactions, leading to necrosis, abscess and eventual tooth loss (Reeves & Stanley 1966, Bergenholtz et al. 1982). In experimental animal models, bacterial products diffuse through the dentinal tubules in test cavities inducing pulpitis even before the pulp is exposed (Warfvinge & Bergenholtz 1986); however, the permeability of dentine and pulpitis will likely be reduced in carious teeth due to the presence of tubular sclerosis subjacent to the carious dentine. Notably, as the external bacterial stimuli moves towards the pulp, the inflammatory response continues to intensify (Mjör & Tronstad 1972, Bjørndal & Ricucci 2016); however, pulp has an innate ability to heal if the challenge is removed and the tooth is suitably restored (Mjör & Tronstad 1974, Cooper & Smith 2016).

Management of deep caries has traditionally been with complete (or nonselective) caries removal and in the event of pulp exposure root canal treatment (RCT) (Bjørndal et al. 2006, Swedish Council on Health Technology Assessment 2010), rather than minimally invasive biologically based approaches aimed at maintaining the vitality of the pulp (Ricketts et al. 2013, Smith et al. 2016). The contribution diet plays in the aetiology of caries offers the opportunity to manage the condition by modifying diet, changing biofilm growth and isolating the advancing microbial biofilm from the nutrient supply; therefore, the disease can be managed by selective caries removal without having to eradicate or target the entire bacterial population (Bjørndal et al. 1997, Banerjee et al. 2017). As a result, predictable outcomes have been achieved with selective caries removal (Maltz et al. 2012) and stepwise techniques (Biørndal et al. 2017) compared with nonselective caries removal, which has altered consensus (Schwendicke et al. 2016b) about the most appropriate management of deep asymptomatic carious lesions. Similarly, in cases of carious pulpal exposure, classically reported to have poor prognosis (Barthel et al. 2000), new biomaterials, techniques and understanding of pulpal repair mechanisms have improved the outcome of symptomatic exposures treated with pulp capping (Marques et al. 2015), partial pulpotomy (Taha & Khazali 2017) and full pulpotomy (Simon et al. 2013).

Preserving pulp vitality is at the core of Operative Dentistry and offers a biological-based concept, which reduces intervention and maintains the pulp's developmental, defensive and proprioceptive functions



Figure 1 Classification for deeper stages of caries. (a) Deep carious lesion reaching pulpal quarter with a zone of dentine separating the lesion from the pulp (b) and extremely deep penetrating the entire thickness of the dentine.

(Randow & Glantz 1986, Paphangkorakit & Osborn 1998, Smith 2002), whilst vital pulp treatment (VPT) is considered technically easier to carry out than pulpectomy and RCT (Stanley 1989). Furthermore, it has been advocated that teaching less aggressive dentistry reduces overtreatment and the so-called 'restorative cycle' (Elderton 1993), whilst preserving tooth substance and improving the cost-effectiveness of treatment (Schwendicke & Stolpe 2014). The aim of this review was to summarize current views on the biological response to deep caries as well the diagnosis, classification and management of deep carious lesions and carious pulp exposures.

Review

Actiology of caries

As dental biofilm consists of commensal and noninvading microorganisms, the contemporary understanding, known as the 'ecological plaque hypothesis', suggests caries is a result of an ecologic imbalance within the dental biofilm with acidogenic and aciduric species dominating within the biofilm under frequent intake of carbohydrates (which are metabolized to acids) (Marsh 1994, 2003). Numerous studies have shown a strong positive correlation between mutans streptococci, lactobacilli and bifidobacteria and the initiation of demineralization of the tooth surface (Marsh 2012). More advanced lesions tend to have a more diverse microflora with high levels of Streptococcus mutans and Lactobacilli spp.; however, other taxa such as a novel Prevotella spp., Selenomonas spp., Dialister spp., Eubacterium spp. and Fusobacterium spp. have found to be abundant in such lesions (Nadkarni et al. 2004, Chhour et al. 2005).

For bacteria to play a role in the carious process, they must possess certain characteristics that

promote the disease (Loesche 1986). The ability to process sugars efficiently, to maintain sugar metabolism in an extreme environment (low pH) and produce intra/extracellular polysaccharides is important characteristics for cariogenic bacteria. Notably, mutans streptococci possess multiple sugar transport systems including the phosphoenolpyruvate phosphotransferase system and can enzymatically thrive at a low pH. Furthermore, they are also able to pump out protons in an acidic environment and produce specific acid-stress response proteins. These properties are not exclusive to mutans streptococci, and strains of other streptococci such as Streptococcus mitis, Streptococcus gordonii, Streptococcus anginosus and Streptococcus oralis are acidogenic and aciduric (van Houte 1994, van Ruyven et al. 2000, de Soet et al. 2000). These organisms are early colonizers (Nyvad & Kilian 1990) and may help establish an environment or niche, which mutans streptococci and lactobacilli will thrive in.

Histopathology of caries within dentine

As enamel is a microporous solid, the carious process and response of the dentine–pulp complex can frequently start before it is breached (Brännström & Lind 1965, Bjørndal *et al.* 1998). It is important to consider the dentine and pulp as one entity since their physiological processes during development homeostasis; pathology and repair are intertwined and reliant upon one another. The pulp and dentine thus form a complex or continuum via the communication provided by the dentinal tubule and the odontoblast process, which projects into the tubule. This structural arrangement results in the dentinal tubules being fluid-filled throughout their entire length, and this fluid act as a conduit for communication. The initial pulpal response to caries is activated by bacterial acids, their cell wall components such as lipopolysaccharide (LPS) and soluble plaque metabolic products, which diffuse towards the pulp against the natural direction of pulp tissue fluid movement (Hahn & Liewehr 2007).

The initial response of the pulp includes an increase of secretory activity by the odontoblast leading to increased tertiary dentine formation (reactionary dentinogenesis) (Smith et al. 1995), which can be seen strictly related to the subjacent enamel-dentine lesion complex (Bjørndal et al. 1998). The zone of dentine demineralization is characterized by a wave of acid diffusing in front of the advancing enamel lesion. Notably, the dentine demineralization takes place in the zone of sclerosis and not sound dentine. The demineralization is thought to be absent of bacteria as long as the dentine is not clinically exposed (Kidd & Fejerskov 2004). The most superficial part of the exposed dentine starts to decompose by the action of acids and proteolytic enzymes produced by the bacteria themselves (zone of destruction; Fig. 2). Clinically, it is difficult to distinguish each zone. In particular, it is not possible to distinguish the delicate broader between infected and affected dentine both being discoloured and demineralized, which also explains the recently suggested simplified terminology on removal of carious tissue (see later).

What is the defensive response of the pulp to caries?

The dental-pulp complex reacts to irritation by a combination of inflammation and the promotion of mineralization; the balance between pulpitis and repair is critical to preserving pulp vitality (Cooper et al. 2010). Specifically, various types of pulp cell react immunologically to the microbes, initially via pathogen recognition by odontoblasts and later fibroblasts, stem cells (SCs) and immune cells; thereafter, a complex series of antibacterial, immune, vascular and localized inflammatory responses are activated (Farges et al. 2009, 2015, Soden et al. 2009). Although the odontoblast has an immunocompetent role (Couve et al. 2013), its principal function is as a secretory cell, forming primary dentine during tooth development and later the production of secondary dentine, as well as tertiary dentine production when challenged (Simon et al. 2009). Tertiary dentine forms alongside inflammation locally beneath the area of challenge (Lesot et al. 1994, Smith 2002). There are two types of tertiary dentine formed, depending on the severity of the irritating stimulus. Mild irritation induces an up-regulation of existing odontoblast activity to form reactionary dentine, whilst stronger stimuli result in odontoblast death and the initiation of complex processes involving the recruitment of dental pulp stem/progenitor cells, which differentiate into odontoblast-like cells to form reparative dentine (Lesot et al. 1994). Alternative theories disagree with the accepted theory of odontoblast-like cytodifferentiation, highlighting that other cells such as fibroblasts or fibrocytes may in fact produce the mineralized tissue (Ricucci et al. 2014a, Yoshiba et al. 2018). Notably, for didactic purposes, the processes of reactionary and reparative dentinogenesis are considered separately, and it is likely that in a deep carious lesion both processes will occur simultaneously particularly at the periphery of the cavity (Smith et al. 2016). That is, in established and most advanced parts of the lesion, it would be reparative dentinogenesis, whereas for younger parts of the lesion, reactionary dentinogenesis takes place (Bjørndal et al. 1998). The cellular events associated with reparative dentine formation are orchestrated and regulated by bioactive molecules, including growth factors (GFs), which are 'fossilized' in the dentine matrix (Cassidy et al. 1997, Smith 2003, Grando Mattuella et al. 2007) prior to being released by caries, irrigants and dental materials (Graham et al. 2006, Tomson et al. 2007, Galler et al. 2016a; Fig. 3).

If the pulp is exposed, the reparative dentine forms a mineralized bridge, which is generally not in the form of tubular dentine (Nair *et al.* 2008), but does protect the pulp tissue from further insult (Glass & Zander 1949, Nyborg 1955). From a histological viewpoint, pulp exposure healing should be described as formation of a continuous hard tissue barrier over the exposure and a residual pulp free of inflammation (Schröder 1973). However, treatment outcomes for pulp capping can only be evaluated clinically and radiographically (Woehrlen 1977, Fuks *et al.* 1982).

Role of dentine in repair

The carious process will progressively demineralize dentine as it advances towards the pulp, releasing dentine matrix components (DMCs), stored within the dentine matrix during development (Dung *et al.* 1995). Selected matrix metalloproteinases (MMPs), a family of tissue proteases, contained with the DMCs will propagate the breakdown of dentine matrix (Mazzoni *et al.* 2015), whilst releasing other bioactive molecules that migrate down the dentinal tubules



Figure 2 (a) Macroscopic view of an extracted mandibular molar with a proximal extensive carious lesion. (b) Longitudinal mesial/distal crosscut of the same molar, exposing an occlusal enamel-dentine lesion (insert C), and an extremely deep carious lesion originating from the proximal surface (insert D). (c) Magnified image of the pre-cavitated enamel-dentine lesion showing the following zones in a sectioned tooth half (i = demineralized enamel with initial cracks, ii = black/dark brown discoloration of demineralized dentine, iii = light brown discoloration of demineralized dentine (the dark discoloured zones reflect areas of arrested caries), iv = hypermineralized dentine (zone of sclerosis), and v = tertiary dentine (reactionary dentine)). (d) Magnified image of the extremely deep cavitated dentine lesion (i = retrograde enamel demineralization as typically shown in dentine exposed environments, ii = loose fragment of dark brown discoloured contaminated dentine, iii = large zone of destruction (necrotic dentine), iv = contaminated and demineralized dentine, v = contaminated and demineralized tertiary dentine)

and stimulate tertiary dentine formation and other pulpal reparative processes (Finkelman *et al.* 1990, Bègue-Kirn *et al.* 1992, Smith *et al.* 1994). Indeed, a problem with pulpal biomarkers and MMPs in particular is that they are not just destructive in nature; they also increase the bioactivity and reparative capacity of DMCs by further digesting the extracts (Okamoto *et al.* 2018). DMCs contain multiple bioactive components, including GFs, chemokines, cytokines, MMPs and bioactive proteins (Smith *et al.* 2016), which modulate a range of processes critical to repair, including chemotaxis (Smith *et al.* 2012, Galler *et al.* 2016a, Tomson *et al.* 2017), angiogenesis (Roberts-Clark & Smith 2000), mineralization (Tomson *et al.* 2013), stem cell (SC) recruitment (Fayazi *et al.* 2017) and neurogenesis (Marquardt *et al.* 2015). GFs, in particular, orchestrate and modulate pulpal regeneration with several members of the transforming GF superfamily (Cassidy *et al.* 1997, Galler *et al.* 2015) and insulin-like GFs (Finkelman *et al.* 1990) present in DMC extracts. Other GFs including angiogenic molecules, such as fibroblast GF 2 (FGF-2), vascular endothelial GF (VEGF), and placenta GF (PIGF) (Roberts-Clark & Smith 2000, Tomson *et al.* 2013), and the neurogenic factors brain-derived neurotrophic factor (BDNF) and growth/differentiation factor 15 (GDF-15) (Duncan *et al.* 2017) were also identified in dentine extracts.

Harnessing bioactive molecules in DMCs for therapeutic benefit has been the focus of considerable



REPARATIVE DENTINOGENESIS AFTER PULP EXPOSURE

Figure 3 Reparative dentine formation involves a complex sequence of events in which a severe stimulus (e.g. increasing carious involvement of dentine, pulp exposure) causes death of the primary odontoblast, which are subsequently replaced following differentiation of progenitor cells into odontoblast-like cells under the regulation of bioactive molecules, including dentine matrix components (DMCs) release from the dentine matrix. Although the nature of the cellular response is likely to be dependent upon the pulp environment, the mineralized tissue deposited at the pupal wound site will likely display a spectrum of dysplasia.

recent research activity (Smith et al. 2016). The ability of ethylenediaminetetraacetic acid (EDTA) (Graham et al. 2006, Galler et al. 2016a), hydraulic calcium silicate cements (Tomson et al. 2007), calcium hydroxide (Graham et al. 2006), dental resins (Ferracane et al. 2013), ultrasonic agitation (Widbiller et al. 2017) and epigenetic modifying agents (Duncan et al. 2017), to sequester DMCs and augment the regenerative response, has been demonstrated. Irrigation strategies aimed at biological response, rather than disinfection capacity, have used EDTA demonstrated to release TGF- β family members from the extracellular matrix of dentine (Galler et al. 2016a). Conversely, sodium hypochlorite (NaOCl) had a deleterious effect on SC survival and differentiation ability, leading to suggestions that at least in revitalization procedures the final rinse should be with a 17% EDTA solution (Martin et al. 2014). In VPT, however, EDTA irrigation (although releasing DMCs) may stimulate renewed pulpal bleeding.

Role of pulp cells in repair

Dental pulp cells (DPCs) when challenged by the presence of a carious microbial biofilm will directly respond by expressing a range of genes and proteins, promoting defensive cellular processes such as cell migration, proliferation and differentiation (Farges et al. 2015). Numerous in vitro culture studies using DPC (Ko et al. 2015), purified dental pulp SC (DPSC) populations (Li et al. 2014) and in vivo studies (Renard et al. 2016) have demonstrated changes in cellular transcription and protein expression when inflamed. Furthermore, cells cultured in mineralizing, angiogenic and neurogenic culture conditions express a range of extracellular molecules, which promote an autocrine and paracrine healing response (Duncan et al. 2013, Gervois et al. 2015). Although the bulk of attention has focused on the role of odontoblast (Simon et al. 2009) or SC populations in repair (Frozoni et al. 2012), fibroblasts, the principal cell of the pulp, are also able to secrete complement fragments and GFs important to mineralization and SC recruitment (Jeanneau et al. 2017). In addition, bone marrow fibrocytes migrate to the injured pulp site to participate in early wound healing (Yoshiba et al. 2018). Progenitor cells migrate and differentiate to form odontoblast-like cells during reparative dentinogenesis. Several progenitor cell populations may contribute including DPSCs (Gronthos et al. 2002), undifferentiated mesenchymal cells from cell-rich and central pulp perivascular regions, that is pericytes (Fitzgerald *et al.* 1990, Machado *et al.* 2016), and SCs migrating from outside the tooth (Feng *et al.* 2011, Frozoni *et al.* 2012). At present, there is a lack of consensus regarding the progenitor population responsible for reparative dentine formation, although surface marker analysis generally confirms a mesenchymal origin (Simon & Smith 2014).

The relative influence of dentine and pulp cellderived factors to the repair process is impossible to quantify and is influenced by short, temporal bioavailability of expression in cells (Smith *et al.* 2016); suffice to say that it is clear that both are likely to contribute significantly in a complimentary and possibly symbiotic manner to the overall repair process.

Caries and pulpal diagnosis

Dentine and the pulp are one functional entity, the pulp-dentine complex (Pashley 1996); however, for diagnostic purposes at least, hard tissue (caries) and soft tissue disease (pulpitis) should be considered separately. This is in order to reflect current views and establish clear treatment protocols.

Although caries is a common disease, making an accurate diagnosis of the precise disease state can be challenging for even the most skilled clinician. In order to develop the most appropriate treatment strategy for the patient, the clinician will assimilate information from the patient's history (symptomology, diet, oral hygiene regime, etc.), visual-tactile examination, appropriate radiographs and other tools such as caries dyes, fibre-optic/fluorescent light and electrical conductance/impedance metres. Identification of deep carious lesions by visual means and radiographs should be straightforward (Pitts 1996), but determining the effect on the pulp, its depth/extent, activity and the restorability of the tooth in order to advise on prognosis is much more difficult.

An estimate of the depth of a carious lesion can be made on a bitewing radiograph. A more accurate impression of the extent of a lesion can be given on a cone-beam computed tomograph (CBCT); however, this has limitations such as the higher dose, image distortion due to the presence of radiopaque restorations, cost and availability. The radiographic image in general only gives an approximation of the level of mineral content within the tissue being investigated and is limited by the fact it cannot inform with regard to the activity of the lesion nor the status of the pulp within the dentine–pulp complex. It is not possible to determine objectively the precise level of activity within a carious lesion; therefore, clinical judgement and subjective measures are used. Based on appearance, an actively progressing carious dentine lesion tends to have a light yellow/ beige colour, the surface texture is wet/moist, and it is easy to disintegrate/penetrate the soft organic matrix with a dental probe. A lesion that is still active but less so tends to be darker with a colour closer to brown; it is dry and firmer when probed. When caries ceases to be active and is thought to have arrested, these features will be more marked; therefore, it is darker, no excess moisture is present, and it is not possible to penetrate with a probe (Fig. 4) (Bjørndal *et al.* 1997).

As the cavitated carious dentine lesion progresses, Gram-negative bacteria release LPS, which diffuses down the dentinal tubules and is recognized by Tolllike receptors 4 (TLR-4) that are expressed on pulp nociceptors. These nociceptors can extend within 0.16 mm of dentinal tubules and act as an early warning signal to the pulp and indeed the patient (Buyers 1980). LPS tends to advance more rapidly than bacteria through the dentine–pulp complex (zone of demineralization), and when LPS levels are high, the severity of pulpal inflammation is likely to be greater (Khabbaz *et al.* 2001).

For several decades, it has been considered that there is a poor relationship between clinical signs and symptoms and the histological state of the pulp in mature teeth (Seltzer et al. 1963a,b, Garfunkel et al. 1973, Dummer et al. 1980) with a more recent review corroborating this viewpoint (Mejáre et al. 2012). This long held view has, however, been questioned in a study, which compared clinical diagnosis with the histological findings, where the clinical diagnosis was made before the teeth were extracted and compared to histology post-extraction (Ricucci et al. 2014b). It was demonstrated that in the teeth that were clinically diagnosed as either a normal pulp or with reversible pulpitis, only two out of the 59 teeth studied had histological signs of irreversible inflammation. Alternatively, in the patient group that had a clinical diagnosis of irreversible disease, five of 32 teeth had a histological diagnosis of reversible pulpal inflammation. Taking the limitation of an observational study into account including the pooling of normal and reversible pulpitis, the authors concluded that there was good agreement between making a clinical diagnosis and the histological status of the pulp (Ricucci et al. 2014b). It is also not clear from



Light yellow (actively progressing) Light brown (slowly progressing)

Dark brown (Slowly progressing/arrested)

Figure 4 Colour classification of carious lesions (modified from Bjørndal et al. 1997).

this study the reason for the extraction of teeth with only reversible disease.

The crude clinical (categorical) diagnostic system for pulpal disease of reversible and irreversible pulpitis has recently been questioned (Wolters et al. 2017). The word 'irreversible' means that it is 'cannot be undone, repealed, or annulled; unalterable, irrevocable' (Oxford English Dictionary). According to this definition, there are only two possible options for treatment of irreversible pulpitis, either RCT or extraction. However, emerging evidence suggests that when VPT procedures such as partial or complete pulpotomy are carried out in teeth with symptoms indicative of irreversible pulpitis, pulp preservation is possible (Asgary et al. 2017, Qudeimat et al. 2017, Taha & Khazali 2017, Taha et al. 2017). Research in this area will inevitably develop in the future and challenge whether irreversible pulpitis is an appropriate term to use. Indeed, it may even call into question the need for pulpectomy at all, as by definition an '- ectomy' denotes surgical removal of part of the body. However, in terms of pulp diagnosis, it remains to be seen if further subdivision into three or four categories (Hashem et al. 2015, Wolters et al. 2017) will be possible and beneficial in the clinic in developing associated treatment strategies? Only future clinical trials will demonstrate potential usefulness.

Current challenges to decision-making in deep caries management

The prevention of apical periodontitis begins with a clinical evaluation of whether the pulp can be maintained or not; however, the task of evaluating accurately if the pulp is irreversibly inflamed remains a significant challenge (Mejáre *et al.* 2012). Unfortunately, the dental community lacks a device that can (i) accurately establish the point at which the inflammatory process become irreversibly damaged and necrosis ensues, and (ii) decide whether exposing the pulp is necessary or is best avoided. Furthermore, if the pulp is cariously exposed, can VPT procedures such as pulp capping or partial pulpotomy provide predictable outcomes or is more aggressive tissue removal or even RCT necessary?

The diagnostic problem of accurately estimating the level pulp inflammation has led to different treatment concepts emerging within general dental practice. Questionnaire-based surveys in which dentists study radiographs of 'deep carious lesions' have analysed the dilemma of whether a tooth should be treated conservatively by avoiding pulp exposure, or a VPT approach or whether a more invasive approach is required. The results have highlighted that there was no uniform management option for pulp exposures during carious tissue removal, with huge variation between respondents (Oen et al. 2007, Schwendicke et al. 2017, Stangvaltaite et al. 2017). In clinical practice, the decision on whether to maintain the pulp or not also varies (Stangvaltaite et al. 2013), even when important subjective (e.g. symptoms) and objective diagnostic data (e.g. radiograph, pulp sensibility testing) are added to the scenario. Notably, the majority of dentists adopt an invasive approach choosing either a VPT or a pulpectomy (Oen et al. 2007, Schwendicke et al. 2017). So what is the reason for this variation? The fluctuation in the chosen therapy could be the result of a paucity of high-quality clinical evidence, or simply an unclear definition and understanding of the nature of a deep carious lesion. Alternatively, some dental practitioners may prefer pulpectomy to VPT, because it is more predictable in their hands (i.e. tooth retention, absence of signs and symptoms), even when performed poorly. Whilst pulpectomy usually takes 1 or 2 years to fail, by contrast, VPT usually fails within months as a result of severe pain (Bjørndal et al. 2010). Economic factors may also alter treatment decisions as remuneration for a RCT in a molar tooth will be radically different to a VPT procedure on the same tooth. Unfortunately, at present from a patient perspective, the critical factor in the treatment chosen by the dentist is whether the operator is pulp 'friendly' or not. Moving forward, treatment variation needs to be reduced, and therapeutic solutions should be cohesive and biologically based on a clear definition of a deep lesion as well as sound clinical evidence. In addition, dentistry perhaps needs to embrace and develop nextgeneration diagnostic devices to accurately determine the inflammatory state of the pulp.

Are endodontists the best candidates for maintaining pulp vitality?

Established borders of a dental specialty may create traditions or obstacles for providing the best possible platform for optimal 'pulpal care'. Clearly, endodontists have the expertise on aseptic strategies, fundamental to optimal maintenance of pulp vitality. This includes preparation of an aseptic working field using rubber dam isolation, cleaned with a disinfectant. Unfortunately, due to the nature of secondary care it is unusual for the endodontist to make a decision on whether the pulp should be saved or removed, as these decisions are carried out in general dental practice. Indeed, the endodontic tradition of an aseptic working field using rubber dam is not widespread in general practice (Jenkins *et al.* 2001, Slaus & Bottenberg 2002, Bjørndal & Reit 2005, Markvart *et al.* 2018); this jeopardizes the VPT procedure from the very onset. Clear guidelines are required, both for treatment and for referral, which should include underlining the importance of selective referral for perceived simpler treatments such as VPT to a specialist environment (Komabayashi & Zhu 2010), and this may result in more standardized treatment and less pulpectomies. At the very least, increased education for practitioners in the optimum way to handle pulp tissue should be considered a priority.

Caries lesion depths and pulp inflammation

The link between histologically and the reversibility or irreversibility of pulpitis is difficult to confirm clinically (Seltzer *et al.* 1963a,b, Dummer *et al.* 1980). From a histopathological perspective, the threshold for irreversible pulpal inflammation can be defined as the stage where the cariogenic microorganisms are entering the pulp space either through tertiary dentine or directly into the pulp. Clinically, it is uncertain how this critical threshold of infection can be detected; however, do clinicians actually use prevailing clinical and radiographically data optimally?

The penetration depths of carious lesions – deep and extremely deep

What should be considered a 'danger threshold' of a deep lesion? Attempts to define more precisely a deep carious lesion can be based on a dental practitioner's expectations on reaching pulp exposure following excavation (Bjørndal & Thylstrup 1998). In this context, the majority of general practitioners selected the 'deep' carious dentine lesion as one that penetrates radiographically into the pulpal quarter of the dentine, but still with a well-defined zone of radiopague dentine separating the infected demineralized dentine from the pulp (Fig. 1). In contrast, the extremely deep lesions, the carious demineralized dentine is defined as penetrating the entire thickness of the dentine, without a radiopaque zone separating the lesion from the pulp. The extremely deep carious lesion has microorganism penetrating into the critical zone of tertiary dentine including the pulp (Reeves & Stanley 1966, Bjørndal 2018). Moreover, a relatively high agreement of more than 80% was highlighted between a clinical definition of irreversible pulpitis and the presence of bacteria within necrotic areas in the pulp (Ricucci et al. 2014b). This could potentially indicate that the simple examination of lesion depths on bitewing radiographs is an opportunity to introduce a diagnostic tool for evaluating the risk of bacterial

invasion into the pulp. Interestingly, the exact degree of carious lesion penetration has rarely been described in the literature in relation to VPT, including partial or full pulpotomy (Bjørndal *et al.* 2014). This could potentially explain the difficulties in predicting direct pulp capping outcome, that is the large heterogeneity between carious lesions; however, more evidence is needed before radiographic appearance can be mapped with bacterial penetration into the pulp.

Pulp inflammation – destruction and repair

Understanding of pulpal repair mechanisms has highlighted the need for a low-grade inflammatory process to stimulate the regenerative response (Cooper et al. 2010). When the irritant is removed, the pulp has the capacity and potential to provide an up-regulation of odontoblastic activity (reactionary tertiary dentinogenesis) or the recruitment of progenitor cells, which can cytodifferentiate into odontoblast-like cells (reparative tertiary dentinogenesis). The pulp responds to caries in a dynamic manner demonstrating different pulp reactions to slowly progressing carious lesion and the rapidly progressing lesion (Bjørndal 2018). The pulp reacts to a low-grade lesion (e.g. old patient, carious lesion penetrating halfway into dentine) by forming reactionary dentine, whilst the tertiary dentine formed under rapidly progressing lesion (e.g. voung patient with a deep carious lesion in pulpal quarter) is less well organized, with a reduced volume dentinal tubules eventually being completely atubular (also called fibrodentinogenesis) (Baume 1980).

Treatment to avoid pulp exposure

Both complete caries removal and the classic indirect pulp capping concept, advocated in the 1960s, were invasive strategies, leaving either no or only residual carious dentine behind, resulting in a higher risk of pulpal exposure (Kerkhove et al. 1967). Indeed, recent consensus reports have stated that the complete or nonselective carious removal is now overtreatment (Innes et al. 2016, Schwendicke et al. 2016b). Based on a 5-year follow-up of a randomized clinical trial, a stepwise excavation approach for the management of deep carious lesions was superior to a complete carious removal procedure carried out in one visit, with less pulpal exposure, less pain and more teeth with vital pulps in the stepwise group (Bjørndal et al. 2017). Although not the focus of this review, studies in the primary dentition have also shown that a one-stage selective carious removal

procedure performs successfully (Casagrande *et al.* 2010, Franzon *et al.* 2014), including the concept of sealing the entire carious lesion with a stainless-steel crown in the Hall Technique (Innes *et al.* 2017).

Notably from an endodontic viewpoint, a clear definition of lesion depth is lacking in many studies and the available evidence on well-defined deep carious lesions in adult teeth remains limited. The treatment of permanently leaving carious dentine in a one-stage selective approach for caries in the pulpal third has shown comparable results with stepwise excavation. Less evidence is available for deep carious lesion in the pulpal quarter. If residual carious dentine remains in situ, the dentine may shrink and potentially impair the coronal restoration, which could lead to pulpal complications (Bjørndal 2018). It is accepted that an inadequate temporary restoration and lack of a permanent coronal seal during the less invasive carious removal strategies will lead to failure including pulpal and apical pathosis (Bjørndal & Thylstrup 1998, Maltz et al. 2012). Although a one-stage selective caries removal technique saves on both clinical and patient time, another potential limitation is that if the patient moves to a new dentist it may appear that caries remains and further intervention may be suggested.

Stepwise excavation in detail

This is a selective caries removal technique carried out in two visits. The aim of the first stage is to change the cariogenic environment. Selective carious dentine removal to soft dentine is performed to the extent that a temporary restoration can be properly placed. The clinical result of leaving behind carious dentine is that over time the appearance changes to that of arrested carious dentine (Massler 1978, Bjørndal et al. 1997). The initial active carious environment can be identified clinically as soft discoloured and wet tissue, which turns into a darker, harder and drier appearance after the first stage. The second-stage excavation several months later is carried out to firm dentine following the recommendation of carious tissue removal (Schwendicke et al. 2016b). It is easier to perform, as the consistency of the retained dentine has changed. A calcium hydroxide $(Ca(OH)_2)$ base material is used between visits, or a hydraulic calcium silicate cement and the tooth are restored with a glass-ionomer restorative material.

The physiological response of the pulp to capping

Formation of reparative dentine by odontoblast-like cells is possible after pulp exposure, where hard tissue

(mineralized bridge) formation should replace the lost dentine if successful. The quality of the mineralized bridge formation after pulp capping procedure has been evaluated histologically and reveals many nonmineralized defects, so-called 'tunnel defects', that can easily be invaded by microorganisms (Cox *et al.* 1985). This is more evident with traditional Ca(OH)₂ materials compared with hydraulic calcium silicate cements (Nair *et al.* 2008). Therefore, it is mandatory after a direct pulp capping or pulpotomy procedure that a permanent bacteria-tight restoration is placed immediately to prevent infection by invading microorganisms.

Haemostasis and disinfection

A prerequisite for a successful outcome following pulp capping is control of bleeding and the avoidance of blood clot formation between the capping material and the pulp tissue. Practically, it is challenging to place a capping material on a wet surface such as a blood clot, whilst the presence of a blood clot has been linked to higher risk of post-operative infection (Schröder & Granath 1972, Schröder 1985). A clinical trial investigated different methods of attaining haemostasis using either saline, NaOCl or chlorhexidine digluconate, prior to pulp capping with $Ca(OH)_2$ (Baldissera *et al.* 2013). It was shown that the various approaches did not affect the expression of bioactive glycoproteins related to repair (Baldissera et al. 2013). Furthermore, a randomized clinical trial has reported improved outcomes, if a disinfection agent such as NaOCl is applied the haemostatic protocol prior the application of a capping material (Tuzuner et al. 2012). Blood clots also contain numerous bioactive molecules (e.g. GFs), which could potentially contribute and augment a repair process with current revitalization protocols advocating a bleeding sequence and the formation of a clot in the healing response (Galler 2016b).

Pulp capping classification

As a consequence of the variation in the reported success of pulp capping after carious exposure (Bogen *et al.* 2008, Marques *et al.* 2015), a classification has been proposed, which a view to assisting clinical management (Bjørndal 2018). The classification reinforces the need for a more focused or enhanced approach after carious exposure (class II), which is not as critical if the pulp is traumatically exposed (class I) due to a reduction in the microbial load close the pulp tissue. It is recognized that this classification may of particular benefit to workers in primary care to assist decision-

making after exposure and that certain dentists (including specialists) may in fact use an enhanced protocol for the treatment of all pulp exposures.

Pulp capping (class I)

This conventional pulp capping procedure (Schröder 1985) is indicated after a complicated traumatic fracture, which involves a superficial exposure of the pulp or after an accidental perforation (Bjørndal 2018). Clinically, the pulp would be considered healthy and relatively free of inflammation. Other factors likely to be important prior to undergoing class I pulp capping are small exposures (preferably <1 mm diameter), located in the coronal third of the pulp chamber ideally corresponding to a pulp horn (Fig. 5).

Pulp capping (class II)

In the preoperative presence of a deep or extremely deep carious lesion (Bjørndal 2018), the pulp exposure judged clinically to be through a zone of bacterial contamination with an expectation that the underlying pulp tissue is inflamed. Symptoms may be present but not indicative of irreversible pulpitis. The prefix class II indicates that an altered treatment protocol is required. because a severe microbial challenge is expected. The proposed protocol should ideally include carious removal guided by the use of the operating microscope, haemostasis attained within 5 min, the use of 5.25% NaOCl (Bogen et al. 2008) and restoration with a hydraulic calcium silicate cement. Based on 1-year observational data (Marques et al. 2015), the procedure seems promising at advanced stages of caries penetration; however, at present randomized clinical data are absent. Notably, in class II procedures the use of high concentration of disinfection prior to placing the capping material is recommended as well as magnification to improve control of the carious removal procedure (Fig. 6). The enhanced protocol utilized may explain the high success of these studies (Bogen et al. 2008, Marques et al. 2015), compared with the previously reported randomized clinical trial data demonstrating a very low 5% survival of traditionally pulp capping after caries exposure at 5 years without an enhanced protocol (Bjørndal et al. 2017).

Cost-effectiveness analysis and evidence from clinical trials

The use of simulated scenarios

Available evidence (pre-2014) has been used to simulated scenarios for establishing a cost-effectiveness



Figure 5 Class I pulp capping. Classical capping approach of a small pulp exposure, (a) before and (b, c) during and after calcium hydroxide application.



Figure 6 A successful class II pulp capping. (a) Preoperative radiograph reveals a deep lesion and no apical pathosis. (b) After nonselective carious removal (former complete excavation) using the operative microscope, there is an absence of any retained carious dentine, and there is good haemostasis of the exposed pulp. (c) Placement of the mineral trioxide aggregate capping agent. (d) Post-operative radiograph with permanent restoration in place. (e) One-year follow-up and (f) two-year follow-up. Case courtesy of Dr Phu Le.

analysis (Schwendicke & Stolpe 2014). In conclusion, both direct pulp capping and RCT were cost-effective. Direct pulp capping was most cost-effective in younger patients (<40 years) in occlusal sites (Fig. 7). In contrast, RCT was preferred in older patients (>40 years) with interproximal exposure sites.

New and future expectation of improved clinical evidence Which treatment will be the 'gold standard' for treating the deep and extremely deep carious lesion? Randomized clinical trials are the best way to answer this question, but there are currently only a few which address this issue. In order to plan a new randomized controlled trial, there are some important rules to be considered:

 Well-defined inclusion criteria: For example, penetration depth of the carious lesion may lead to more accurate data analysis, including perhaps more details of lesion activity or exact detail of patients' pulpal symptoms with a diagnosis.



Figure 7 An unsuccessful class II pulp capping. Direct pulp capping (class II) (male, 48-years). (a) Preoperative radiograph reveals a deep lesion and no apical pathology. (b) Carious lesion located at approximal site. (c) Restoration placement at the gingival margin to improve moisture control, isolation and asepsis, (d) a dark bleeding exposure is noted. (e) Haemostasis is difficult to achieve. (f) Mineral trioxide aggregate is applied, and an adequate thickness can be compromised in approximal cavities. (g) Three months post-operatively, a sinus tract and apical periodontitis are noted. (h) A post-operative radiograph of completed root canal treatment. Case courtesy of Dr Pim Buurman.

- The task of choosing identical outcome measures: For example, a reliable comparison between coronal pulpotomy and direct pulp capping may be a difficult task, as a reliable pulp sensibility test cannot be performed for the pulpotomy intervention arm.
- Informed power calculation: The number of treatments required to reveal a significant difference between control and experimental groups is

essential. This often relies on pre-selected power settings (the assumption of the expected intervention effect is too large, whereby the actual number enrolled is too small and there is a high risk of type 2 statistical error). The power calculation should ideally be based on previous literature or informed by a pilot study, which accounts for dropouts.

- Central randomization of patients: Data from published trial reports have revealed a lack of adequate randomization. The resulting report may be associated with a more positive estimate of the intervention effect (Gluud 2006).
- Blinded follow-up examination: An examiner who is not aware of which group the material or the patient belongs (blinded outcome evaluation).

The lack of global consensus reflected in most recent randomized clinical trials

Analysis of recent randomized clinical trials on the management of deep caries lesions (Table 1) highlights that inclusion criteria are similar with a defined caries lesion and signs of reversible pulpitis. However, the treatments vary from pulpotomy to extensive carious removal (indirect pulp capping) and stepwise excavation, which perhaps reflects that no global consensus or tradition currently exists in the treatment of the deep carious lesion. The most recent randomized controlled clinical trials in humans (Table 1) are limited by low numbers and resulting weak conclusions. At present, no high level, scientific-based recommendation can be made for selecting a 'gold standard' capping material (Schwendicke *et al.* 2016a).

Is pulp exposure a negative factor?

Dental pulp exposure results in irreversible damage to the affected odontoblastic palisade and death of the primary odontoblast. In order to establish a new mineralized barrier, it is necessary to induce the growth of neo-odontoblasts, the only cells capable of secreting dentine. Unfortunately, as odontoblasts are highly differentiated post-mitotic cells, a new layer cannot be created, as in other connective tissues, by inducing mitosis of cells at the wound periphery. The only way to rebuild the odontoblastic palisade is to recapitulate in situ the original developmental process (Goldberg & Smith 2004). To accomplish this, a source of progenitor cells (erroneously referred to as 'SCs') is required. These cells must first be directed from their niche to the damaged area through chemotaxis or plithotaxis (Hirata et al. 2014). Once the cells have migrated to contact the biomaterial, they must differentiate into mineral-secreting cells, at which point dentine synthesis is triggered.

From an operator's perspective, exposure of the pulp to the oral cavity permits placement of the biomaterial in direct contact with the pulp. Furthermore, by having direct access to the tissue, it is easier to evaluate the health of the pulp and to manage it, for example pulpal bleeding. On the other hand, avoiding exposing the pulp lessens the risk of bacterial infection and preserves the odontoblast palisade to facilitate reactionary (or reparative) dentinogenesis. Moreover, dentine contains a reservoir of GFs which can be released by the capping materials and participate in stimulating the reparative process. In terms of prevention of bacterial infection, it should be remembered that dentine has a tubular structure, and if the residual dentine layer is <1 mm, it is likely to be as permeable to bacterial challenge as a pulp exposure (Murray *et al.* 2003).

Comparing the outcome of various strategies to treat deep caries is complex, and as a result, the debate about whether or not to preserve a layer of dentine continues. This issue divides endodontists, who regularly manipulate pulp tissue and highlight that nonselective caries removal and pulp capping can be successful in 90% of cases (Hilton *et al.* 2013, Marques *et al.* 2015, Hegde *et al.* 2017), from operative dentists and cariologists who prefer to maintain a dentine layer if at all possible.

Pulp exposure management

Confusion frequently arises when defining the difference between pulp capping and partial pulpotomy. Partial pulpotomy removes 2–3 mm of the pulp tissue at the site of exposure; this technique is used for removing the superficial layer of infected or inflamed tissue. Pulp capping does not involve any pulp tissue removal; instead, the biomaterial is placed in direct contact with the pulp tissue (ESE 2006). After traumatic pulp exposure, the pulp can be capped without tissue removal as the wound has not been contaminated with microorganisms for an extended period. In practice; however, because the pulp has been exposed to the oral environment, it is common to remove the superficial layer. It was classically demonstrated that after 24 h of exposure, the pulp contamination and inflammation extended to a depth of 1.5 mm (Cvek & Lundberg 1983).

A deep carious lesion stimulates a pulp defence response in conjunction with inflammatory processes. The pulp capping procedure protects the tissue, but may not reverse a superficial inflammatory processes; therefore, it is recommended that 2–3 mm of tissue is removed in a partial pulpotomy procedure. The clinician should be able to distinguish between inflamed and noninflamed tissue if the pulp is exposed;

Table 1 Status of recent rai	ndomized clinical trials (since	2010) of capping agents and	pulp preserving interventions		
	Tooth type and	Trial power			
	age	and randomization			Success of analysed
	Preoperative status and	quality		Outcome assessment	cases
Study	diagnosis	Variables tested	Treatment protocol	Follow-up	Conclusions
Jang <i>et al.</i> 2017 (1 year)	Permanent teeth (>19 years)	Trial: Intervention effect 15%,	After complete caries	Blinded outcome	Experimental (Endocem): 87%
Song et al. 2000 (12 weeks)	Direct pulp exposure from	Power 80%, $P < 0.05$.	excavation with sterile	assessment: yes	success.
Comparing capping	trauma or dental caries	Randomization: No	spoon excavator exposed	Success: Positive response	Control (ProRoot MTA): 85%
materials	(depth not further defined)	concealed allocation	pulp disinfected with 2.5%	to pulp test. No evidence of	success
	Reversible pulpitis	sequence.	NaOCI. Haemostasis should	irreversible pulpitis (not	Nonsignificant (NS). between
		Capping mat: ProRoot MTA	be reached within 10 min.	defined) and pulp necrosis,	tested capping materials. Axial
		(control) $n = 23$; versus	Thickness of the capping	no well-defined apical	exposure site (class V cavity)
		Endocem $n = 23$	materials (3 mm or close as	radiolucency (not defined).	showed significantly poorer
		Stratification variable: Age	possible)	Follow-up: 1, 2 and	outcome
		and exposure site (occlusal		4 weeks, and 3, 6 months	
		or axial)		and 1 year	
Kang <i>et al.</i> 2001	Primary dentition (3-	Trial: No power calculation	After removal of carious	Blinded outcome	Experimental (OrthoMTA): 97%
Comparing capping	10 years)	<i>Randomization</i> : No	dentine. Coronal pulp	assessment: yes	clinical and 100% radiographic
materials	Deep caries with a potential	concealed allocation	removed and rinsed with	Success: Positive response	success
	risk of exposure (lesion	sedneuce	sterile saline for 2 min	to pulp test. No evidence of	Experimental (RetroMTA): 94%
	depth not defined, no	Capping mat: ProRoot MTA	(haemorrhage control).	irreversible pulpitis (not	clinical and 94% radiographic
	widening of PDL or	(control) $n = 47$ versus	ProRoot and OrthoMTA	defined) and pulp necrosis,	success
	periapical (PA) – or furcal	OrthoMTA $n = 47$ and	(two-visit procedure),	no PDL widening, no	Control (ProRoot MTA): 100%
	lesion)	RetroMTA $n = 48$	RetroMTA (one visit) filled	external and internal	clinical, and radiographic
		Stratification variable: None	with a resin-modified GI	resorption, no periapical or	success
			after 5 min and final	furcal bone resorption	NS difference between capping
			restoration.	Follow-up: 3, 6 12 months	materials
Kundzina <i>et al.</i> 2010	Permanent teeth (18-	Trial: Intervention effect 30%,	Hand excavator was used,	Blinded outcome	Experimental (ProRoot): 85%
Comparing capping	55 years)	Power 95%, $P < 0.05$	and following pulp	assessment: yes	cumulative survival rate
materials	Deep caries(depth defined as	Randomization: Concealed	exposure, haemostasis was	Success: Survival of the	Control (Dycal): 52% cumulative
	either 2/3 into the dentine,	allocation (central	controlled within 10 min	capped pulp being	survival rate
	>2/3 and 'into the pulp' (=	procedure)	using 0.5% NaOCI	nonsymptomatic,	Secondary outcome: NS
	extremely deep caries)	<i>Material:</i> Calcium hydroxide	<i>CH arm:</i> Dycal applied to	responding to sensibility	Significant difference between
	Reversible pulpitis	(CH) (control) $n = 37$ versus	exposure	test and no periapical	cumulative survival rate in
		MTA $n = 33$	MTA arm: white ProRoot	changes radiographically	favour of MTA (lesion depth not
		Stratification variable: None	(two-visit procedure)	Secondary outcome: Pain	equally distributed between
				1 week post-operatively	arms)
				Follow-up: 6, 12, 24 and	
				36 months	

Study	Tooth type and age Preoperative status and diagnosis	Trial power and randomization quality Variables tested	Treatment protocol	Outcome assessment Follow-up	Success of analysed cases Conclusions
Hashem <i>et al.</i> 2007 Comparing restorative procedure and pre-clinical radiographic and CBCT assessments	Permanent dentition (median 28 years) Carious dentine into pulpal quarter of the dentine, no signs of irreversible pulpitis (no widening of PDL or PA lesion)	<i>Trial</i> : Intervention effect ~20%, Power 80%, $P < 0.05$ <i>Randomization</i> : Concealed allocation (central procedure) <i>Material:</i> GLC (control) $n = 36$ versus Biodentine $n = 36$ <i>Stratification variable:</i> Cavity size	Superficial soft infected dentine was removed by bur and deeper located areas by chemo-mechanical gel and hand instrumentation, but left at a residual level, whereby any added removal would lead to exposure.	Blinded outcome assessment: Unclear Success: Positive response to pulp test at 12 months. No irreversible pulpitis (defined); absence of PA radiographically (defined as ≥ 2 times with of PD space). CBCT scan detecting so-called early PA lesions <i>Follow-up</i> : 1, 6 and 12 months	<i>Experimental</i> (Biodentine): 83% clinical success <i>Control</i> (GIC): 83% clinical success. No clinical and radiographic differences. CBCT-PA alterations at baseline had a significantly higher failure rate at 1 year follow-up versus teeth without CBCT detected PA alterations
uprillion er ar. 2000 (18 months) Comparing excavation interventions and subsequent pulp capping intervention if exposure occurred accidentally during excavation	car yearsy Carious dentrine into pulpal quarter of the dentrine, no signs of irreversible pulpitis (undisturbed night sleep) (no radiographic PA lesion)	Andomization: Concealed allocatization: Concealed allocation (central procedure) <i>Intervention</i> : Complete/ nonselective excavation (control), $n = 158$, Stepwise excavation, $n = 156$ Stratification variable: Age and centre	Vast. remover or superimound dentine, so a GIC temporary seal placed. 2. visit: (8-12 weeks) Final exc. leaving central yellowish or grey/sh hard dentine and permanent seal and a resin restoration <i>Complete excavation arm:</i> Final exc. leaving central yellowish or greyish hard dentine and permanent seal. In case of perforation a nested capping trial	<i>Success:</i> Pos. response to pulp test at follow-up. No unbearable pain (no disturbed night sleep); absence of PA radiographically (defined as > 2 times with of PD space) <i>Follow-up:</i> 1 and 5 years	<i>Experimenty at o years.</i> <i>Experimental</i> (stepwise): 60% success. <i>Control</i> (complete excavation): 46% success. Significant difference Nested pulp capping trial at 5 years: <i>Experimental</i> (partial pulpotomy): 11% success. <i>Control</i> (direct pulp capping): 6% success. NS difference between capping interventions
			comparing <i>direct pulp</i> <i>capping</i> versus <i>partial</i> <i>pulbotomy</i>		

however, this visual analysis may not be sufficiently accurate. Before placing the capping material, the pulp wound and the cavity are disinfected. NaOCl is generally the disinfectant of choice, but has drawbacks as it is corrosive due to its organic tissue dissolution ability (Hewlett & Cox 2003, Sauro *et al.* 2009, Kim *et al.* 2017). Furthermore, NaOCl interacts with dentine interfering with subsequent bonding processes because of collagen collapse (Thanatvarakorn *et al.* 2014). Chlorhexidine digluconate solution (2%) has been suggested as an alternative to NaOCl (Mente *et al.* 2010).

Pulp inflammation and in situ diagnosis

Inflammation is destructive, but the resulting pathophysiological response is necessary to stimulate healing. Indeed, inflammation marks the first step of tissue convalescence. In the clinic, pulpitis is classified as either reversible or irreversible. Pulpitis can be reversed if the irritant is removed and the tooth adequately restored (Mjör & Tronstad 1974). Alternatively, if the inflammation process is severe and 'irreversibly' damaged the only option is to completely remove the inflamed tissue. As discussed earlier, establishing whether the pulp is reversible or irreversibly inflamed is not completely predictable using current diagnostic techniques (Dummer *et al.* 1980).

Several studies have investigated inflammatory pulpal biomarkers and their potential use as a diagnostic test (Nakanishi et al. 2005, Karapanou et al. 2008, Shin et al. 2011. Zehnder et al. 2011. Elsalhy et al. 2013, Rechenberg et al. 2014). A quantitative analysis (the actual number of inflamed cells, inflammatory markers) and a qualitative analysis have been described and correlated to caries depth, caries proximity to the pulp and the inflammatory state of the pulp (McLachlan et al. 2003). Potentially discriminatory biomarkers have been identified, which could potentially set an inflammatory threshold above which the pulp is not viable (Rechenberg et al. 2016, Zanini et al. 2017); however, at present biomarkers are not specific enough to predictably dictate treatment (Zehnder et al. 2011). Further clinical studies investigating molecularbased assays are required to develop reliable diagnostic tools and better reproducibility.

Until next-generation diagnostic tools are validated and commercially available, practitioners must make do with the existing methods of detailed history and pulp sensibility tests. Other options include assessing the level of pulpal haemostasis as inflammation is associated with hypervascularization. Practically, the exposed pulp is packed with a damp cotton wool pellet and pressure is applied for at least 5 min. This should be enough time to achieve haemostasis under physiological conditions, which will facilitate a 'dry' working field. If bleeding persists, it may be assumed that some of the pulp tissue is still inflamed and further pulp removal is necessary until healthy tissue is exposed.

Pulp capping procedure

The primary aim of pulp capping is to protect the exposed tissue from external irritation, principally bacterial in nature. For many years, it was thought that the quality of the seal alone determined the success of the procedure (Bergenholtz *et al.* 1982). In the 1990s, direct pulp caps with dental adhesive materials initially offered promising results (Cox *et al.* 1998); however, after several months, marginal bond deterioration and subsequent infiltration by bacteria occurred, leading to pulpal inflammation or necrosis (Pameijer & Stanley 1998, Bergenholtz 2000). Resinbased adhesive materials were discouraged, and new biologically based materials were developed with the principal aim of promoting mineralized bridge formation (Pitt Ford *et al.* 1996).

As the clinical evaluation of pulpitis remains empirical, treatment failure may result if the diagnosis is not accurate. Recently, the removal of all the coronal pulp tissue in a pulp chamber pulpotomy has been proposed as an alternative treatment to pulp capping (Asgary & Eghbal 2010, Simon et al. 2013). This concept is based on histological research observation that in cases of irreversible pulpitis the inflammation is confined to the coronal pulp and the tissue in the roots is largely free of inflammatory disease (Ricucci et al. 2014b). Pulp chamber pulpotomy is routinely used in Paediatric Dentistry to preserve the radicular pulp on immature teeth to allow the radicular process to grow and apexogenesis to occur. The application of this treatment on mature teeth of adults is preliminary and remains under investigation, but numerous published case series suggest it may have promising long-term outcomes (Simon et al. 2013, Taha et al. 2017). In the future, practical issues surrounding coronal pulpotomy will also need investigation, including the lack of response to pulp sensibility testing and the likelihood of pulp canal obliteration, which will compromise potential re-entry.

Materials for pulp capping

Capping material should ideally have three characteristics: (i) create an immediate seal of the dental cavity to protect the pulp in the first few weeks as the mineralized bridge is forming; (ii) be biocompatibility and noncytotoxic; and (iii) possess bioactive properties that trigger the biological processes involved in forming a mineralized barrier at the tissue/material interface.

For years, Ca(OH)₂ has been the 'gold standard' capping material (Glass & Zander 1949, Stanley & Lundy 1972, Tronstad 1974, Pitt Ford & Roberts 1991). The best known commercial Ca(OH)₂ product is the hard-setting Dycal® (Dentsply Sirona, Weybridge, UK), although nonsetting proprietary products are also used. Although applying this material directly to the pulp does induce formation of a mineral barrier (Schröder 1972), the barrier is neither uniform nor bonded to the dentine wall and a good seal is not produced (Cox et al. 1996, Nair et al. 2008). Although the exact mechanism of $Ca(OH)_2$ remains unclear, biologically it stimulates the production of mineralized tissue, albeit often a porous osteodentine (Cox et al. 1996, Nair et al. 2008). Ca(OH)₂ is successful clinically (Brizuela et al. 2017), but limitations including solubility, handling and biological response have led to the development of new materials such as hydraulic calcium silicates (Pitt Ford et al. 1996).

Recent reviews provide the evidence for a superior outcome for the use of the hydraulic calcium silicate cements, in particular various forms of the mineral trioxide aggregate (MTA), and another recent available type BiodentineTM (Septodont, Sant-Maur-des-Ditch Cedex, France). A recent randomized clinical multicenter trial demonstrated that MTA performed better than $Ca(OH)_2$ (Kundzina *et al.* 20172017). Although the study contained information about the depth of the carious lesion, depth was not randomly distributed between the two materials (MTA and Ca $(OH)_2$) investigated. At present, there remains a paucity of high-quality randomized clinical trials comparing and testing capping materials in order to make definitive conclusions on the best material to use.

Mineral trioxide aggregate is applied directly onto the pulp using a special applicator. The MTA is not packed into the pulpal cavity, but instead lightly tapped into contact with the pulp and dentine wall using a 'thick paper' point or cotton pledget. The material takes over four hours to set, and it is recommended that the tooth should be temporized before the permanent restoration is placed. Recently, alternative MTA-based materials, including Biodentine, have been developed, which have a reduced setting time (<15 min) and are recommended for one-visit VPT procedures. The biological properties of these materials have been described in the literature from both in vitro and in vivo studies (Careddu & Duncan 2018, Parirokh et al. 2018), as well as in clinical trials comparing it to other materials (Hilton et al. 2013). Moreover, the hard tissue bridges formed against MTA have higher histological quality compared with those induced by Ca(OH)₂ (Nair et al. 2008). Biodentine has potential to overcome some of the issues of discoloration associated with MTA after pulp capping (Parinyaprom et al. 2018) and favourably induces mineralization (Laurent et al. 2012) and cellular differentiation in vitro (Zanini et al. 2012). In addition to the biological effects of Ca(OH)₂ and calcium silicates on DPCs, they also have the ability, as discussed earlier to induce the release of DMCs (Graham et al. 2006, Tomson et al. 2007). The release of DMCs by pulp capping materials boosts chemotaxis, angiogenesis (Zhang et al. 2011) and the differentiation of progenitor cells into dentinogenic cells (Liu et al. 2005). Although from a biological vantage these effects are promising, there are currently no therapeutic solutions available that use previously extracted DMCs and apply them directly in situ.

Outcome

Due to differences in study design, it is impossible clinically to make a strict comparison between available VPT studies (Table 1). Indeed, there is a wide range of reported success rates for pulp capping procedures after carious exposure. One randomized clinical multicentre study, based in a clinical general practice environment (without the use of a class II equipment such as the operating microscope, etc.), had an outcome of 32%dropping to below 10% after 5 years (Bjørndal et al. 2010, 2017). Other studies using a class II concept (use of microscope, etc.) reported an outcome of 91% (Marques et al. 2015) after 3 years, perhaps highlighting the reasons for such a large difference. A systematic review on the subject (but with the same limitations as above) concluded the overall success rate is in the range of 72.9%-99.4% (Aguilar & Linsuwanont 2011). Analysis of the literature highlights that two types of failure may be occurring: (i) early failure within days of the treatment and leading to symptomatic pulpitis, and (ii) long-term failures detected several months later and characterized by the presence of an apical lesion related to root canal infection after pulp necrosis. These two types of failures could

potentially have a different aetiology. Early failures could be related to misdiagnosis of the severity of the pulpitis disease and insufficient pulp tissue removal, which may explain the need for tissue removal in these cases, whereas late failures could be related to the quality and sealing ability of the restoration and mineralized bridge that becomes compromised by secondary infection. The volume of literature investigating the outcome of coronal pulpotomy has increased recently, but is still limited to case reports or case series (Kunert *et al.* 2015) with short-term follow-up and low numbers of patients. More robust data are required going forward to confirm that pulp chamber pulpotomy can be considered a permanent treatment for teeth with 'irreversible' pulpitis.

Conclusions

The maintenance of pulp vitality and the promotion of biologically based management strategies are at the core of deep caries management. Pulp exposure can be avoided in radiographically deep caries and asymptomatic or mildly symptomatic teeth by selective removal of caries and restoration in one or two visits. Alternatively, strategies to nonselectively remove the caries will result in more frequent pulp exposure; however, it seems from the limited evidence available that careful management of the damaged pulp and VPT may also have favourable success rates. Decision-making in this area is currently hampered by the crude diagnostic techniques available to assess accurately the state of the pulp as well as a paucity of adequately powered, well-controlled randomized studies addressing key questions. From a scientific perspective, further understanding of the processes of inflammation, repair and material interaction is important to deepen understanding and develop novel diagnostic and therapeutic solutions. Clinically, a focus on high-quality primary research investigating the efficacy of management strategies for the treatment of deep caries is a priority.

Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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