



How to intervene in the caries process: proximal caries in adolescents and adults—a systematic review and meta-analysis

C.H. Splieth¹ · P. Kanzow² · A. Wiegand² · J. Schmoeckel¹ · A. Jablonski-Momeni³

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Abstract

Objectives For an ORCA/EFCD consensus, this systematic review assessed the question “How to intervene in the caries process in proximal caries in adolescents and adults”.

Material and methods Separating between the management of initial and cavitated proximal caries lesions, Medline via PubMed was searched regarding non-operative/non-invasive, minimally/micro-invasive and restorative treatment. First priority was systematic reviews or randomized controlled trials (RCTs), otherwise cohort studies. After extraction of data, the potential risk of bias was estimated depending on the study type, and the emerging evidence for conclusions was graded.

Results Regarding non-invasive/non-operative care (NOC), no systematic reviews or RCTs were found. In cohort studies ($n = 12$) with a low level of evidence, NOC like biofilm management and fluoride was associated with a low proportion and slow speed of progression of initial proximal lesions. Minimally/micro-invasive (MI) treatments such as proximal sealants or resin infiltration (four systematic reviews/meta-analyses) were effective compared with a non-invasive/placebo control at a moderate level of evidence. Data on restorative treatment came with low evidence (5 systematic reviews, 13 RCTs); with the limitation of no direct comparative studies, sample size-weighted mean annual failure rates of class II restorations varied between 1.2 (bulk-fill composite) and 3.8% (ceramic). Based on one RCT, class II composite restorations may show a higher risk of failure compared with amalgam.

Conclusions Proximal caries lesions can be managed successfully with non-operative, micro-invasive and restorative treatment according to lesion stage and caries activity.

Clinical relevance Proximal caries treatment options like non-operative, micro-invasive and restorative care should be considered individually.

Keywords Caries · Proximal · Proximal · Non-operative · Micro-invasive · Minimally invasive · Restoration

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✉ C.H. Splieth
splieth@med.uni-greifswald.de

¹ Clinic for Preventive and Paediatric Dentistry, University of Greifswald, Fleischmannstr. 42, 17475 Greifswald, Germany

² Department of Preventive Dentistry, Periodontology and Cariology, University Medical Center Göttingen, Göttingen, Germany

³ Department of Orthodontics, Dental School, Philipps-University Marburg, Marburg, Germany

Introduction

Caries is a highly prevalent disease and, therefore, a relevant global burden [1–3], in spite of considerable caries reductions in children and adolescents in many countries [4–6]. From adolescence on, the proportion of proximal caries increases and eventually dominates the decayed filled surfaces (DFS) score [7].

A range of treatment options for managing proximal lesions are available, including non-operative/non-invasive and minimally/micro-invasive approaches as well as restorative treatments [8, 9]. Different terms for caries management options have been used in the literature in the past and suggested for future terminology [10, 11]. Therefore, in this review, a compromise using the terms non-operative/non-invasive as well as minimally/micro-invasive parallel is used to give credit to the original literature and recent terminology.

Non-invasive treatment tries to reduce the caries activity via biofilm control and fluoride applications. Micro-invasive treatments include proximal sealants and resin infiltration which build a mechanical border against the cariogenic challenge [12–14]. For more advanced lesions, caries on proximal surfaces of permanent teeth mostly require operative treatment to substitute the hard tissue loss. Most studies in this direction assessed the filling material [15], but also the design of various cavity preparations has been discussed [16].

Due to the high prevalence and relevance of proximal caries [17], the aim of this review was to systematically evaluate the current state of knowledge on how to intervene in the caries process with respect to primary proximal caries in permanent teeth in adolescents and adults. This review is part of the basis for three consensus papers of ORCA and EFCD on caries treatment in children, adults and seniors.

Material and methods

In succession of the international consensus paper on “When to intervene in the caries process” [10], the question arises on how to intervene. Due to the different clinical approaches for non- and cavitated proximal lesions, this systematic review tries to answer the two following PICO questions (participants, interventions, comparisons and outcomes):

1. “How to intervene in the caries process: What is the effect of non- and minimally-invasive treatment in adolescents and adults with proximal initial caries lesions (E1: caries within outer half of enamel; E2: caries within inner half of enamel; EDJ: caries at the enamel-dentin junction) regarding caries progression?”
2. “How to intervene in the caries process: What is the effect of restorative treatment in adolescents and adults with proximal caries defects (well into dentin, cavitation) regarding survival rates (of the restoration)?”

The authors discussed the review protocol a priori. No further registration was performed as the topic was given to the authors by the joined chairs of the ORCA/EFCD consensus workshop on how to intervene in the caries process.

Search strategy

For the comprehensive search strategy, Medline was searched via PubMed for appropriate papers up to and including March 2019. The used search terms and the full search strategy are shown in Fig. 1. Titles and abstracts were screened to exclude papers not related to the topic. The remaining full-text articles were screened for eligibility and references hand-searched for additional sources. Publications on humans in English language were included.

The inclusion criteria were as follows:

- Patients: adolescents and adults, permanent dentition
- Intervention: non-, micro-invasive and restorative treatment of proximal caries lesions
- Outcome: caries or lesion progression (non-, micro-invasive), survival of restoration
- Meta-analyses, systematic reviews and in case of no studies for these high evidence levels also randomized controlled trials (RCTs) and/or cohort studies

The exclusion criteria were as follows:

- Primary teeth, occlusal caries
- Case presentations, case series
- No clinical outcomes reported
- Studies comparing different treatment techniques (e.g. selective vs non-selective carious tissue removal)
- Endodontically treated teeth

As selected, systematic reviews (see below) were based on RCTs on class I/II or load-bearing restorations in posterior permanent teeth in general; it was decided to extract data on class II restorations from the original RCTs, if possible. Furthermore, as the included systematic reviews were published between 2013 and 2018, further recent RCTs on class II restorations were searched in Medline via PubMed. Thus, the same term (Fig. 1) was used to search with the filters “randomized controlled trial” and “published in the last 5 years”.

As studies used different outcome measures, categories Charlie/Delta (U.S. Public Health Service) and 4/5 (FDI World Federation criteria) were counted as failure. In case of multiple publications (with different follow-up periods) from the same study, only data from the most recent publication were extracted.

Screening and selection

The title and abstract lists, containing 117 (non-operative/non-invasive) and 42 hits (micro-/minimally invasive) for PICO 1 and 251 hits for PICO 2, were independently assessed by three authors, respectively. Each of them screened the titles and abstracts of eligible papers regarding non-operative, micro-invasive and restorative treatment in proximal caries independently (CS/JS/AJM, AJM/AW/JS, AW/PK/CS). Papers with questionable inclusion were discussed in three telephone conferences among the authors (CS/AJM/AW/JS).

Eligible papers were read in full text by the authors especially for methodology, bias and outcome. Disagreement between the authors was resolved in additional telephone interviews. The papers that fulfilled all of the selection criteria were processed for data extraction (Fig. 1).

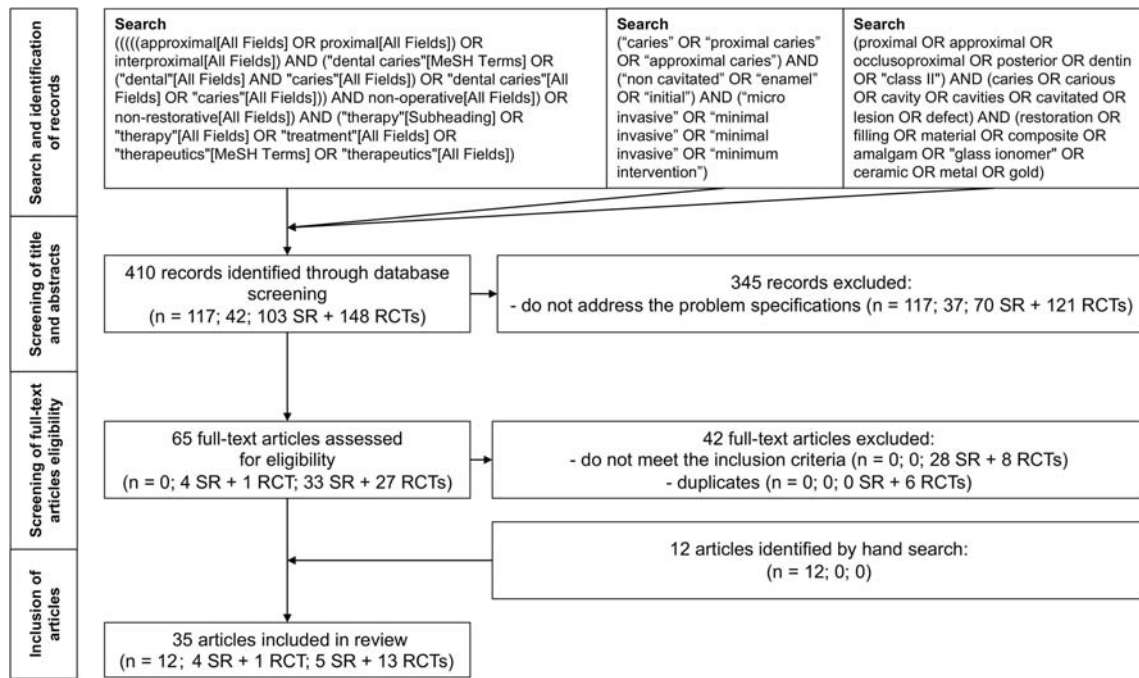


Fig. 1 Flow chart of the systematic review on how to intervene in the caries process in proximal caries in adolescents and adults (n is given separately for studies focussing on non-operative/non-invasive, minimally/micro-invasive, and restorative treatment)

Assessment of heterogeneity

The heterogeneity across studies was detailed according to the following factors as retrieved by the included literature:

- Study and subject characteristics
- Methodological heterogeneity (variability in study design and risk of bias).
- Analysis performed (descriptive or meta-analysis)
- For PICO 2, a meta-analysis was performed. Hence, Cochrane’s Q and I^2 statistics were used to assess statistical heterogeneity [18]. Publication bias was evaluated using funnel plots as well as Egger’s regression intercept test [19].

Quality assessment

The reviewer teams (CS/JS, AJM/AW, AW/PK) estimated the risk of bias by scoring the reporting and methodological quality of the included systematic reviews on operative/restorative treatment of proximal caries according to a combination of items described by the PRISMA guideline [20] for reporting systematic reviews and the AMSTAR checklist for assessing the methodological quality of systematic reviews [21].

Risk of bias of RCTs was assessed and classified according to the Cochrane guidelines [22]. For restorative treatment, (1) blinding of participants was not assessed as failure is not an outcome determined by patients, and (2) selective reporting

was determined based on missing survival data as only a minority of studies had published protocols available. A list of 27 items adopted from the PRISMA checklist [20] was assessed, and if all individual items were given a positive rating by summing these items, an overall score of 100% was obtained. Only systematic reviews including meta-analysis could achieve a full score of 100%. The estimated risk of bias was interpreted as follows: 0–40% may represent a high risk of bias; 40–60% may represent a substantial risk of bias; 60–80% may represent a moderate risk of bias; 80–100% may present a low risk of bias.

The quality assessment for the non-operative treatment of proximal caries was performed (CS/JS) according to the Newcastle-Ottawa Scale (NOS, Supplement Table 1) for assessing the quality of non-randomized studies [23].

Data extraction

Information extracted from the studies included publication details, focused question, search results, descriptive or (weighted) mean outcomes and conclusions. Disagreements between the reviewers were resolved by discussion in telephone conferences.

Outcome measures and statistical analysis

For restorative/operative treatment, the outcome was survival, i.e. restorations not needing any restorative re-intervention (replacement or repair). Random-effects meta-analyses of

pairwise comparisons between composite and different other restorative materials in class II restorations were performed using Comprehensive Meta-Analysis 3.3.070 (Biostat, NJ, USA). For all restorative materials, annual failure rates (AFRs) and (sample-size weighted) mean annual failure rates (mAFRs) were calculated according to the following formula [24]:

$$(1-y)^z = 1-x$$

where y is the mean annual failure rate; x is the failure rate; and z is the number of observation years.

Results

Non-operative/non-invasive treatment of proximal caries lesions

As no RCTs and no systematic reviews for non-operative treatment in proximal initial lesions in permanent teeth in adolescents or young adults were retrieved, two other kinds of studies were included (Fig. 1):

1. Longitudinal cohort studies analysing the progression of proximal initial lesions where various measures of non-operative caries management were administered ($n = 4$, Table 1).
2. The control cohort of the RCTs on proximal sealants or infiltrations who also received non-operative caries management for regular home care such as instructions in flossing and fluoride treatment/use for their initial control lesions ($n = 8$, Table 2).

This leads to a total of 12 eligible papers (Tables 1 and 2). Already, the oldest study [25] was aiming at alternatives for restorative treatment by evaluating the development of proximal lesions under different fluoride regimes in Swedish and US cohorts. A variety of further studies published the effectiveness of “preventive measures”, meaning non-operative/non-invasive treatment on proximal caries lesions in posterior teeth at the beginning of the 1980s [26], but mostly without randomisation or a control group. Still, the feasibility of non-operative measures, especially fluoride varnish, fluoride rinses and fluoridated toothpaste for slowing down the progression of proximal lesions, was demonstrated [27]. Similarly it was stated that the “progression through the inner half of the enamel was slower in the Swedish children than in the U.S. children, perhaps due to greater exposure to topical fluorides in Sweden” [25]. For older Swedish children, progression of the lesions through the outer and

inner part of the enamel was much slower than in younger children. Apart from age, the included studies found a clear association of lesion progression with the overall caries risk/activity of the individual. Already in the 1970s, lesions remained confined to for 4–7 years [28], and a series of studies concluded that lesion progression is not inevitably the outcome of initial carious lesions [26].

The longest follow-up of non-invasively managed proximal initial lesions was performed in Sweden with a preference for non-operative caries management [9]. In adolescents and young adults, 46% of the lesions extended into the inner enamel at baseline did not progress into dentine within a 15-year observational period. In contrast, more than 70% of the proximal caries lesion initially extending to the EDJ progressed into dentin within the first 3 years of adolescents. Lesion progression was considerably lower in premolars (11%) than molars (66%). Lesion progression is slower in young adults than adolescents: The rate of lesion progression was 2–3 times higher during adolescence (12–15 years of age) than during young adulthood (32.5 vs 10.9/100 surface years) [9].

Thus, even in adolescents, a considerable part of the initial caries lesions does not progress when treated non-operatively, especially in premolars, when limited to the enamel, or in young adults [9], while lesions at the EDJ or in molars as well as adolescents show faster progression.

These findings were confirmed by data on incidence and progression of proximal carious lesions in adolescents in Western Australia [29] which concluded that enamel lesions in proximal surfaces occur relatively rapidly, but the progression into dentine is relatively slow. Clinicians were able to assign the risk of lesion progression, and individuals residing in a water-fluoridated area showed slower lesion progression.

One of the few studies in adults examined Danish soldiers and demonstrated a relatively high progression rate of lesions over 6 years (57%) under non-operative care. This group, however, showed a poor compliance to regular flossing/tooth-stick use (18%) and also possibly a lower SES and, overall, high caries risk [30]. Non-operative treatment may be less effective in such individuals.

In the studies on proximal sealants or infiltration, non-operative measures were employed for the control teeth, but to a greatly varying extent, including oral hygiene advice and motivation as well as fluoride application (Table 2). These control groups were included in our assessment of non-operative treatments. In studies from Germany [11, 12, 14], the vast majority of enamel and even dentin lesions did not progress into a different lesion status within 3 years when treated non-operatively, and even dental subtraction radiography detected that about 60% of the lesions in young adults remained stable. Even when no improvement of plaque and gingivitis scores was observed over 3 years indicating that oral

Table 1 Summary of included studies for the review on how to intervene in the caries process in approximal caries in adolescents and adults with non-operative/non-invasive treatment

Author/year	Country	Sample	Study design	Analysis	Main results
Shwartz et al. (1984)	USA and Sweden	5 groups: Swedish gr. 1 10–11 years old, N = 100 Swedish gr. 2 17 years old, N = 99 Swedish 3 21–22 years old, N = 100 US gr. 1 117 4–17 years old US gr. 2 17–18 years old, N = 337	4–10-year longitudinal cohort study in 5 cohorts of different ages with differences in (regular) fluoride exposure (e.g. mouthrinse, topical fluoride, fluoridated water) and socio-economic status	Lesion progression on bitewing radiographs	Different lesion progressions in primary and permanent dentition; also affected by age and fluoride exposure/use. Lesion progression on in settings with fluoride exposure generally slow, taking a lesion at least 4 years to progress through the enamel of permanent teeth. Progression extremely variable between individuals and also between lesions. Fewer new enamel lesions developed on approximal surfaces during young adulthood than during adolescence; the caries incidence rates for enamel lesions decreased from 4.3 in the age group 12–15 years to 2.7 new caries lesions/100 surface years in the age group 20–27 years. Lesion progression rate of lesions extending to enamel-dentin border was 32.5/100 surface years for the youngest and 10.9/100 surface years for the oldest age group. Caries incidence of outer dentin lesions on approximal surfaces was low but increased from 0.2 in the age group 12–15 years to 0.9 new outer dentin lesions/100 surface years in the age group 20–27 years. The incidence rates varied considerably between different tooth surfaces. At the age of 26–27, the proportions of occlusal and approximal DFS were almost equal. Time to occurrence of enamel lesions in approximal surfaces relatively short while progression into dentine took longer. Clinicians were able to assign the risk of lesion progression in a child. Residence in a fluoridated area has a marked retarding effect on enamel lesion progression but not on initiation of enamel lesions.
Mejäre et al. (2004)	Sweden	536 children aged 11–13 years at baseline; 250 re-examined at age 26–27 examinations in community dental services	15-year prospective cohort study with regular non-operative caries care	Caries incidence (DFT/DFS) lesion progression on bitewing radiographs	Mean number of filled surfaces was 7.5; of which, 23% were posterior proximal. Radiographically, the mean number of proximal lesions was 5.5. Over the 6-year period, there was progression of lesions into deeper radiolucency or fillings in 57% of cases. The questionnaire showed a poor compliance with regular flossing/tooth-stick use (18%).
Arrow (2007)	Australia	157 children aged 7 within school dental service	5-year longitudinal cohort study	Lesion progression on bitewing radiographs	
Martignon et al. (2010)	Denmark	115 male 20 years old Danish recruits	6-year prospective cohort study with regular non-operative caries care	Caries incidence lesion progression on bitewing radiographs	

Table 2 Non-operative/non-invasive care provided in RCTs on minimal/micro-invasive caries treatment of proximal lesions in permanent teeth

Author/year	Study group and design	Non-operative intervention (control group)	Evaluation system	Outcome for non-operative (control group/teeth)
Martignon et al. (2006)	1.5-year split-mouth RCT on resin sealing 15–39 years old, <i>N</i> = 82 Columbia and Denmark	Instruction to floss all the proximal lesions 3 times per week	Pairwise analysis and subtraction radiography	Progression pairwise 47% and with subtraction radiography 84% progression. Compliance concerning flossing was poor (15%).
Trairatvorakul et al. (2011)	1-year split mouth RCT on sealing with glass-ionomer cement; 7–19 years old; <i>N</i> = 41, Thailand	Twice daily use of 1000 ppm sodium-fluoride dentifrice, tray application of 1.23% acidulated-phosphate fluoride gel at baseline and at 6-month recall; no flossing instructions	Blinded examiner bitewing radiograph recording of lesion depths with software	Stable mean lesion depth
Alkilzy et al. (2011)	3-year split mouth RCT on sealing with polyurethane tape; mean age 21.3 ± 5.6 years, <i>N</i> = 50, Germany	Oral home care with dental floss and fluoridated toothpaste	2 blinded examiners radiographic bitewing evaluation (D0–D4)	Only two (7%) of the control teeth with oral home care progressed
Meyer-Lueckel et al. (2012), Paris et al. (2010)	3-year split-mouth RCT on resin infiltration, placebo-controlled young adults (<i>N</i> = 22), 29 pairs of proximal caries lesions, Germany 1.5 year results	Risk-related instructions for diet, flossing and fluoridation	Radiographic bitewing evaluation digital subtraction radiography (DSR) and pairwise comparison (E1–D3)	35% progression in pairwise, 42% with digital subtraction radiography
Martignon et al. (2012)	3-year split-mouth RCT on sealant vs infiltration adult students/patients from Universidad El Bosque (<i>N</i> = 90), Columbia	Placebo treatment (non-invasive treatment unclear, but likely regular home care without specific instructions)	Pair-wise and digital-subtraction radiography	74% of lesions in outer third of dentin progressed while 64% of lesions around the EDJ progressed
Meyer-Lueckel et al. (2016)	1.5-year RCT on resin infiltration, split mouth in several private practices high caries risk children and young adults, <i>N</i> = 87; 238 pairs of proximal caries lesions, Germany	Instructions for a non-cariogenic diet, flossing and fluoridation, and individualized non-invasive interventions	Pairwise comparison of radiograph evaluated independently by 2 blinded evaluators	Progression in 58 of 186 control lesions (31%)
Arthur et al. (2018)	3-year split-mouth RCT on infiltration; high caries risk participants, <i>N</i> = 22, Brasil	Placebo infiltration (regular home care)	Radiographic pair-wise comparison	5/27 (18.5%) of control lesions had progressed no significant additional effect
Peters et al. (2018)	2-year split-mouth RCT on resin infiltration + fluoride varnish high caries risk 18–23 years old, <i>N</i> = 42, USA	Mock infiltration (placebo) + fluoride varnish	Subtraction radiography, pair-wise comparison, non-cavitated initial carious lesions (E2/D1) patient and evaluators blinded	Progression rate of 22% (7/32) in the control group

hygiene instructions and motivation may not have been effective [12], only 7% exhibited a progression in radiographic lesion scores (E1, E2, D1, D2) and 27% showed a regression, which may, however, be artefactual.

A study on adolescents in Thailand observed a progression for 7% in non-operative treatment with proximal GIC sealing, 20% regressed [31]. Again, the study failed to demonstrate that oral hygiene advice and motivation are effective to improve flossing uptake or an improvement in oral hygiene.

In contrast to this, another study [13] found the most varying results for the different assessment techniques: While the pair-wise visual comparison of the X-rays found only 47% of progression in the controls with non-operative measures

within 18 months, this increased to 84% for the subtraction radiography.

On the other hand, also 43% of the sealed lesions progressed according to the subtraction radiography which is physically not very likely. The clearly higher progression rate in the Danish/Columbian can possibly be explained with the higher caries activity in the group presenting moderate to high caries risk, while the first infiltration study employed dental students with much lower caries risk scores according to the Cariogram [32].

A “pragmatic” randomized trial in private dental practices in Germany found 31% of non-operatively treated lesions to progress after 18 months in high caries risk patients [33]. A South American study found a considerable reduction of

caries risk over 3 years and a low progression rate of 18.5% over 3 years [34].

In conclusion, when managed non-operatively, initial proximal lesion progress at a rather slow velocity which seems to allow for a non-operative approach of the training in flossing and fluoride application. In high risk and younger patients, in molars and lesions extending to the EDJ or into dentin instead of enamel may show higher progression speed making micro-invasive treatment more advisable.

Micro-invasive treatment of proximal caries lesions

For micro-invasive treatment options on proximal caries, five publications were included (Table 3). Four papers were systematic reviews and meta-analysis [35–38] and one study was a RCT [39], which was not included in the mentioned reviews.

The systematic review and meta-analysis by Ammari et al. [35] was based on ten studies (401 participants, split-mouth design), performed in primary and permanent dentition. From the included studies, seven were concluded studies [13, 30, 31, 40–43] and the others were ongoing studies with partial [44, 45] or follow-up results [46] of already published studies [14, 47]. Four of the studies were selected for a meta-analysis due to their low risk of bias. Ammari et al. [35] concluded from their results that the technique of sealing non-cavitated proximal caries seemed to be effective in controlling proximal caries in the short and medium term (up to 36-month follow-up), compared with placebo treatments or with non-operative treatment options such as flossing instruction, or use of fluoride gel/varnish (see above).

A Cochrane systematic review and meta-analysis by Dorri et al. [36] was published based on eight trials (365 participants, split-mouth design). Six of the studies evaluated the effects of micro-invasive treatments in the permanent dentition [12, 13, 31, 40, 43, 47]. The authors of this review [36] judged seven of the studies to be at high overall risk of bias, primarily due to lack of blinding of participants and personnel. The caries risk of the patients in the included studies ranged from low to high or was unknown. The available evidence showed that micro-invasive treatment of proximal caries lesions arrests non-cavitated enamel and initial dentinal lesions (limited to outer third of dentine, based on radiograph) and is significantly more effective than non-operative professional treatment (e.g. fluoride varnish) or advice (e.g. to floss). Nevertheless, due to the small number of studies, it remained unclear which micro-invasive technique offered the greatest benefit, or whether the effects of micro-invasive treatment confer greater or lesser benefit according to different clinical or patient considerations.

The systematic review and meta-analysis by Krois et al. [37] included 15 split-mouth studies. Of these studies, six were the same as in the publication by Dorri et al.

[36]. The caries risk of the patients in the included studies ranged from moderate to high or was not stated. One study compared infiltration vs sealing and found no significant difference [43]. The other studies compared the efficacy of sealing/infiltration over non-invasive treatment [12–14, 30, 31, 33–35, 40, 41, 47–50]. For a mixed analysis in primary and permanent teeth, firm evidence on the superior efficacy of either sealing or infiltration over non-operative treatment was reached. It was concluded that sealing or infiltration was likely to be more efficacious for arresting early (non-cavitated) proximal lesions than non-operative treatment [37]. The certainty of the evidence was graded as moderate. For the decision between sealing and infiltration, the authors recommended that to be guided by practical concerns beyond efficacy. It must be noted that some of the included studies were performed in primary teeth only, where most of the participants were classified as being at moderate to high risk of caries development and progression in primary teeth [30, 35, 41, 48]. Sub-analyses for primary and permanent teeth separately were not performed.

Another systematic review and meta-analysis [38] aimed to evaluate the caries-arresting effect of micro-invasive interventions for non-cavitated proximal caries for lesions of different depths. The authors included randomized clinical trials. In total, eight papers were included. All these studies were included in the publication by Krois et al. [37] as well. The subgroup analysis showed that resin infiltration and resin sealant, but not glass ionomer cement (GIC), reduce the lesion progression compared with the control (no treatment or placebo, fluoride gel or fluoride varnish). It is important to note that the use of GIC was reported in one study only [31], and while this study showed a beneficial effect of GIC, it was likely under-powered to demonstrate this with statistical significance.

Liang et al. [38] found that both sealing and resin infiltration arrest enamel lesions and those around the EDJ, while only infiltration was effective for lesions involving the dentin. Liang et al. [38] concluded that resin infiltration is effective in arresting the progression of non-cavitated proximal caries involved in EDJ, while the therapeutic effects of resin sealant for different caries depths still need to be further confirmed. The authors suggest that dentists should carefully select appropriate micro-invasive interventions according to the different depths of non-cavitated proximal caries.

A recently published randomized controlled clinical trial [39], not included in any of these reviews, demonstrated that resin infiltration was superior over non-operative standard-of-care including repeated professional F-varnish applications alone. The study was performed in a high caries risk population (cadet-candidates and cadets), and hence, the results cannot be generalized.

Table 3 Summary of included studies for the review on how to intervene in the caries process in proximal caries in adolescents and adults with minimal/micro-invasive treatment

Author/ year	Country	Sample	Study design	Analysis	Main results
Ammari et al. (2014)	Chile, Brazil, Colombia, Denmark, Germany, Greenland, Thailand, USA	401 subjects from 7 to 40 years of age Navy clinic, dental school, public health clinic	Systematic review and meta-analysis of RCTs	Lesion progression on bitewings	The results suggest that sealing non-cavitated proximal caries seems to be effective in controlling proximal caries in the short and medium term (up to 36-month follow up), compared with non-invasive treatment. The authors conclude that further long-term randomized clinical trials are necessary to increase this evidence.
Dorri et al. (2015)	Brazil, Colombia, Chile, Denmark, Germany, Greenland, Thailand	365 subjects from 4 to 30 years of age University or dental public health clinics	Cochrane review (systematic review and meta-analysis) of RCTs	Lesion progression using digital subtraction radiography (DSR)	The quality of evidence for micro-invasive treatments was moderate. It remains unclear which micro-invasive treatment is more advantageous, or if certain, clinical conditions or patient characteristics are better suited for micro-invasive treatments than others. The available evidence shows that micro-invasive treatment of proximal caries lesions arrests non-cavitated enamel and initial dentinal lesions (limited to outer third of dentin, based on radiograph) and is significantly more effective than non-invasive professional treatment (e.g. fluoride varnish) or advice (e.g. to floss).
Krois et al. (2018)	Brazil, Chile, Colombia, Denmark, Germany, Greenland, New Zealand, Thailand	486 subjects with mean ages from 6 to 27 years Dental school, public health clinics, public schools, navy clinic, practices	Systematic review and meta-analysis of RCTs	Lesion progression on bitewings	There is robust evidence that micro-invasive treatment (sealing and infiltration) is more efficacious than non-invasive treatment for arresting proximal carious lesions. Practitioners should strive to perform micro-invasive treatment instead of NI for early proximal lesions. The decision between sealing and infiltration should be guided by practical concerns beyond efficacy.
Liang et al. (2018)	Chile, Colombia, Denmark, Germany, Greenland, Thailand	303 subjects from 6.5 to 39 years of age Dental school, public health clinics, navy clinic, practices	Systematic review and meta-analysis of RCTs	Lesion progression on bitewings	Resin infiltration and resin sealant, but not glass ionomer cement (GIC), could reduce the caries progression rate. Resin infiltration is effective in arresting the progression of non-cavitated proximal caries involved in EDJ, while the therapeutic effects of resin sealant for different lesion depths still needs to be further confirmed. Dentists should carefully select appropriate micro-invasive interventions according to the different depths of non-cavitated proximal lesions.
Peters et al. (2018)	USA	42 subjects from 18 to 23 years of age Military academy	RCT	Split-mouth RCT, lesion progression on bitewings	Resin infiltration demonstrated significant adjunctive support for the management of progressing early carious of high caries risk individuals. However, longer-term evidence from clinical trials in such populations is needed.

Study outcome results and assessment of heterogeneity

The studies on the “natural” progression of initial proximal lesion under the standard non-operative caries managements such as tooth brushing with fluoridated toothpaste additional fluoride use and partially recommendations for flossing showed a mostly low progression rates and velocities in adolescents and young adults. These studies were predominantly performed in countries with advanced preventive systems such as the USA, Sweden or Australia which had experienced a general caries decline. Even under these conditions, the prevalence of proximal initial caries lesions was high [17].

The progression rate decreased clearly with age or fluoride exposure, while it increased with caries activity or risk. It was higher for lesions at the EDJ compared with solely enamel lesions and for molars than for premolars.

Even in studies on proximal caries, the willingness in participants to improve their oral self-care was very low if flossing was recommended, resulting mostly in unchanged caries risk scores, persistent low self-reporting of flossing as well as considerable plaque and gingivitis scores around the lesion. Micro-invasive treatment was effective at a moderate level of evidence. The heterogeneity of the study samples and evaluation methods was moderate, but the trends were very similar in all studies (Supplement Table 1 & 2).

Restorative treatment of proximal caries lesions

The search for systematic reviews with and without meta-analysis resulted in 103 publications (Fig. 1); out of which, 33 were selected for full text reading. Hand-searching of the reference lists revealed 6 publications that were checked for suitability. Totally, 39 publications were read in full text. Thirty-four systematic reviews were excluded, the most reviews as they were based not only on RCTs, but included also clinical trials and/or cohort studies. Finally, five systematic reviews were included in this meta-review (Supplemental Table 3). However, as these systematic reviews were based on RCTs on class I/II or load-bearing restorations in general, data on class II restorations were extracted from the original publications, if possible (Supplemental Table 4). Otherwise, these RCTs were removed.

The second search for more recent RCTs revealed 148 publications (Fig. 1); out of which, 27 were selected for full text reading. After removing publication duplicates and publications that did not meet the inclusion criteria, thirteen additional RCTs were included in this review.

Supplemental Table 3 shows the survival, AFRs and (sample-size weighted) mAFRs of posterior restorations based on the included systematic reviews. Supplemental Table 4

shows AFRs of class II restorations that were extracted from the respective RCTs.

The systematic review by Fron Chabouis et al. [51] compared ceramic and indirect composite restorations. Two studies were included, both on class II restorations. The 3-year overall failure risk was not significantly different among the materials.

The meta-analysis by Rasines Alcaraz et al. [15] on composite vs amalgam fillings for restoration of posterior permanent teeth was based on seven studies (Supplemental Table 3), but only one RCT allowed for extraction of class II restorations (Supplemental Table 4). The meta-analysis revealed that composite restorations had a significantly higher risk of failure compared with amalgam fillings. The only study that allowed for extraction of class II data was performed in children aged 8–12 years and reported a mAFR of 1.5% (amalgam) and 3.6% (composite) after 7 years (Supplemental Table 4).

The systematic review and meta-analysis by da Veiga et al. [52] analysed the longevity of direct and indirect resin composite restorations in permanent posterior teeth and found no significant difference (Supplemental Table 3). Only two studies allowed for extraction of class II restorations and found a mean mAFR of 1.8 ± 0.4 (direct composite) and 2.9 ± 1.8 (indirect composite) (Supplemental Table 4).

Schwendicke et al. [53] performed a network meta-analysis on directly placed load-bearing restorations based on 28 RCTs (Supplemental Table 3). The authors concluded that conventional and bulk-fill composites are most suitable for load-bearing posterior restorations. Also, when considering publications on class II restorations only ($n = 14$, Supplemental Table 4), sample-size-weighted mAFRs were lower for bulk-fill composites (1.1%) and conventional composites (1.5%) than for ormocers (2.3%) and siloranes (3.2%) restorations.²

The meta-analysis by Kruly et al. [54] was based on 14 studies and compared conventional composites with bulk-fill composites, silorane or ormocer restorations. Failure rates between the conventional composite and the tested materials were not significantly different (Supplemental Table 3). Considering data on class II restorations ($n = 7$, Supplemental Table 4), sample-size-weighted mAFRs amounted to 0.9% (bulk-fill composite), 2.0% (conventional composite), 2.5% (silorane) and 3.2% (ormocers).

In Supplemental Table 5, study characteristics of additional RCTs on class II restorations as well as survival and AFRs, and (sample-size weighted) mAFRs of the restorative materials, are displayed. The follow-up period of the included RCTs ranged from 3 to 30 years.

Table 4 summarizes survival, AFRs and (sample-size weighted) mAFRs of class II restorations (both extracted from systematic reviews and found by search for additional RCTs) of various materials. Bulk-fill composite exhibited lowest sample-size-weighted mAFRs and ceramic highest.

Table 4 Annual failure rates of different restorative materials in class II restorations based on RCTs found in included systematic reviews and additional RCTs

Material	N	n	Follow-up time of included studies (years)	n failure	Survival proportion ± SD (%)	AFR ± SD	mAFR ± SD	Sample-size-weighted mAFR
Amalgam	1 [5]	427	7	43	89.9	1.4	1.5	1.5
Bulk-fill composite	9 [11, 13, 18, 19, 21, 31, 36–38]	386	2–10	20	94.8 ± 7.7	1.1 ± 0.9	1.1 ± 1.0	1.2
Chemical-cured composite	2 [28, 29]	83	27–30	31	62.7 ± 0.3	1.3 ± 0.1	1.6 ± 0.1	1.6
Conventional composite	21 [5, 7, 8, 10–12, 14–16, 24–29, 32–35, 37, 38]	1481	1–30	210	85.8 ± 12.1	1.4 ± 1.4	1.5 ± 1.5	2.2
Glass ionomer-based restoration system	1 [26]	25	4	2	92.0	2.0	2.1	2.1
Indirect composite	2 [7, 8]	158	5–11	28	82.3 ± 2.1	2.7 ± 1.7	2.9 ± 1.8	2.9
Ormocer	9 [10, 12, 13, 19–22, 31, 36]	515	2–8	56	89.1 ± 7.3	2.1 ± 1.3	2.3 ± 1.5	2.2
Silorane	5 [15, 18, 20, 24, 25]	249	1–10	17	93.2 ± 5.0	2.4 ± 2.2	2.5 ± 2.2	2.5
Ceramic	3 [2, 3, 30]	112	3–10	26	76.8 ± 16.8	3.0 ± 2.0	3.5 ± 2.4	3.8

N number of included RCTs, n number of followed restorations, AFR annual failure rate, SD standard deviation, mAFR mean annual failure rate according to $mAFR = 1 - \sqrt[n]{1-x}$ (x, failure rate; z, number of observation years). In case of multiple reports of the same study, only the source with the longest follow-up was considered to avoid overlapping data

Based on this table, risk of failure between composite (control) and different restorative materials was compared by pairwise random-effects meta-analyses (Fig. 2). Composite showed a significantly higher risk of failure than amalgam (mean risk ratio 2.247; $p < 0.001$). All other materials performed not significantly different than conventional

composite. Studies focussing on the comparison between conventional composites and chemical-cured composites showed moderate heterogeneity ($I^2 = 55.8\%$). Furthermore, an asymmetric funnel plot and Egger’s regression intercept test indicate possible publication bias ($p = 0.004$; Supplemental Figure 2).

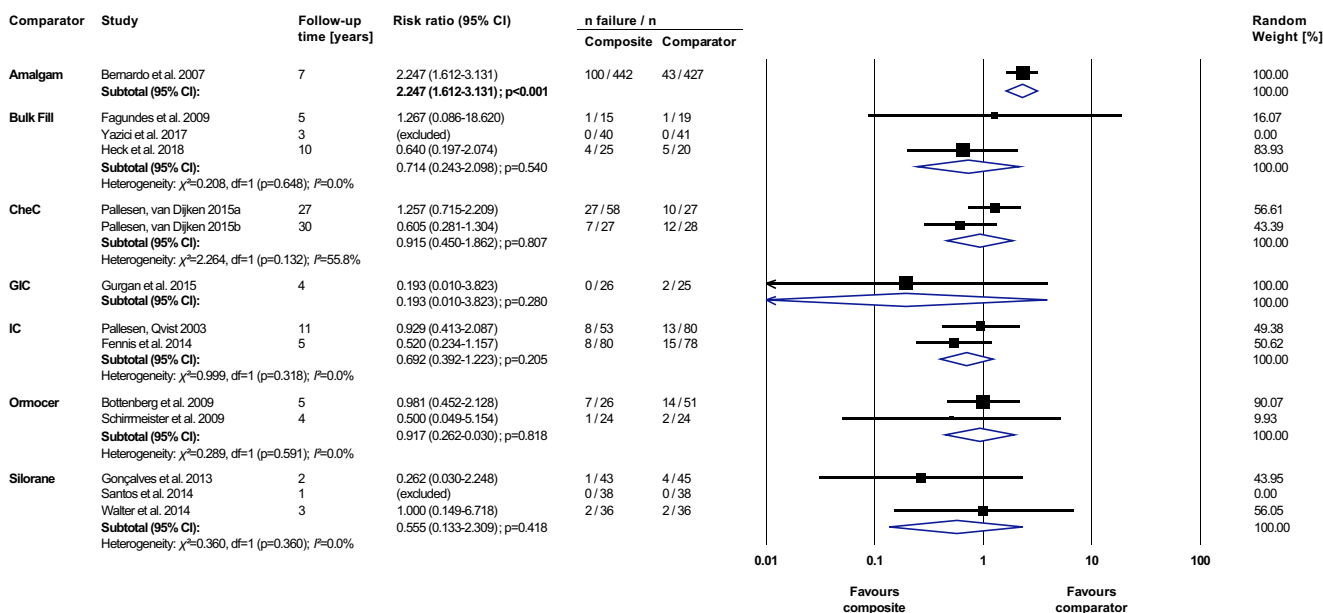


Fig. 2 Forest plots of pairwise comparison of the risk of failure between different materials (comparators) and composite in class II restorations. Risk ratio and 95% confidence interval (95% CI) of risk of failure among different restorative materials (comparators) vs the control (composite) are shown. Risk ratio < 1 indicates increased risk of failure compared with

composite. Diamonds indicate pooled effect estimates. Studies without failures (100% survival in both groups) could not be included in meta-analysis. CheC, chemical-cured composite; GIC, glass ionomer based restoration system; IC, indirect composite

Overall, considerable heterogeneity was observed in the five included systematic reviews with respect to restorative materials under analysis, the subject characteristics, and outcome measures. Furthermore, quality assessment scales and reporting of effect scores varied among the publications.

Quality assessment and grading the “body of evidence”

Estimation of the risk of bias related to the reporting and methodological quality of the included primary publications is presented in Supplement Table 1–6 and Supplemental Fig. 1. Due to the nature of mostly longitudinal cohort studies in non-operative interventions and resulting limitations, this systematic review indicates that there is low evidence to support non-operative management of proximal caries lesion (Supplement Table 1).

The more recent RCT on micro-invasive techniques and the resulting systematic reviews (Supplement Table 2) were of considerably better quality and present with a low estimated potential risk of bias. For micro-invasive treatment, there is moderate evidence of superiority over non-operative care, especially in high caries groups or lesions in molars or extending into dentin.

Regarding restorative care in cavitated proximal lesions, many studies did not report on allocation concealment leading to unclear risk of bias in this domain. Blinding of patients and/or personnel was either not reported, or it was stated that blinding was impossible due to different treatment strategies/materials. However, in these cases, the review team found the information provided insufficient to judge whether the outcome was likely to be influenced by lack of blinding (Supplement Figure 1, Supplement Table 6). Thus, there was low evidence that conventional composites show a significantly higher risk of failure than amalgams. The 5 systematic reviews and 13 recent RCTs showed varying sample size-weighted mean annual failure rates of class II restorations between 1.2 (bulk fill composite) and 3.8% (ceramic) at a low level of evidence and the limitation of no direct comparative studies between these materials.

Discussion

The prevalence of proximal lesions in adolescents and young adults remains to be high, even in low risk populations [10]. However, these lesions progress at low proportions and velocity, at least in countries with established caries preventive systems which have experienced a considerable caries decline.

The slow progression of initial lesions allows for non-invasive treatment which ideally involves improved site-specific oral home care and fluoride application.

Unfortunately, self-performed or unsupervised flossing does not seem to prevent proximal caries at least in adolescents, possibly because they do not comply. But even adults in clinical trials on proximal caries exhibit considerable and constant plaque and gingivitis around initial caries lesions, and they report a very low rate of flossing [13]. The theoretical potential of flossing could be higher as supervised, and professional flossing clearly prevents the initiation of new proximal lesions [55]. Fluorides are clearly beneficial for initial proximal lesions, as they are for the general caries process [29], and this approach was already employed in the 1970s and 1980s [25]. But even then, the poor compliance with instructions to floss regularly was detected [56].

This systematic review found several indications that the progression of proximal caries is very closely associated with the individual caries risk or activity which is also biologically plausible. Thus, it seems reasonable to restrict minimally invasive approaches to cases where non-operative caries control of initial proximal lesions has failed over time or a high caries risk cannot be reduced.

The superiority of sealants or infiltrations has been shown, although the systematic reviews and meta-analysis for micro-invasive approach on proximal surfaces included both primary and permanent teeth, mainly without sub-group analysis. Hence, the outcome and recommendations cannot be transferred to permanent dentition only and should be interpreted with care. Especially in primary molars, lesion progression is faster than in permanent molars [25] leading to an overestimation of the effect in permanent teeth or adults. Here, Mejare et al. [9] found consistently decreasing proximal caries progression with age. In addition, the individual caries risk was not taken into account for the analyses. Subjects with caries lesions were recruited in the studies representing per se a moderate to high caries activity. When this was lowered, the progression was minimal [34], while persisting high caries activity resulted in higher progression rates [13].

Almost all studies included resin sealants and resin infiltration only which does not allow sub-group analyses for the different techniques. Especially, the only study on proximal application of glass ionomer cement does not allow for a final judgement. Still, the aspects that GICs release fluoride of and proximal caries activity decreases with age give biological plausibility to this approach applying a “temporary” proximal sealant for the time at risk [31].

With regard to lesion progression which is detected radiographically, the technique of sealing or resin infiltration of non-cavitated was effective in controlling proximal caries. The overall quality of evidence for micro-invasive treatments was moderate, and a potential publication and funding bias cannot be excluded. It also remains unclear which micro-invasive treatment is more advantageous. Factors which vary in different studies are patient’s caries activity status and depth of the non-cavitated lesion (i.e. in enamel or beyond the EDJ)

and the duration of follow-up controls. These variables should be taken into account for further studies and be standardized as much as possible.

When cavitation of proximal lesion has occurred in the permanent dentition or lesions have progressed well into dentine, non- or minimally invasive approaches do not seem to be useful options, and a restorative technique should be employed. Class II restorations last long in RCTs with sample size-weighted mAFRs varying between 1.2 and 3.8% (Table 4). However, the meta-analysis of different restorative materials used for class II restorations comes along with some limitations: (1) RCTs on specific restorative materials for class II, e.g. amalgam and glass ionomer cement, are very limited, thus the risk of bias is increased. Only one 4-year RCT was included in this review comparing a glass ionomer based restoration system with a conventional composite [57]. Also, only one RCT comparing amalgam and composite in class II restorations was available [58], and no further RCT including more recently developed composite materials, e.g. bulk-fill composites, could be identified in the additional search. Also, the most recent RCT included in the systematic review by Rasines Alcaraz et al. [15] comparing posterior composite and amalgam restorations (class I and II) was published in 2007. Thus, the higher survival of amalgam compared with composite found in the RCT for class II [58] and also in the systematic review by Rasines Alcaraz et al. (for class I and II) [15] gives low-quality evidence to suggest that resin composites lead to a higher risk of secondary caries and potentially higher failure rates than amalgam. The benefits of amalgam are particularly important for countries where amalgam is still the material of choice for posterior restorations despite the global phase down of dental mercury use. Besides, some of the RCTs reported on restorative materials that are no longer available, which also limits the validity of this meta-review. (2) Survival of restorations depends on various patient-related risk factors [59–61] which were not addressed in this meta-review. Only about a quarter of the RCTs assessed the caries risk of the patients as, e.g. [62–64], showing more failures due to secondary caries in the high-risk groups. Few studies indicated that the type of restorative material might also affect the development of secondary caries, as caries as reason for failure was more frequently observed in composite than in amalgam restorations [58], especially in high-risk patients [24]. However, more recent systematic reviews demonstrated that not only caries risk, but various patient-related factors might affect survival of the restoration [60, 61]. (3) Most RCTs included not only class II restorations placed due to primary caries, but also replacement restorations of failed fillings, which are probably larger and more likely to fail (again) than newly placed restorations. A recent study [59] also showed that

restorations placed due to caries were less prone to fail than restorations placed due to fracture. In view of this, survival of class II restorations for cavitated proximal caries lesions might be even slightly better than demonstrated in the present review.

Further research

The benefit of non- and micro-invasive treatment options for initial proximal caries lesion should be assessed in clinical studies with respect to the participants' caries risk or activity and their compliance with reducing it. Also cost benefit analyses are needed for a comprehensive evaluation of the different treatment approaches in order to gain information on their efficiency rather than efficacy. Regarding the improved composite materials, their long-term effectiveness for proximal restorations should be evaluated. The emerging evidence should finally lead to an evidence and expert-based decision tree supporting dental practitioners in decision taking on how and when to intervene in proximal caries.

Conclusion

Proximal caries lesions can be managed successfully with non-operative/invasive, minimal/micro-invasive and restorative treatment depending on lesion stage and caries activity. Non-operative care should be employed mainly in adults and on enamel lesions, while micro-invasive treatment is especially suited for higher caries risk patients like adolescents and lesions extending to the EDJ or dentin. In cavitated proximal lesions, restorative treatment should be performed. Even in these cases, non-operative care for the reduction of the overall caries activity should be performed as restorations potentially fail due to secondary caries.

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Compliance with ethical standards

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Ethical approval For this systematic review, no ethical approval was needed.

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