Concept Guideline Cleft lip and/or palate

INITIATED BY
Nederlandse Vereniging voor Plastische Chirurgie/ Dutch Society for Plastic and Reconstructive Surgery

IN ASSOCIATION WITH
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Nederlandse Vereniging voor Schisis en Craniofaciale Afwijkingen
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Nederlandse Vereniging van Pedagogen en Onderwijskundigen

WITH THE ASSISTANCE OF
Knowledge Institute Federation of Medical Specialists

FINANCED BY
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Colofon

CONCEPT GUIDELINE CLEFT LIP AND CLEFT PALATE

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Members of the Working Group

Working group

A multidisciplinary guideline panel was appointed by the Dutch Society for Plastic and Reconstructive Surgery in October 2019. The guideline was initiated by the Dutch Society for Plastic and Reconstructive Surgery and they are responsible for the revisions. The guideline panel updated the guidelines cleft lip and cleft palate (counselling 'Counseling na prenataal vastgestelde schisis'(2011)' and treatment 'Behandeling van patiënten met een schisis' (2018)'). The panel consisted of representatives from all relevant specialties involved in the care for patients with cleft lip or palate. Members were mandated by their professional organizations. The panel worked on the update of the guideline for two years. The panel is responsible for the full text of this guideline.

- Dr. A.B. Mink van der Molen, MD, plastic surgeon, Universitair Medisch Centrum Utrecht, (chairman), NVPC
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Chapter General Introduction

Rationale behind the creation of this clinical practice guideline

Clefts of the lip and/or palate (CLP) are one of the most commonly occurring congenital abnormalities in The Netherlands, with a prevalence of about 16.6 per 10,000 live births per year (Luijsterburg and Vermeij-Keers, 2011). CLP differs from many other congenital defects due to the fact that effective and lasting treatment is available, which is generally finite around age 18. Children with an isolated cleft generally have the similar social chances and opportunities as children without a cleft.

Following the examples set by The United Kingdom and the Scandinavian countries, the care of CLP in the Netherlands is offered by a limited number of multi-disciplinary cleft teams. At the moment, the care offered by a cleft team usually stretches from antenatal care or care at birth to the age of approximately 22 years. Transitional care by the teams into adulthood is mandatory. Preferably cleft teams should remain available for lifetime consultation and service for their patients.

The first initiative to create this multidisciplinary guideline was made when advancement of ultra sound technology and new legislation regarding centralisation of prenatal screening in the Netherlands (Advies Wet bevolkingsonderzoek: prenatale screening op downsyndroom en neuralebuisdefecten 17 december 2007) forced cleft teams to rethink their role in prenatal counselling for CLP. Consequently, a multidisciplinary clinical guideline regarding prenatal counselling for CLP was completed in 2009. Upon completing this latter guideline in 2009, it was decided that a second guideline should be composed on the post-natal trajectory. This post-natal guideline, including several additional modules, was eventually completed and authorized in 2018.

National clinical guidelines in the Netherlands are updated every 5 years (if advancement of scientific evidence mandates such a procedure). In 2019 funds became available to update the prenatal guideline on CLP and check and extend the postnatal guideline. This provided the opportunity to combine both guidelines - the prenatal and the postnatal guideline - into one comprehensive evidence based clinical practise guideline on CLP. It will be stated per module whether it was either a newly drafted module or a revised module from an earlier version. Future updates can now be executed per module, as is in fact currently the case, as well. A new working group was formed for this new project, which was partly comprised of people who previously worked on these guidelines, as well as new representatives from various scientific associations and patient/parent groups.

Key issues were analysed prior to the establishment of both the prenatal and the postnatal guideline. The main key issue turned out to be the large variation in practices between CLP care teams, which was considered confusing and undesirable by both patients and care givers. The working group assessed the key issues again at the start of the development of this guideline. It turned out that significant practice variation between cleft teams in the Netherlands still is a point of concern.

Patients and parents recognize that differences in practices on one hand can be explained by the fact that the treatment of CLP should remain tailormade for the individual patient, yet on the other hand they experience differences in protocols between teams as frustrating as they cannot judge which protocol is best or most suitable for an individual child. For both patients and parents, it is very important that the professionals should work together to determine what they see as the scientific foundation for their medical actions and define the

standard of care the patient and parents may expect. Patient representatives from the patient organisation 'Schisis Nederland' participated in the working group and were involved in every step of the guideline development.

In summary, patients and parents have expressed their desire to identify and diminish variations in practices based on scientific evidence. Moreover, the availability of high quality and trustworthy information about treatments should be improved.

Objectives of the guideline

The aim of this guideline is to improve the care of children/patients with CLP in The Netherlands ranging from prenatal detection to young adulthood, substantiated by scientific knowledge from research where possible. 'Improving' also means providing insight in the differences in practices between CLP teams and discriminating between wanted and unwanted (i.e. scientifically based or non-scientifically based) practice variation. This resulted in proposals for a more uniform treatment. However, the lack of high-quality studies and evidence remains a serious limiting factor and forced the working group to define some conclusions in a more generalized way than was wished for at the start.

Specific attention will be given to the following aspects:

1. reducing undesirable/unfounded practice variation in the working method and treatment protocols of the Dutch cleft teams, without hampering custom work, innovation or research;
2. making objective / evidence-based information about the treatment of CLP available and accessible to healthcare providers, patients, parents and other parties;
3. determine to what extent the existing organisation of care needs to change in order to meet the requirements regarding "state of the art" treatment of a child or adult with clefts of the lip and palate and the follow-up to this treatment.

In this manner, the guideline offers a tool to create more uniform care in the field of the postnatal treatment of a child with clefts of the lip and palate and the implementation of this care in the Netherlands.

Delineation of the guideline

The guideline focuses primarily on the treatment of patients with isolated clefts of the lip and palate, including the following subtypes: a cleft lip with or without a cleft alveolus (cheilognathoschisis; cheiloschisis; CL±A), cleft lip, alveolus and palate (cheilognathopalatoschisis; CLAP) and a cleft palate (palatoschisis; CP), without other anomalies (as seen on ultrasound screening during pregnancy) in the age range from 0 to 22 years. The literature that was consulted for this guideline was limited to these categories of cleft.

The last 12 years of the Dutch national cleft registry by the Nederlandse Vereniging voor Schisis en Craniofaciale Afwijkingen (NVSCA) have yielded on average n = 323 new unoperated patients registered per year (2016). These patients can be divided as follows across the three categories of orofacial cleft: cleft lip with or without cleft alveolus (25%), cleft lip, alveolus and palate (40%) and cleft palate (35%).

Many of these recommendations will also apply to patients with clefts of the lip and palate in combination with other anomalies - whether they form part of a syndrome or not - though the recommendations may need to be adjusted per patient according to the underlying disease or situation.

A wide range of interventions and treatments related to clefts of the lip and palate take place in the period from birth to the age of 22 years. The guideline task force was forced to prioritise and to select in order to fit the amount of work within the available financial resources. The following factors were taken into consideration in the selection of the topics for this guideline:

1. The wishes from the patients' perspective regarding the need for insight into and - where possible - reduction of undesirable practice variation between cleft teams (for example, variations in feeding, the time of closure of the soft palate or the best technique to close the cleft in the alveolar arch, post-operative management).
2. The wishes from the treating physician's perspective regarding variations in treatment protocols; particularly creating insight into the differences between teams leading to an improved understanding.
3. Relevance of problems for children and parents (for example, feeding as a primary necessity of life after birth).
4. Rapid technological developments that need to be acted upon (for example, advancements in clinical genetic diagnostics).

The following list of topics will be discussed in this guideline: prenatal diagnostics and counselling, genetic diagnostics, feeding (after birth and after surgery), nase-alveolar moulding (NAM), lip and palate closure (timing and technique), dentistry, hearing problems, hypernasality (diagnostics and treatment), bone grafting procedure (timing and technique), orthodontics (ventral traction and retention), nose corrections, surgical corrections of the maxilla (orthognathic surgery), and psychosocial care. In addition, a chapter has been included in the guideline about the organisation of care for orofacial clefts in the Netherlands.

Intended users of the guideline

The guideline is primarily intended for all healthcare professionals who are involved in caring for a child with clefts of the lip and palate: general practitioners, midwives, gynaecologists, paediatricians, ENT physicians, plastic surgeons, maxillofacial surgeons, orthodontists, clinical geneticists, specialised nurses, speech therapists, (paediatric) dentists, medical psychologists, remedial educationalists and social workers. The secondary target group involves patients, parents and their surroundings.

Literature

Luijsterburg AJ, Vermeij-Keers C. Ten years recording common oral clefts with a new descriptive system. Cleft Palate Craniofac J. 2011;48:173–182.

Chapter Methods

Methodology guideline development and revision

Validity

The Board of the Dutch Society for Plastic and Reconstructive Surgery (NVPC) will assess whether this guideline module is still up-to-date in 2026 at the latest. If necessary, a new guideline panel will be appointed to revise the guideline module. The validity of the guideline or modules of the guideline may lapse earlier when new developments arise. As the holder of this guideline, the NVPC is chiefly responsible for keeping the guideline up to date.

Responsible party[1]	Year of autorisation	Next assessment of actuality guideline[2]	Frequency of assessement of actuality[3]	Supervising party of actuality[4]	Relevant factors for changes in recommendations[5]
NVPC	2021	2026	every 5 years	NVPC	None

[1] Responsible party for the module
[2] maximum of 5 years
[3] half a year, every (other, ..) year
[4] supervising party or parties
[5] Current reseach, changes in organizations/restitions, new available rescourses

Other scientific organizations participating in the guideline or users of the guideline share the responsibility to inform the chiefly responsible party (NVPC) about relevant developments within their fields.

Authorization

This guideline module is authorized by:
(Wordt toegevoegd na de autorisatiefase)

General details

The revision of this guideline module was supported by Knowledge Institute Federation of Medical Specialists (www.kennisinstituut.nl) and was financed by the Quality Foundation of the Dutch Medical Specialists (SKMS). The funding organization did not have any influence on the content of the guideline in any way.

Declaration of interest

According to the KNMG-code, all panel members have declared in writing if, in the last five years, they have held a financially supported position with commercial businesses, organisations or institutions that may have a connection with the subject of the guidelines. Enquiries have also been made into personal financial interests, interests pertaining to personal relationships, interests pertaining to reputation management, interests pertaining to externally financed research, and interests pertaining to valorisation of knowledge. These Declarations of Interest can be requested from the secretariat of the Knowledge Institute of Medical Specialists. See below for an overview.

Member	Profession	Side jobs	Declared conflicting interests	Actions
Dr. A.B. Mink van der Molen	plastic surgeon,	None	None	No actions
Dr. M.F. van Dooren	clinical geneticist	Vicepresident VKGN	None	No actions
Dr. M.J.H. van den Boogaard	clinical geneticist	None	None	No actions
Dr. L.N.A. van Adrichem	plastic surgeon	DGA van Adrichem Medical B.V. Chairman Concilium plastico chirurgicum Member Raad Opleiding Member BBC NVPC Advisor Hoofdmaatje Chairman Medical Council Equipe Zorgbedrijven Member Medicatie Commissie Equipe Zorgbedrijven Member stuurgroep STW project TU-Twente	None	No actions
Dr. H.F.N. Swanenburg de Veye	psychologist	None	None	No actions
Dr. C.J. Bax	gynaecologist	Volunteer hospice Member NIPT consortium Member committee quality documents NVOG Secretary committee Otterlo NVOG Treasurer working group infectious diseases NVOG	None	No actions
Dr. C.C. Breugem	plastic surgeon		None	No actions
Drs. F. Bierenbroodspot	Oral and maxillofacial surgeon	Working Group Esthetische Aangezichtschirurgie	None	No actions
Drs. M. Haasnoot	paediatrician	None	None	No actions
Dr. J. de Gier	otolaryngologist	Board member NVSCA	None	No actions
Dr. M. Kuijpers	orthodontist	Guideline committee Mondzorg voor jeugdigen preventie diagnostiek behandeling	None	No actions
Dr. M. Nienhuijs	Oral and maxillofacial surgeon	Boardmember NVSCA	None	No actions
Dr. D. de Haan	patient representative,	Teacher/ education advisor HU-PABO, Hogeschool Utrecht	None	No actions

Patient involvement

Patients were represented by Schisis Nederland. Schisis Nederland is an independent organization representing patients with a cleft lip and palate and their parents in the Netherlands. Representatives from Schisis Nederland participated in the guideline panel. The concept guideline module was presented to Schisis Nederland for their comments.

Implementation

Guideline implementation and practical applicability of the recommendations was taken into consideration during various stages of guideline development. Factors that may promote or hinder implementation of the guideline in daily practice were given specific attention. The

guideline is distributed digitally among all relevant professional groups. The guideline can also be downloaded from the Dutch Society for Plastic and Reconstructive Surgery website: www.nvpc.nl, and the guideline website: www.richtlijnendatabase.nl. The implementation table can be found in the related products.

Methods and proces

AGREE

The guideline has been drafted in accordance with the requirements outlined in the 'Guidelines 2.0' report of the Guideline Advisory Committee of the Council on Science, Education and Quality (WOK). This report is based on the AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II) (www.agreecollaboration.org), an instrument designed to assess the quality of guidelines with broad international support (Brouwers, 2010). The development of a evidence-based guideline module is described step-by-step in "Ontwikkeling van Medisch Specialistische Richtlijnen" of Knowledge Institute for Medical Specialists.

Inventory of the problem areas

During the preparation phase the working group used an inventory to find the problem areas. A report of this inventory can be found in the related products.

Primary questions and outcome measures

Based on the outcomes of the bottleneck analysis, the president and advisor formulated draft primary questions. These were discussed and defined together with the guideline panel. Subsequently, the guideline panel determined which outcome measures were relevant for the patient for each primary question, examining both desired and undesirable effects. The guideline panel valuated these outcomes based on their relative importance as crucial, important and unimportant.

Literature search and selection strategy

Specific search terms were used to identify published scientific studies related to each individual primary question in electronic databases like Medline, Cochrane, and Embase. Additionally, the references of the selected articles were screened for additional relevant studies. Studies offering the highest level of evidence were sought out first. Panel members selected articles identified by the search based on predetermined criteria. The selected articles were used to answer the primary question. The searched databases, the search string or terms used during the search and selection criteria applied are listed in the chapter for each individual primary question.

Quality assessment of individual studies

Individual studies were assessed systematically based on predefined methodological quality criteria in order to assess the risk of biased study results. These assessments may be found in the column 'Study quality assessment' in an evidence table.

- AMSTAR - voor systematische reviews.
- Cochrane - voor gerandomiseerd gecontroleerd onderzoek.
- ACROBAT-NRS - voor observationeel onderzoek.
- QUADAS II - voor diagnostisch onderzoek.

Summary of the literature

The relevant study results from all selected articles were presented clearly in evidence tables. The key findings from the literature are described in the literature summary. If

studies were sufficiently similar in design, data were also summarized quantitatively (meta-analysis) using Review Manager 5.

Assessment of the level of scientific evidence

With regard to intervention questions, the level of scientific evidence was determined using the GRADE method. GRADE is short for 'Grading Recommendations Assessment, Development and Evaluation' (see http://www.gradeworkinggroup.org/)

GRADE distinguishes four grades of quality of evidence, i.e. high, moderate, low and very low. These grades indicate the degree of confidence in the conclusions in the literature (see http://www.guidelinedevelopment.org/handbook/).

GRADE	Definition
High	• There is a high degree of confidence that the true effect of treatment is very close to the estimated effect of treatment as reported in the conclusion in the literature. • It is very unlikely that the conclusion drawn in the literature will change if further research is done.
Moderate	• There is a moderate degree of confidence that the true effect of treatment is very close to the estimated effect of treatment as reported in the conclusion in the literature. • It is possible that the conclusion drawn in the literature will change if further research is done.
Low	• There is a limited degree of confidence that the true effect of treatment is very close to the estimated effect of treatment as reported in the conclusion in the literature. • It is probable that the conclusion drawn in the literature will change if further research is done.
Very low	• There is little confidence that the true effect of treatment is very close to the estimated effect of treatment as reported in the conclusion in the literature. • The conclusion is very uncertain

According to the GRADE methodology the clinical decision threshold should play an important role in assessing the level of evidence (grading) in guidelines (Hultcrantz, 2017). To set the threshold all critical outcomes, and the considerations should be determined. The clinical decision threshold is not exactly the same as the Minimal Clinically Important Difference (MCID). In situations in which an intervention has no important disadvantages and low costs, the clinical decision threshold with regard to the efficiency of an intervention can be lower (closer to zero/ no effect) than MCID (Hultcrantz, 2017).

Formulation of conclusions

For interventions, the conclusion does not refer to one or more articles, but is drawn based on the body of evidence. The guideline panel looked at the net benefits of each intervention. This was done by determining the balance between favourable and unfavourable effects for the patient.

With regard to questions about the value of diagnostic tests, harm or adverse effects, aetiology and prognosis, the scientific evidence is summarized in one or more conclusions, listing the level of evidence for the most relevant data.

Considerations

When making recommendations, scientific evidence was considered together with other key aspects, such as expertise of the panel members, patient preferences, costs, availability of facilities and/or organizational aspects. Insofar as they are not part of the systematic literature review, these aspects are listed under 'Considerations'. The considerations are written using a structured format based on the evidence-to-decision framework of the international GRADE Working Group, and part of the GRADE methodology.

Formulation of recommendations

Recommendations provide an answer to the primary question and are based on the best scientific evidence available and the most important considerations. The level of scientific evidence and the importance given to considerations by the guideline panel jointly determine the strength of the recommendation. In accordance with the GRADE method, a low level of evidence for conclusions in the systematic literature review does not rule out a strong recommendation, while a high level of evidence may be accompanied by weak recommendations. The strength of the recommendation is always determined by weighing all relevant arguments.

Preconditions (Organisation of care)

In the analysis of problem areas, the organisation of care (all those aspects that are preconditions for the provision of care) were explicitly taken into account. These aspects include coordination, communication, materials, financial means, work force and infrastructure. Preconditions that are relevant to the answering of a specific clinical question are part of the considerations related to that specific question.

Knowledge gaps

During the development of this guideline, systematic searches were conducted for research contributing to answering the primary questions. For each primary question, the guideline panel determined whether (additional) scientific research is desirable.

Commentary and authorization phase

The draft guideline was submitted to the (scientific) organizations involved for comment. The guideline was also submitted to the following organizations for comment: Dutch College of General Practitioners (NHG), Healthcare Insurers Netherlands (ZN), The Dutch Healthcare Authority (NZA), the National Health Care Institute (ZINL), the Health Care Inspectorate (IGJ), Dutch Organisation of Hospitals (NVZ), Dutch Federation of Academic Hospitals (NFU), Dutch Organisation of Independent Clinics (ZKN), the Netherlands Patients Federation, Dutch Organisation of nurses and caregivers (V&VN), Dutch Association of Physician Assistants, and Collaborating Top Clinical Training Hospitals (STZ). Comments were collected and discussed with the guideline panel. The draft guideline was updated and finalized by the guideline panel based on the comments. The final guideline was submitted for authorization to the (scientific) organizations involved and authorized or approved by them.

Literature

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Module 1 Diagnostic genetic testing

Clinical question

What is the yield of the different genetic tests in isolated clefts of the lip and palate?
Wat is de opbrengst van verschillende genetische testen bij patiënten met geisoleerde lip- en palatumschisis?

Introduction

A cleft of the lip and/or palate (CL/P) is a congenital abnormality with a complex etiology and a broad spectrum of causes consisting of - among other factors - chromosomal abnormalities, several gene mutations, teratogens, nutritional deficiencies and infections during pregnancy (Dixon, 2011; Leslie, 2013; Conte, 2016).

CL/P is often an isolated condition but can be associated with multiple congenital anomalies, development delay and/or be part of a syndromic diagnosis. More than 275 syndromes have been described in which CL/P is a characteristic symptom (Setó-Salvia, 2014). Depending on the underlying cause, monitoring for specific features might be required. (Maarse, 2012; Setó-Salvia, 2014).

Therefore, recognition of a syndromic/genetic cause for the cleft is important for tailored and personalized care and long-term management, but also crucial for accurate genetic counselling. The recurrence risk for non-syndromic and syndromic cleft can differ considerably.

However, it might be difficult to distinguish syndromic and non-syndromic orofacial clefts. The abnormalities associated with syndromic orofacial cleft are not always recognizable, or only appear at a later stage (van der Veen, 2006; Rozendaal, 2012, Setó-Salvia, 2014). Rittler (2011) reported that 7 to 9 % of the orofacial clefts that are initially thought to be isolated cases are found to have associated abnormalities. Furthermore, various known “syndromic” orofacial cleft genes can also be responsible for non-syndromic orofacial clefts (Jezewski, 2003; Leoyklang, 2006; Leslie, 2015a and b, Moreno, 2009; Rahimov, 2012, Setó-Salvia, 2014, Brito, 2015).

At present, there are various options for genetic testing to obtain a diagnosis, including targeted gene testing, gene panel analysis, Whole Exome (and Genome) Sequencing and CNV analysis and in specific cases methylation assays.

However, the optimum strategy for genetic testing, considering the clinical impact, effect on treatment outcomes and benefit for patients and parents, still has to be determined.

Search and select

A systematic review of the literature was performed to answer the following question:

What is the effect of different genetic tests in isolated clefts of the lip and palate on the diagnostic yield in isolated clefts of the lip and palate?

P: patients with isolated cleft lip and/or palate or pregnant women undergoing prenatal screening for cleft lip and/or palate in their child;
I: diagnostic genetic tests (copy number variant (CNV) analysis (e.g. array comparative genomic hybridization (CGH), SNP array, CMA), next generation sequencing, e.g. gene panels, whole exome sequencing);
C: comparison of the tests above;

R: long term follow-up of children with apparently isolated cleft to identify late onset features an underlying genetic/ syndrome diagnose;
O: yield, sensitivity, specificity, diagnostic accurateness.

Relevant outcome measures
The guideline development group considered yield as a critical outcome measure for decision making. The yield of a diagnostic test is defined as the ability to identify underlying genetic variants as cause of CL/P. Sensitivity, specificity, and diagnostic accurateness were considered as important outcome measures for decision making. The working group considered a sensitivity or specificity above 80% as sufficient.

Search and select (Methods)
The previous module on genetic testing in the 2018 edition of the guideline was based on expert opinion and did not provide a systematic search. The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 13th of February 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 165 hits. Studies were selected based on the following criteria: patient population consisting of children (< 18 years) with CL/P (both syndromic and non-syndromic) and first-degree relatives (parents or siblings), or pregnant women of a child with possible CL/P. The intervention was a diagnostic genetic test: copy number variant (CNV) analysis (for example array comparative genomic hybridization (CGH), SNP array, CMA), next generation sequencing, e.g. gene panels, whole exome sequencing). Eight studies were initially selected based on title and abstract screening. After reading the full text, these eight studies were excluded since they did not compare diagnostic tests (see the table with reasons for exclusion under the tab Methods). Thus, no studies were selected for the literature summary.

Results
No studies were found that compared the yield and benefit of the genetic test and provided insight into the total yield, sensitivity, specificity, and diagnostic accurateness of these different tests.

Conclusions
No conclusions could be drawn based on the literature.

Considerations
Advantages and disadvantages of diagnostic tests
Despite no studies were found in which the yield of different diagnostic tests in isolated clefts of the lip and palate has been compared, studies do provide information about the different diagnostic genetic tests.

In general, the diagnostic tests could be divided into two types; array-based methods (identifying minor chromosomal anomalies; microdeletions and microduplications) and sequencing methods (identifying gene variants).

Copy number variant analyses (invasive genetic testing)
Large structural alterations of the genome and deletions and duplications of genomic regions termed copy number variations (CNVs), have been studied in CL/P patients using classical genetic analyses such as FISH, array CGH or, more recently, SNP arrays (Conte, 2016). Also, some studies mention karyotyping; identifying numerical and large

chromosomal anomalies. However, small microdeletions and - duplications will be missed by conventional karyotyping.

Maarse (2012) conducted a systematic review to provide a basis for prenatal invasive diagnostics by investigating the prenatal and postnatal prevalence of associated anomalies and chromosomal defects related to CL/P. They provided a systematic search and used data from the Dutch Oral Cleft Registry to investigate the prevalence of associated anomalies and chromosomal defects both prenatal and postnatal. This review also provided recommendations for diagnostic genetic testing for different types of CL/P. This review included 20 studies: 3 prenatal, 13 postnatal and 4 combined. This review concluded that array CGH should be considered in case of isolated oral cleft lip on prenatal ultrasound, because the absence of associated anomalies does not exclude the possibility of the presence of an underlying chromosomal defect. The chance of finding chromosomal deficits seems to depend on the type of CL/P. For example, in presumed isolated CLP or CP array-based methods are recommended. However, it should be taken into account that genetic techniques included in the review of Maarse (2012) are nowadays at least (partially) replaced by newer diagnostic genetics tests.

The study of Szczaluba (2015) assessed the utility of array comparative genomic hybridization in 53 Polish newborns with presumed isolated CL/P. Szczaluba identified 8 unique CNVs in a total of 8/52 patients (15%) using array CGH, including 3 deletions and 5 duplications. The largest rearrangement could be confirmed by karyotyping.

The study of Cao (2016) highly recommends chromosomal microarray analysis (CMA) in prenatal invasive genetic testing, not only for syndromic oral cleft cases but also for non-syndromic cases with soft markers in ultrasound (such as a single umbilical artery). CMA is a variant of array CGH/ SNP array method. The CMA analysis showed an improved detection rate of 15.3% for pathogenic copy-number variants compared with 10.5% for conventional chromosome analysis. Candidate genes including *CRKL, AKAP8, SYDE1, BRD4* are worthy of further investigation regarding their role in human palatogenesis.

In the study of Conte (2016) 45 potential candidate genes for deletions and 27 for duplications were found, including several known causative genes for CL/P, such as *SATB2* and *MEIS2*, and genes that are associated with CL/P or development of CL/P. This study found 34 deletions and 24 duplications in genes that have not previously been associated with CL/P.

Genetic testing policy in the prenatal setting slightly differs among clinical genetic centers. The first approach is to start with Quantitative Fluorescence-Polymerase Chain Reaction QF-PCR (this technique detects the presence of additional chromosomes (aneuploidy, e.g of chromosome 13,18 and 21 and sex chromosome aneuploidy), followed by SNP array in case of a normal QF-PCR result. Another approach is to start directly with SNP array. The resolution of the SNP array itself is set for 0,15 Mb, however there can be differences between centers.

<u>Next-generation sequencing methods</u>

Next-generation sequencing methods like whole exome sequencing (WES) in family-based designs offer important advantages for identifying gene variants causing complex and heterogeneous disorders like CL/P (Bureau, 2014, Basha, 2018).

Bureau (2014) conducted a study with WES to search for variants causing CL/P using affected relatives from 55 multiplex families. Rare single nucleotide variants (SNVs), detected with WES, shared by affected relatives in 348 recognized candidate genes were examined. These 348 candidate genes consisted of 334 autosomal candidate genes for oral clefts (Jugessur, 2009) plus 14 recently confirmed genes and regions yielding genome-wide significance in a meta-analysis (Ludwig, 2012) and a replication study (Beaty, 2013). Bureau (2014) found five novel and potentially damaging SNVs shared by affected distant relatives (*CDH1, FGF8, FGFR4, TRPS1, FTCD*). One damaging SNV in *CDH1* was shared by three affected second cousins from a single family, indicating that this SNV is very unlikely to occur by chance alone.

The study of Basha (2018) also reports on gene variants causing syndromic CL/P using WES. They tested a cohort of 84 individuals diagnosed with non-syndromic CL/P from multiplex families (n=46) to find rare variants in genes causing syndromic CL/P. Patients included in this study had a normal karyotype, the majority had been tested for for a 22q11.2 deletion and an*IRF6* mutation (Van der Woude syndrome). Patients were diagnosed with bilateral CLP (n=7), unilateral CL/P (n=16), unilateral cleft lip (CL)(n=8), cleft palate (CP)(n=33), CP-posterior (n=7), submucous cleft palate (SMCP)(n=2), SMCP with bifid uvula (n=2) and velopharyngeal insufficiency (n=9). Genetic variants were analyzed independently in each family and each subject. The following four mutations were found in four different genes in five patients: *TP63* (1 family), *TXC1* (one family), *LRP6* (one family) and *GRHL3* (two families). The four mutations co-segregated with the oral cleft in an autosomal dominant manner in all families. This study shows that patients diagnosed with isolated CL/P still can carry a mutated gene causing the CL/P, whole-exome sequencing (WES) / next generation sequencing is therefore recommended when there is a family history with CL/P (Basha, 2018). In 10% of the patients with non-syndromic CL/P with a positive family history a causative Mendelian mutation could be identified. It could be that in an important percentage of the remaining cases, the same genes are involved due to an indel or copy number alteration (CNVs) not easily detectable by WES. Whole genome sequencing will therefore likely be the best choice for diagnostic screens of families with a history of non-syndromic CL/P (Basha, 2018).

WES is increasingly used in the Netherlands in both isolated as syndromic CL/P. In the Netherlands, however several strategies are used in different centers. At first, a cleft gene panel analysis CL/P based on WES can be done. When multiple congenital anomalies are present, analyses of all OMIM morbid genes (based on WES) or a complete trio WES with analyses of the total exome (open exome) can be performed. In trio WES analyses DNA of the parents are included. These tests are offered in a postnatal, but also in a prenatal setting. Gene panels do have differences regarding content, and also filtering (single versus trio analysis) and classification of variants can differ among centers.

Methylation assays to identify specific imprinting disorders can be performed when a specific syndromic diagnosis is suspected. Also, genome wide methylation tests (Episign ©) can be offered to confirm a suspected diagnosis, associated with a specific methylation profile (Aref-Eshghi, 2019; 2020).

Recently, a retrospective study was performed for the diagnostic yield of a WES based cleft gene panel n UMCU (unpublished data). The yield of the gene panel analysis was evaluated from 2015-2020. In this period the gene panel was updated, and the number of genes included in the gene panel is expanded (156 to 195 cleft related genes) (https://www.umcutrecht.nl/nl/next-generation-sequencing-ngs).

In this study 212 CL/P patients were included. Most genetic tests were done for CP (103, 48.6%), followed by CLP (77, 36,3%) and CL (25, 11,8%). In 7 cases (3.3%) cleft type was not defined. All cases underwent the WES- based cleft gene panel analyses and in some cases additional genetic testing (for example ID gene panel, mendeliome or trio WES) was performed.

In this study cleft gene panel analyses revealed a genetic (syndromic) diagnose, by identification of a pathogenic variant (P) and clinical confirmation of the diagnosis in 11.3 % (24/212) of the cases. In (3.8 % (8/212) a causative genetic diagnosis was confirmed by additional genetic testing.

Most genetic diagnoses could be confirmed in CP cases (50 %, n=16); versus CL(A)+P) (40.6 %, n=11) and CL (9.4 %, n=3). In one case the cleft type was not defined.

We realize this retrospective inventory probably reflects the outcome of a biased population, because in general practice genetic testing is probably more often performed in children with additional minor or major anomalies or congenital abnormalities and in cases with a positive family history for clefting.

Based on literature and the study conducted by UMCU, which showed that (complex) genetic testing can be used to diagnose rare disorders, the advice is to refer all children with CL/P to a clinical geneticist for an extensive medical and family history, specific physical examination and dysmorphological evaluation of index and their parents (see attachment "intakeformulier", in Dutch). When considering genetic testing, it is important to bear in mind the type of cleft and the presence of additional morphological anomalies and / or positive family history and also take into account whether it is a prenatal or postnatal case.

Although broad genetic testing can prevent a long *Diagnostic Odyssey* one should realize that most studies are performed in a biased population and further research is necessary to identify those children in which genetic testing will have most benefit.

It is also important that the clinical impact and effect on treatment outcomes of the genetic diagnosis will be further studied.

<u>Values and preferences of patients and their parents or guardians</u>

Both prenatal and postnatal diagnosed CL/P patients and their parents should be offered referral to a clinical geneticist with, if there is consent, diagnostic genetic testing, in addition to medical, genetic and psychological counselling. However, there is an essential difference between prenatal and postnatal CL/P.

It is of great importance that genetic testing is based on shared decision making and personalized medicine, where clinicians (clinical geneticist, gynaecologist, and/or plastic surgeon) and patients work together to make individual decisions about invasive prenatal diagnostics and the choice of the genetic test. In this process the outcome is based on clinical evidence and expected outcomes with inclusion of parents' preferences and values.

Parents should be informed about all options of genetic testing with the pro and cons, including information on incidental findings, and the possibilities of advanced ultrasound research.

Professionals should realize that some parents do not prefer invasive prenatal testing when a CL/P is observed in an unborn child and individual considerations of pregnant couples can differ enormously. Also, religion can play a significant role in the decision-making process. However, referral of parents with a fetus with CL/P to a clinical geneticist is important to discuss the options for further clinical genetic testing and outcomes of these tests.

Guidance of parents in this process is of great importance. Moreover, some parents might be confronted with a severe (lethal) disorder in their child and have to decide on continuation or termination of pregnancy. However, it is also possible that a clinical genetic diagnosis helps in making a decision for optimal peri- and postnatal care.

Parents should also be informed about their recurrence risk and options for future pregnancies, e.g. preimplantation genetic testing (PGD). Furthermore, it is important that parents are aware of their right to get a second opinion and they can contact patients organizations for more information and empowerment, for example: www.schisisnederland.nl, www.erfelijkheid.nl.

Costs/Finances

With clinical application of whole-exome and whole-genome sequencing, a diagnosis could be made earlier, also in initially presumed isolated cleft cases, and Diagnostic Odyssey can be avoided, which will lead to reducement of costs. Due to the introduction of broad genetic testing, fewer genetic tests will be performed sequentially.

The Dutch Health Council indicates that early diagnosis is extremely important and should be used instead of introducing heel prick screening for untreatable conditions. The main benefit is early recognition of a genetic diagnosis. Knowing the right diagnosis, optimal care can be provided to patients and their parents. Also, parents can be informed about risks of recurrence.

Knowing the genetic origin will lead to better treatment and timely interference for possible future symptoms related to their genetic disorder. Moreover, early diagnosis prevents a Diagnostic Odyssey with unnecessary second opinions and diagnostic tests and can thus limit the negative consequences for the well-being of the child and the parents.

On the other hand, an early diagnosis can also be stressful for the parents, while it may take a long time for symptoms to arise. Also, the clinical spectrum of certain diagnoses can be broad, which can create uncertainty.

DNA testing in the Netherlands is totally reimbursed by the basic insurance, however, the mandatory excess will be paid first. It is important that patients are informed about this.

The actual cost-effectiveness of genetic testing cannot be determined until the yield of genetic testing has been determined in a unbiased population, and follow-up studies have been performed to analyse the effect of a specific diagnosis, taking into account the quality of life of people with CL/P and their parents.

Acceptance, feasibility and implementation

Nowadays, genetic counselling and testing is offered although it is not always used) to (future) parents when a cleft lip has been diagnosed in both prenatal and postnatal settings. We have inquired at our eight genetic centres which policy they currently used and despite variations they all at least offered the possibility of genetic testing. Depending on personal,

cultural, and familial considerations and possible consequences, parents can decide which testing will be performed. This decision should be made on accurate information, therefore shared decision making and counselling is essential, and even more important than diagnostic outcome.

To increase quality of care for patients with a cleft lip/palate the ICHOM measurement and the NVCA database have been implemented. Ideally, genetic data should also be added to this quality system. Diagnostic genetic tests are performed in several accredited genetic laboratories with their own genetic testing strategies and way of classifying variants.

It would be desirable to have a national database for all genetic data in CL/P patients in which phenotype and both pathogenic variants as well as variants of unclear significance (VUS) can be documented and also a national discussion group in which cases with CL/P with genetic variants can be discussed. Privacy issues and government rules are complicating factors in implementation of such a database. Moreover, splitting up of the genetic data of isolated CL/P may be important.

Recommendations/Aanbevelingen

Aanbeveling voor de arts/professional die schisis vaststelt

Rationale

The literature study and the inventory of the outcome of genetic analyses in a Dutch cleft population demonstrates genetic testing can identify (extreme) rare genetic disorders.

Knowing the genetic origin of the cleft can lead to better treatment and timely interference for possible future symptoms. Furthermore, identifying the genetic diagnosis can influence the recurrence risk of a cleft for the parents and/or offspring of the affected individual. However, clinical practice also learns genetic analyses can be associated with uncertain outcomes and unsolicited findings which can be difficult to interpret. Furthermore, parents can be confronted with an uncertain diagnosis, one with a broad clinical spectrum, or a diagnosis with a bad prognosis.

Therefore, it is recommended to refer parents of a child with a cleft to a clinical geneticist for genetic counseling and genetic testing. Consequently, parents can be informed about the pro and cons of genetic testing. The choice of performing genetic testing should be made in a process of shared decision making.

The interpretation of and the outcome of a genetic test should be performed in close collaboration with the clinical and molecular geneticist, gynecologist and/or pediatrician/plastic surgeon involved.

Aanbevelingen-1

Bespreek met ouders van iedere patiënt (geboren/ongeboren) met een schisis de mogelijkheid van verwijzing naar een afdeling klinische genetica, bij voorkeur in een schisis expertisecentrum.

Houdt bij een prenataal vastgestelde schisis rekening met zwangerschapsduur in relatie tot de uitslagtermijn voor genetische diagnostiek en keuzes rondom continuering danwel terminering van de zwangerschap. Bij een sterke verdenking op een trisomie 13, 18 is met een QF-PCR binnen enkele dagen een uitslag te realiseren.

Bespoedig de verwijzing bij een postnataal vastgestelde schisis naar een klinisch geneticus indien sprake is van bijkomende problemen zoals groei- en voedingsproblemen, geassocieerde afwijkingen, ontwikkelingsachterstand, specifieke verdenking op een syndroomdiagnose en/of chromosoomafwijking.

Aanbeveling voor de klinisch geneticus/medisch specialist

Rationale

The type of cleft, the presence of possible additional minor and major anomalies or abnormalities and the family history are important factors in deciding to do genetic testing, as well as whether the diagnosis has been made prenatally or postnatally. Therefore, it is our recommendation to use an extensive and structured history and physical exam, specifically focusing on possible cleft syndromes or underlying genetic etiology including inspection of the oral region of both parents (high palate, bifid uvula) and possible additional ectodermal features (for example hypodontia, oligodontia, nail dysplasia, pigmentation abnormalities) or lymphedema.

One should be more reluctant to perform genetic testing in a child with an isolated cleft lip and a negative family history. Most studies showed that CL/P and CP are more often associated with an underlying genetic cause. On the other hand, also in cases with isolated CL a genetic disorder can be identified.

One should realize sequential DNA testing can be associated with increased costs and extensive DNA testing might increase the chance detecting variants of uncertain (or unknown) significance or unsolicited findings. In addition, an important aspect to keep in mind by using next-generation sequencing technologies such as WES trio analysis, is that autosomal dominant gene variants with a reduced penetrance (e.g.*CDH1, IRF6, SIX3*) segregating in a family, might be filtered out in the data analyses.

It is important that parents are informed about the different aspects of DNA testing, as yield for different cleft type, broad spectrum of cleft syndromes, variablility in severity of those syndromes even within families that might be identified and the possible identification of variants of uncertain (or unknown) significance. Parents should be informed about their recurrence risk and possible choices concerning future pregnancies.

Aanbevelingen-2

1

Vraag een anamnese en familieanamnese uit gericht op schisis volgens het intakeformulier (zie bijlage intakeformulier).

2

Verricht een uitgebreid lichamelijk en dysmorfologisch onderzoek bij patiënt en ouders bij vastgestelde schisis en maak klinische foto's van patiënt en ouders (zie bijlage checklist).

3

Bespreek met ouders/patiënt de optie van genetische diagnostiek en dat de opbrengst van genetische diagnostiek kan afhangen van type schisis en andere bijkomende aangeboren afwijkingen en belaste familieanamnese.

4

Bespreek met ouders/patiënt de mogelijkheden van eventueel onduidelijke uitslagen of nevenbevindingen en vul gezamenlijk een informed consent voor genetische diagnostiek in.

5

Verricht bij een zuigeling met schisis, met de verdenking op een microdeletie/duplicatie of chromosoomafwijking, in eerste instantie een single nucleotide polymorphism (SNP) array

met een korte uitslagtermijn voorafgaande aan de eerste operatie en eventueel in tweede instantie aanvullend genetisch onderzoek na consent van ouders door middel van een schisis genpanel analyse (incl. CNV analyse) met eventueel aansluitend een Whole Exome Sequencing.

6

Overweeg bij een zuigeling met CLP en CP, zonder aanwijzingen voor een specifieke diagnose, het verrichten van een schisis genpanel analyse (inclusief CNV analyse) en bespreek dit met ouders.

7

Bespreek met ouders/patiënt bij een geïsoleerde CL zonder belaste familieanamnese dat de kans op een genetische oorzaak klein is maar biedt hen wel de optie van genetische diagnostiek.

8

Overweeg bij een hele sterke verdenking op een syndroomdiagnose ook andere genetische testen waaronder gerichte Sanger sequencing van een specifiek gen, een trio genpanel analyse met eventueel aansluitend een open exoom analyse na informatie en informed consent.

9

Realiseer dat overgeërfde varianten met verminderde penetrantie of hele variabele expressie bij een trio WES weg gefilterd kunnen worden.

10

Voer een regelmatige update (1 tot 2 x per jaar) uit van schisis genpanel.

11

Plan een regulier (video-)overleg (1x per 2 maanden) in tussen de verschillende expertisecentra en andere aanvragers van genetische diagnostiek naar oorzaak CL/P om uniforme genetische counseling en diagnostiek bij schisis na te streven en bij te dragen aan optimale zorg voor de schisis-patiënt en ouders. Bij urgente vragen dit overleg ad hoc inplannen tussen de verschillende betrokkenen.

12

Verwijs ouders/patiënt naar websites/andere informatiebronnen over genetische diagnostiek/onduidelijke en neven-bevindingen.

13

Verwijs ouders/patiënt naar zorgprofessionals of Schisis Nederland voor informatievoorziening en diagnostiek, psychosociale begeleiding en lotgenotencontact.

Aanbeveling voor optimale strategie voor genetische diagnostiek bij schisis

Rationale

The performed literature search and the inventory of the results of the cleft gene panel in the Dutch cleft population showed that diagnostic genetic testing can identify pathogenic CNV's and pathogenic variants and therefore a specific underlying (rare) genetic disorder can be found. Diagnosis can be made in all cleft types, with or without additional morphological anomalies and/or abnormalities and with or without a positive family history for clefting.

In CLP cases, suspected of an underlying chromosomal abnormality, SNP array is the first choice of testing. In CLP cases, without a suspected syndrome diagnosis or chromosomal abnormality, cleft gene panel analyses, including CNV analyses, (WES targeting cleft related genes) should be considered as the first choice of genetic testing. By performing a trio WES, inherited variants with reduced penetrance and/or variable expression segregating in a family might be filtered out and can be missed.

In CLP cases with associated anomalies combined SNP array and WES based cleft gene panel analyses (including CNV analyses) should be considered.
In cases with specific dysmorphic features and/or associated congenital anomalies and/or intellectual disability broader genetic testing (for example for ID and/ or congenital anomalies, mendeliome), specific single gene sequencing and additional trio WES) should be considered.

In case of a prenatally diagnosed CL/P, prenatal invasive diagnostics is offered (chorionic villus test / amniocentesis). Based on the presence of additional ultrasound anomalies a QF-PCR, SNP array, and/or gene panel analyses and/or trio WES can be performed.

While prenatal genetic testing can be rather complex, for example by revealing (extremely) rare diagnoses with variable phenotypes or unsolicited findings, prenatal counselling should be performed in specialized centres.

Our inventory shows that DNA testing often reveals variants of uncertain (or unknown) significance. To interpret these variants reverse phenotyping, segregation study, literature search and expert opinion are important. Therefore, close and good collaboration between the clinical geneticist, gynecologist and/or pediatrician, and laboratory specialist involved is crucial.

It is important to inform the laboratory about the eventual conclusion and diagnosis in the patient after follow-up. These data are of great importance for classifying variants in future patients.

It is also noted that increasing knowledge urge a regular update of the gene panels. Certain genetic causes of clefting can be missed, because novel cleft genes are not yet included in the gene panel.

Regular overarching meetings for the different centers of expertise should be organized, in which complex patients, results of genetic testing, but also new knowledge can be discussed.

For now, the actual benefit and cost-effectiveness of genetic testing cannot be determined until the yield of genetic testing has been investigated in a unbiased population, and follow-up studies have been performed to analyse the effect of a specific diagnosis, taking into account the quality of life of people with CL/P and their parents.

Aanbevelingen-3

1

Betrek ouders bij de besluitvorming van de genetische diagnostiek en informeer hen goed over de inhoud van het onderzoek en de mogelijke uitslagen. Met name over de mogelijke kans op het vaststellen van een syndroomdiagnose die consequenties kan hebben later in het leven en de mogelijkheid van onduidelijke uitslagen of nevenbevindingen.

2

Zorg voor een goede samenwerking en overlegstructuur tussen de klinisch geneticus en de laboratoriumspecialist.

3

Informeer de laboratoriumspecialist bij de DNA-aanvraag volledig over bijkomende verschijnselen en familieanamnese.

4

Voer met betrokken klinisch geneticus en laboratoriumspecialist overleg over (her)classificatie van gevonden genetische varianten en eventueel aanpassingen van classificatie (in multidisciplinair verband).

5

Informeer de laboratoriumspecialist over de definitieve conclusie ten aanzien van de (syndroom)diagnostiek en informeer de laboratoriumspecialist of de classificatie van een VUS moet worden aangepast.

6

Zorg voor een periodieke update van het gen panel op basis van literatuur search en van casuïstiek.

7

Voer binnen het laboratorium een jaarlijkse evaluatie uit van de resultaten van de uitgevoerde genetische onderzoeken, zodat inzicht wordt verkregen in de opbrengsten van de verrichte diagnostiek.

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Validity and Maintenance

Module[1]	Responsible party[2]	Year of autorisation	Next assessment of actuality guideline[3]	Frequency of assessement of actuality[4]	Supervisor of actuality[5]	Relevant factors for changes in recommendations[6]
Diagnostic genetic testing	NVPC	2021	2026	every 5 years	NVPC	None

[1] Name of module
[2] Responsible party for the module
[3] maximum of 5 years
[4] half a year, every (other, ..) year
[5] supervising party or parties
[6] Current reseach, changes in organizations/restitions, new available rescourses

Appendixes with module 1

Intake schisis *

Medische voorgeschiedenis

Ziekenhuisopnames:

Betrokken behandelaars

Zwangerschaps en perinatale anamnese:

- *Zwangerschap*

  Zwangerschapsproblemen (Diabetes Mellitis, PE, metabool, amnionstrengen, poly-, oligohydramnion, kindsbewegingen):

  Medicatie:

  Foliumzuur:

  Congenitale infecties (meningitis, CMV, reisanamnese):

- *Partus:*

  Amenorroeduur:

  Geboortegewicht <1500 g: ja/nee , geboortegewicht

  Apgar score (1:<5 / 5:<7):

  Prematuriteit: ja/nee

  Verblijf op NICU:

  Ademhalingsproblemen (stridor), Mechanische ventilatie (>5 dg):

- Vaccinaties kind en moeder volgens RVP: ja/nee
- Congenitale afwijkingen:
- Voedings- slikproblemen (nasale regurgitatie):

Anamnese

Beloop:

Huidige situatie:

Geassocieerde aandoeningen opgemerkt:

- schedel (aplasia cutis,craniosynostosis,fontanel),
- gelaat (asymmetrie, micrognathie, mandibulofacaiale dysostosis, vlak middengelaat):
- ogen (hyper- , hypotelorisme, colobomen, ankyloblepharon, distichiasis):
- neus (vorm, choanae atresie of stenose, poliep, afwezig neusseptum):
- mond (lippits, ankyloglossie, tonghamartomen):
- gebit (centrale snijtand agenesie, oligodontie, tandglazuurafwijkingen, vormafwijking:
- oren (vorm (questionmark ear)/microtie, eartag/pits)
- extremiteiten (syn-, polydactylie, contracturen, popiliteal web, patella, varices, oedemen):

- cardiaal/ nieren/genitaal:
- ectodermaal (huid, haren en nagels):

Overig:

- Groei: goed, volgens curve
- Voeding:
- Ontwikkeling:
- Motorische mijlpalen:
- Spraaktaalontwikkeling, nasale spraak:
- Contact name:
- Visus:
- Gehoor:
- Gedrag:
- Slaapproblemen:
- Angsten:

Sociale anamnese:

School:

Huidige begeleiding:

Familie anamnese

Gezin bestaat uit: aantal kinderen ; compleet/ samengesteld

- Consanguiniteit:
- Rediverende miskramen:
- Aangeboren afwijkingen:
  - schisis:
  - lippits:
  - ankyloglossie:
  - micrognathie/ prognathie:
  - asymmetrie gelaat, mandibulofaciale dysostosis, vlak middengelaat:
  - neuraalbuisdefecten/hersenaanleg stoornis (holoprosencephalie):
  - schedelafwijkingen (craniosynostosis, cranium bifidum):
  - congenitale hartafwijkingen:
  - congenitale nierafwijkingen:
  - omphalocele:
  - genitaalafwijkingen:
  - skeletaandoeningen (groeistoornis, wervelanomalie, osteoporose):
  - ledemaatsafwijkingen (poly-,syndactylie, radius anomalie, patella afwijking):

- specifieke andere geassocieerde afwijkingen/ aandoeningen:
  - oogaandoeningen (colobomen, heterochromie, hypertelorisme, hoge myopie, cataract, retinaloslating, distichiasis, traanbuisafwijkingen):
  - oorafwijking (slechthorendheid, vormafwijkingen, tags, pits, halscysten):
  - gebitsafwijkingen (centrale snijtand agenesie, vormafwijking, hypo-/oligodontie):
  - anosmie:
  - cardiale afwijkingen (plots overlijden/ hartritmestoornis):
  - longproblemen:
  - nierafwijkingen/ nierfunctiestoornis (cilia afwijkingen):
  - endocrinologische afwijkingen (o.a. schildklier):
  - varices op jonge leeftijd:
  - lymfoedeem:

- gewrichtsafwijkingen (artrose, reuma, patella afwijkingen, popliteal web):
- ectodermale afwijkingen - haar- en nagel afwijkingen (alopecia, structuurafwijkingen, spaarzaam, depigmentatie (witte haarlok), hyperpigmentatie, atrofie, aplasie, hyperkeratose):
- infertiliteit:

- Ontwikkelingsachterstand:
- Psychiatrie:

Lichamelijk onderzoek

Lengte: (SD), gewicht: (SD), schedelomvang: (SD)

Dysmorfe kenmerken:

- Schedel (vorm, fontanel, haargrens, aplasia cutis):
- Gelaat (asymmetrie, mandibulofaciale dysostosis, vlak middengelaat, retrognathie, prognathie, onderbeet):
- Wenkbrauwen (vorm; gebogen, vol, (lateraal) spaarzaam, synophris)
- Ogen (vorm, stand, kleur (heterochromie), synechieën, distichiasis, euryblepahron, eversie onderooglid, hyper-, hypotelorisme, lange ooglidspleet):
- Neus (vorm, choanae atresie of stenose, cutane poliep, afwezig neusbotje, afwijking neusseptum):
- Mond: schisis/ lippits/ tongafwijkingen (ankyloglossie, harmatoma)
- Oren: vorm, microtie (type, concha type?), eartag/ earpit
- Brachiale regio: aplasia cutis, sinus, tags, pigmentaties
- Thorax (vorm, pectoralis, aplasie sternum, huid, extra tepels):
- Nek, Rug (webbed neck, scoliose, kyphose):
- Genitaal (hypospadie, cryptorchisme):
- Anus:
- Extremiteiten (contracturen, hyperlaxiteit, standafwijking, patella, lymfoedeem, varices):
- Handen (stand, vorm, poly-,syndactylie, stand en vorm dig 2, duimafwijkingen (vorm, stand), handlijnen, fetal pads):
- Voeten (stand, vorm, poly-, syndactylie, sandal gap, voetlijnen):
- Haar (haargrens, spaarzaam, witte haarlok):
- Huid (droge huid, eczeem, hyperkeratose, pigmentatie, aplasia cutis):
- Transpiratie:

* Deze lijst is een handvat en heeft niet de intentie compleet te zijn

Lichamelijk onderzoek formulier voor kind of ouder met schisis

Lichaamsmaten
☐ lengte
☐ lichaamsverhoudingen
☐ gewicht
☐ hoofdomtrek

Schedel
☐ hoofdvorm
☐ fontanel
☐ schedelnaden
☐ voorhoofd (hoog, laag); haargrens

Gelaat
☐ gelaatsvorm
☐ gelaatsasymmetrie
☐ onderontwikkeling middengelaat
☐ asymmetric crying face

☐ micrognathie
☐ retrognathie
☐ prognathie

Wenkbrauwen
☐ vorm; gebogen
☐ vol, (lateraal) spaarzaam
☐ synophris

Ogen
☐ ooglidspleet (evt. meten): kort, lang, upslant, downslant
☐ binnen-, buitenooghoekafstand (ICD, OCD), hypotelorism, hypertelorism
☐ ankyloblepharon
☐ euryblepharon, eversie onderooglid
☐ distichiasis
☐ telecanthus
☐ cleft eyelid, spaarzame/ afwezige wimpers
☐ heterochromie
☐ iris coloboom
☐ strabisme

Neus
☐ neusvorm
☐ neusbrug (vlak, prominent), afwezig kraakbeen
☐ columnella
☐ opgewipte neuspunt
☐ cutane poliep (pai poliep)

Mond
☐ mondvorm
☐ microstomie, beperkte mondopening
☐ lippits
☐ oral frenula/ synechie,

Tong
☐ positie tong, glossoptosis
☐ ankyloglossie
☐ hypoglossie,

Palatum
☐ cleft, shape, type
☐ bifid uvula
☐ submucous cleft palate (palpatie voor afwijking posterior palatum durum)

Gebit
☐ tand agenesie
☐ enkele centrale snijtand
☐ tandglazuurafwijkingen
☐ tandvorm
☐ extra elementen

Oren
☐ dysplasia
☐ microtie (typering; concha type?)
☐ question mark ear
☐ pits helixrand
☐ preauriculaire sinus (pits)
☐ preauriculaire tags

Hals
☐ branchiale huid afwijkingen, aplasie, sinus, tags

Thorax
☐ Nek: kort, webbed, torticollis
☐ Thorax: smal, asymmetrie, afwezige/ hypoplastische claviculae
☐ Hart: cortonen

Abdomen

☐ hernia umbilicalis,
☐ lever/ milt

Genitaal
☐ Man: micropenis, hypospadie, cryptorchisme, shawl scrotum
☐ Vrouw: labiale adhesies, cliteromegalie, labiale zwelling

Extremiteiten
☐ hypermobiliteit,
☐ arthrogryposis, webbing, popeliteal web
☐ radiusafwijkingen, radioulnaire synostosis
☐ patella: afwezig, hypoplastisch
☐ handen/ voeten: syndactylie, brachydactylie, duim afwijkingen (vorm, positie), afwijkende vorm of stand dig.2, clinodactylie, ectrodactylie, fetal pads, contracturen,

Rug
☐ scoliosis,
☐ hypoplastic scapula

Ectodermaal
☐ Haar: spaarzaam, alopecia, afwijkende haar structuur, spiky hair
☐ Huid: vasculaire laesies, hemangiomen, pigment afwijkingen
☐ lymfoedeem,
☐ varices (jonge leeftijd)
☐ nagels: hypoplastisch/ dystrofie

Neurologisch
☐ spiertonus

Deze checklist is ondersteunend in het lichamelijk onderzoek naar mogelijke aanwijzingen voor een onderliggende syndroomdiagnose. Het heeft niet de intentie compleet te zijn.

Knowledge gaps

As already mentioned, the actual benefit and cost-effectiveness of genetic testing cannot be determined until the yield of genetic testing has been determined in an unbiased population, and follow-up studies have been performed to analyse the effect of a specific diagnosis, taking into account the quality of life of people with CL/P and their parents.

What is the effect of different genetic tests in isolated clefts of the lip and palate on the diagnostic yield in isolated clefts of the lip and palate?

- **P:** patients with isolated cleft lip and/or palate or pregnant women undergoing prenatal screening for cleft lip and/or palate in their child;
- **I:** diagnostic genetic tests (copy number variant (CNV) analysis (for example array comparative genomic hybridization (CGH), SNP array, CMA), next generation sequencing, for example gene panels, whole exome sequencing);
- **C:** comparison of the tests above;
- **R:** long term follow-up of children with apparently isolated cleft to identify late onset features an underlying genetic/ syndrome diagnose;
- **O:** yield, sensitivity, specificity, diagnostic accurateness.

Future prospective studies are recommended to resolve these issues.

Implementatieplan

Recommendation	Timeline for implementation: < 1 year,	Expected effect	Preconditions for implementation	Possible barriers for implementation[1]	Supposed actions for implementation[2]	Who is responsible for the	Other comments

	1 to 3 years or > 3 years	s on costs	(within specified timeframe)			action(s)[3]	
1.1	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC, KNOV	Already recommended in previous version of the guideline
1.2	**< 1 year**	nil	Waiting times are not too long	Speed of test results	Publication of the guideline	NVPC, KNOV, VKGN	
1.3	**< 1 year**	nil	Waiting times are not too long		Publication of the guideline	NVPC, KNOV, VKGN	Already recommended in previous version of the guideline
2.1	**1 tot 3 years**	nil	Intake form available for everyone		Publication of the guideline and intake form	NVPC, VKGN	
2.2	**1 to 3 years**	nil	Checklist available for everyone		Publicatie richtlijn en checklist	NVPC, VKGN	
2.3	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC, VKGN	
2.4	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC, VKGN	
2.5	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC, VKGN	Already recommended in previous version of the guideline
2.6	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC, VKGN	
2.7	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC, VKGN	
2.8	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC, VKGN	
2.9	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC, VKGN	
2.10	**1 to 3 years**	nil	Yearly evaluaton of the performed genetic examinations, so that		Publication of the guideline	NVPC, VKGN	

			insight is obtained into the results of the performed diagnostic tests				
2.11	**1 to 3 years**	nil	Sustainable cooperation between expertise centers		Publication of the guideline	NVPC, VKGN	
2.12	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC, VKGN	
1.13	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC, VKGN	
3.1	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC, VKGN	Already recommended in previous version of the guideline
3.2	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC, VKGN	Already recommended in previous version of the guideline
3.3	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC, VKGN	
3.4	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC, VKGN	
3.5	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC, VKGN	
3.6	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC, VKGN	
3.7	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC, VKGN	Already recommended in previous version of the guideline

[1] Barriers can exist at the level of the professional, at the level of the organization (the hospital) or at the level of the system (outside the hospital). Consider, for example, disagreement with regard to the recommendation in different organizations, insufficient motivation or knowledge of the specialist, insufficient facilities or personnel, necessary concentration of care, costs, poor cooperation between disciplines, necessary rearrangement of tasks, et cetera.

[2] Actions that are necessary for implementation, but also actions that are possible to encourage implementation. Consider, for example, checking the recommendation during a quality review, publication of the guideline, developing implementation tools, informing hospital administrators, arranging proper reimbursement for a certain type of treatment, making cooperation agreements.

[3] Who is responsibilities for implementation of the recommendations will also depend on the level of barriers. Barriers at the level of the professional will often have to be resolved by the professional association. Organizational barriers will often be the responsibility of hospital administrators. Other parties, such as the NZA and health insurers, are also important in resolving barriers at system level.

5

Table of excluded studies

Author and year	Reason for exclusion
Lansdon, 2018	Did not provide insight into the value of the array technique for clinical practice
Mouthon, 2019	Article is about micrognathia instead of CL/P.

Literature search strategy

Richtlijn: Schisis	
Uitgangsvraag: Genetische diagnostiek → Hoe vaak leveren genetische testen een oorzaak voor bij geïsoleerde schisis op?	
Database(s): Medline, Embase	Datum: 13-2-2020
Periode: 2010-heden	Talen: Engels
Literatuurspecialist: Miriam van der Maten	
Toelichting en opmerkingen: • Voor deze zoekopdracht is er gezocht op een combinatie van schisis en genetische diagnostiek (inclusief de 3 genoemde soorten). • Er is verder niet beperkt op associated abnormalities (zie PICO) of met een diagnostisch filter (zie uitkomstmaten) omdat de aantallen meevielen en dit de resultaten onnodig beperkt (sleutelartikelen zouden dan ook niet gevonden worden). • De sleutelartikelen van Cox (2019), Conte (2016), Maarse (2012) en Basha (2018) worden gevonden met de zoekopdracht. • Het artikel van Demeer (2019) is geïndexeerd als 'clinical article' en dit valt buiten het filter voor observationeel onderzoek omdat dit normaal gesproken items beschrijft die ander clinical work rapporteren. Verder zou het wel uit de search komen. • Het artikel van Osoegawa (2008) valt uit de search op datum. Verder zou het wel uit de search komen.	
Results of the search	

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	7	17	20
RCTs	11	7	14
Observationele studies	110	46	131
Totaal	128	70	165

Database	Zoektermen
Embase	#20 #17 OR #18 OR #19128 #19 #7 AND #16 NOT (#17 OR #18) 110 #18 #7 AND #15 NOT #17 11 #17 #7 AND #14 7 #16 'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) 5132645 #15 'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti 2983591 #14 'meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de 482181 #7 #1 AND #6 AND (english)/lim AND (2010-2020)/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) 581 #6 #2 OR #3 OR #4 OR #5 322494 #5 'whole exome sequencing'/exp OR 'whole genome sequencing'/exp OR 'high throughput sequencing'/exp OR ((('whole genome' OR 'high throughput' OR 'next generation' OR exome) NEAR/2 sequencing):ti,ab,kw) 129009 #4 'gene panel*':ti,ab,kw OR 'gene package*':ti,ab,kw 5463 #3 'comparative genomic hybridization'/exp OR ((('deoxyribonucleic acid' OR dna OR 'copy number variant' OR cnv OR snp OR 'single nucleotide polymorphism' OR chg) NEAR/2 (analys*s OR assay* OR array*)):ti,ab,kw) 102039

	#2 'genetic diagnosis'/exp OR 'dna determination'/exp OR ((genetic NEAR/2 (diagnos* OR test*)):ti,ab,kw) 117750 #1 'cleft lip with or without cleft palate'/exp OR 'cleft palate'/exp OR 'cleft lip face palate'/exp OR (((cleft* OR fissum OR hare OR schi*is) NEAR/5 (palat* OR lip* OR cheilo* OR oral OR orofacial OR facial)):ti,ab,kw) OR palat*schi*is:ti,ab,kw OR cheilo*schi*is:ti,ab,kw OR labioschi*is:ti,ab,kw OR harelip*:ti,ab,kw 37500
Medline (OVID)	1 exp Cleft Lip/ or exp Cleft Palate/ or ((cleft* or fissum or hare or schi*is) adj5 (palat* or lip* or cheilo* or oral or orofacial or facial)).ti,ab,kf. or palat*schi*is.ti,ab,kf. or cheilo*schi*is.ti,ab,kf. or labioschi*is.ti,ab,kf. or harelip*.ti,ab,kf. (30360) 2 exp Genetic Testing/ or (genetic adj2 (diagnos* or test*)).ti,ab,kf. (71791) 3 exp Comparative Genomic Hybridization/ or (('deoxyribonucleic acid' or dna or 'copy number variant' or cnv or snp or 'single nucleotide polymorphism' or chg) adj2 (analys*s or assay* or array*)).ti,ab,kf. (69893) 4 ('gene panel*' or 'gene package*').ti,ab,kf. (2127) 5 exp High-Throughput Nucleotide Sequencing/ or exp Whole Exome Sequencing/ or exp Whole Genome Sequencing/ or (('whole genome' or 'high throughput' or 'next generation' or exome) adj2 sequencing).ti,ab,kf. (86166) 6 2 or 3 or 4 or 5 (218798) 7 1 and 6 (579) 8 limit 7 to (english language and yr="2010 -Current") (396) 9 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (432102) 10 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1948440) 11 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies) (3364883) 12 8 and 9 (17) 13 (8 and 10) not 12 (7) 14 (8 and 11) not (12 or 13) (46) 15 12 or 13 or 14 (70)

Module 2 Prenatal medical counselling

Clinical question

1. Which medical information should be addressed during prenatal counselling to parents who are expecting a child with a cleft lip and/or palate (according to parents and professionals)?
2. What resources from caregivers are useful in the process of prenatal medical counselling for parents expecting a child with cleft lip and/or palate (resources such as information leaflets and images, but also practical tools like teats and other aids)?

Welke medische onderwerpen zouden er aan de orde moeten komen tijdens de prenatale counseling aan ouders die een kind met een schisis verwachten (volgens ouders en professionals)?
Welke hulpmiddelen van zorgverleners zijn nuttig voor ouders in het proces van prenatale counseling van ouders die een kind met een schisis verwachten?

Introduction

Since the introduction of the structural anomaly scan (SEO) as a routine screenings tool for all pregnant women in the Netherlands in 2007 and the ongoing technological improvement of the ultrasound machines, the prenatal detection of cleft lip and palate has increased over the years (Ensing, 2014). This allows parents to receive detailed information about the short- and long-term implications of the prenatal diagnosis. The care for patients diagnosed with (orofacial) clefts is concentrated in multidisciplinary cleft teams in the Netherlands. There is however variation in both prenatal counselling and postnatal care between individual teams. The goal of the prenatal counselling is to give parents accurate, uniform and unambiguous information about the possible consequences of the diagnosis of a cleft of the lip and palate and future opportunities for their child and to prepare them for birth and the time until the first visit to a cleft clinic. The counselling should include medical as well as psychological information, and tools to prepare parents and their families for the birth of a child with (orofacial) cleft. If diagnosed before 24 weeks of gestation, termination of pregnancy is an option that should be mentioned in the Netherlands and should be discussed in more detail in case parents wish to do so. Questions regarding a possible underlying genetic cause and prenatal genetic diagnostic testing are usually directed to a medical geneticist in the Dutch health care system (referral by the obstetrician) and can be of influence for possible termination of pregnancy.

Search and select

A systematic review of the literature was performed to answer the following question:
What is the effect of prenatal counselling on parents of patients with cleft lip and palate?

P: parents of patients with cleft lip and palate;
I: prenatal counselling (medical counselling);
C: no counselling;
O: satisfaction, anxiety/concerns, informed choice, termination of pregnancy.

<u>Relevant outcome measures</u>

The guideline development group considered satisfaction as a critical outcome measure for decision making; and anxiety, informed choice, termination of pregnancy as an important outcome measure for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the criteria for minimal clinically (patient) important difference for the dichotomous outcome measures; RR < 0.80 of > 1.25) or Standardized mean difference (SMD=0.2 (small); SMD=0.5 (moderate); SMD=0.8 (large).

Search and select (Methods)

The databases Medline (via OVID), Embase (via Embase.com), and Psychinfo were searched with relevant search terms until 14th of April 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 317 hits (16 SR, 21 RCTs, 113 observational studies, and 167 others). Studies were selected based on the following criteria: systematic reviews, RCTs and other comparative studies focusing on medical and/or psychological counselling for parents of patients with cleft lip and palate. A total of 16 studies were initially selected based on title and abstract screening. After reading the full text, all 16 studies were excluded (see the table with reasons for exclusion under the tab Methods), thus no comparative studies were selected for the literature summary.

Results

No comparative studies were found that answered the question: What is the effect of counselling on parents of patients with cleft lip and palate?

Conclusions

No conclusions could be drawn based on the literature.

Considerations

Advantages and disadvantages of counselling

Despite no studies were found in this search which evaluated the effectivity of counselling and did not answer the PICO question, a few studies were found that provide information about the medical and psychological themes and tools that should be mentioned during the counselling of parents expecting a child with cleft lip and/or palate (Greives, 2017; Stock, 2019; Stock, 2019).

1. *What medical information should be addressed during prenatal counselling to parents who are expecting a child with a cleft lip and/or palate (according to parents and professionals)?*

Several studies were found in which parents gave their opinion on the topics to be addressed during counselling for prenatal diagnosed clefts of the lip and palate. The study of Berk (1999) showed that 87% (84/97) of the parents indicated a need for medical information about the disorder and its treatment. Other topics that parents need in counselling are aetiology, chance of additional anomalies, expected medical problems after birth, such as feeding, and treatment (Maes, 1998; Hager, 2002; Jones, 2002; Nusbaum, 2008; Matthews, 1998). The online survey study of Greives, 2017 asked parents (n=112) about the topics that are the most helpful to be discussed during the prenatal visit. The top five consisted of 1. surgical treatments; 2. new-born feeding techniques; 3. team care; 4. genetics; and 5. speech/hearing. Jones (2002) states that, in addition to providing a general overview of treatment, counselling should mainly focus on issues that play a role in the first year of life such as feeding, surgical interventions, ear problems and pain.

The Royal College of Obstetricians and Gynaecologists (RCOG) guideline about prenatal information state that all practitioners performing fetal anomaly screening should be trained

to impart information, and that they or another health professional should be available to provide immediate support to both parents (RCOG, 2010). Further, that all staff involved should adopt a non-directive, non-judgmental approach, and should not assume, even in the presence of a potentially fatal condition, that the parents will choose to terminate (RCOG, 2010).

Prospective parents could therefore benefit from a comprehensive description of the aetiology, likely treatment pathway and prognosis, without health professionals introducing their own values and judgements and/or exceeding their own professional capacity. A referral to cleft specialist should be made soon after prenatal diagnosis, and prospective parents should be directed to reliable parents/patient organizations, such as Schisis Nederland (https://schisisnederland.nl) in the Netherlands as soon as possible.

Referrals to cleft specialist would provide prospective parents with further information, emotional support, and realistic personal accounts of what life is like with a child who was born with CL/P, so that they can decide whether further testing and/or TOP is something they want to pursue. Supplementary written information and trusted website addresses could also be provided, particularly given that prospective parents may be emotionally distressed and less able to process complex information in the moment.

Stock (2019) analysed data from 217 parents of children born with cleft lip (with or without cleft palate) using a mixed-methods online survey. If a cleft lip / palate is detected, the way the diagnosis is communicated can considerably influence prospective parents' decision making in regard to further testing and termination of pregnancy (TOP). Due to unsatisfactory information and a perceived lack of empathy from health professionals, respondents reported feeling upset, offended and / or anxious following the diagnosis. Some respondents had felt under pressure to make a decision quickly, with a minority having regretted undergoing amniocentesis, and / or experiencing significant distress at having come close to TOP unnecessarily. Unfortunately, the legal limit of a certain gestational age to terminate a pregnancy, might feel parents under pressure to make decisions quickly (Stock, 2019).

We need to consider that the above-mentioned survey was only shared with parents who are part of CLAPA's community (Cleft Lip and Palate Association UK). While CLAPA's community is considerable, it cannot be assumed that this group, nor the subgroup who responded to the survey, are representative of the CL/P population in the Netherlands or as a whole. Since all participants were parents of children with CL/P, none of the survey respondents had opted for TOP. It is therefore not possible to gain an understanding of the experiences of those who opted to end their pregnancy on the basis of a CL/P (with or without associated conditions).

The quality of the information received at the time of diagnosis can considerably influence parents' long-term well-being, as well as their attitudes toward the diagnosis, further antenatal testing, and even termination of the pregnancy (Stock, 2019).

Stock (2019) demonstrated that their findings emphasize the importance of providing accurate and individualized information to prospective parents, in a sensitive manner, so they can adjust to their child's diagnosis, consider further genetic testing and termination of pregnancy or prepare for the birth appropriately (Stock, 2019). Given that antenatal screening for cleft lip is becoming more fully integrated into routine practice in the Netherlands more training for health-care professionals, improved access to reliable

information in a variety of formats, and stronger links between local midwifes doing the primary 20-week structural anomaly scan (SEO) and specialist from cleft team may be needed (Stock, 2019 based on the British situation).

2. *What resources from caregivers are useful in the process of prenatal medical counselling for parents expecting a child with cleft lip and/or palate (resources such as information leaflets and images, but also practical tools like teats and other aids)?*

Four studies were found that provided information on the use of aids in counseling parents expecting a child with cleft lip and palate. In the study of Rey-Bellet (2004) 93% (27/29) of parents were happy to see pictures of children with clefts before and after surgery. It was also an aid to help family and friends prepare for the arrival of a child with a cleft lip and palate. In the study of Matthews (1998) 1/9 parents considered the pre- and postoperative pictures of a child with clefts to be too severe.

The previous guideline gives in dept medical information that should be provided after the diagnosis is given.

The following medical topics related to the child with cleft lip and palate should be discussed with the parents in prenatal counseling:

- What is a cleft lip and palate.
- How often does it occur.
- How does it develop.
- Types of cleft lip and palate.
- Characteristics.
- Additional anomalies.
- Functional consequences.
- Treatment by a team of different specialists.
- Nutrition and care.
- Treatment and treatment protocol.
- Operations /surgery.
- Pain and discomfort for the child.
- Out-patient visits to the cleft team.
- Possible hearing problems.
- Possible speech problems.
- Teeth and jaw outgrouth problems.
- Timeline of treatment.
- End result (including limitations such as scars).

Parents' opinions about the internet as a source of information vary. Rey-Bellet (2004) found that 17% (5/29) of parents thought it was a good way to find information. However, the photos published on the internet are perceived by some as scary and because people search at home, this source does not offer the possibility of direct feedback from a healthcare provider (Jones, 2002; Nusbaum, 2008). It is also customary to provide written information.

<u>Values and preferences of patients' parents</u>

It is clear that the parents have a great need for information. The literature does not indicate what the background of the care provider who provides the information should be. It seems justified from studies from Rey-Bellet (2004) that persons experienced in surgical aspects are important, however the healthcare provider(s) in question should have knowledge and expertise in the whole field of cleft palate treatment. The topics that should be addressed in medical counseling previously summarized do not seem to differ from those that are routinely used by the majority of (unprepared) parents in the immediate postnatal phase.

The recommendations regarding the topics are based on this. This suggests that parents were more interested in short-term issues for their child rather than long-term goals for overall cleft care.

Costs (resources required)

Prenatal counseling is not covered under the basic insurance in the Dutch Health Care system and there may be additional - non reimbursable - costs for parents due to prenatal consultation with a cleft team. The ultrasound (including a consultation with a gynecologist) is reimbursed under the basic insurance. We feel this should not be a reason not to refer patients to a cleft team, however, for some patients this could be a consideration not to start counseling until after birth (in the Netherlands).

Acceptability, feasibility and implementation

Clinical experience has shown that both parents and caregivers seem satisfied with prenatal counseling. It gives parents the space to make choices based on good information. There are no practical restrictions in planning an antenatal consultation with a cleft team. This is available in all locations in the Netherlands. Prenatal counseling by the cleft team has already been implemented in all academic centers.

Recommendations/Aanbevelingen

Rationale

The working group would like to emphasize the importance of providing accurate and individualized information to prospective parents. This should be done in a sensitive manner, so the parents can adjust to their child's diagnosis, and consider further genetic testing and termination of pregnancy or prepare for the birth appropriately. It is considered important that every parent should speak to a delegation from a cleft team before a possible termination of the pregnancy will take place. Given that antenatal screening for cleft lip is becoming more fully integrated into routine practice in the Netherlands, access to reliable and accurate information in a variety of formats, should be freely available. The working group recommends that prenatal counseling for clefts of the lip and palate should always be performed by one or two representatives of a cleft team, preferably including a surgeon and a psychologist or social worker . A close relation with the obstetric caretaker is an important factor, so that the counselling can be individualized and based on the ultrasound findings.

Finally, it might be considered to provide parents with an unborn child with a cleft on ultrasound with the opportunity to speak to other parents that have a child with a cleft lip and/or palate. In this way parents could get firsthand information, but it may also introduce possible bias. It is possible that the patients' parents organizations could play an important role in providing peer support. Parents who are willing to act as peer support should receive special training for this purpose.

Aanbevelingen-1

Bied ouders die zwanger zijn van een kind met een schisis prenatale counseling aan en laat de medische informatie betreffende de schisis en de behandeling ervan gegeven worden door een of meerdere behandelaren (waaronder een chirurg en iemand met psychosociale expertise, zoals gedragsdeskundige of medisch maatschappelijk werker), die lid is van een schisisteam en die een breed inzicht heeft in de problematiek en ruime ervaring met de behandeling van kinderen met een schisis.

Aanbeveling-2

Zorg dat de volgende medische onderwerpen met betrekking tot het kind met schisis in de prenatale counseling met de ouders besproken worden:

- Wat is een schisis.
- Hoe vaak komt het voor.
- Ontstaanswijze.
- Vormen van schisis.
- Kenmerken.
- Bijkomende anomalieën en genetische aandoeningen.
- Functionele gevolgen.
- Behandeling door een team van verschillende specialisten.
- Plaats van bevalling.
- (Borst)voeding en verzorging.
- Behandeling.
- Behandelprotocol.
- Operaties.
- Pijn en ongemak voor het kind.
- Controles bij het schisisteam.
- Gehoor.
- Spraak.
- Gebit en kaken.
- Tijdpad behandeling.
- Eindresultaat (ook beperkingen zoals littekens).

Aanbeveling-3

Zorg dat de zorgverlener de mondelinge informatie ondersteunt met schriftelijk informatiemateriaal, dat de ouders mee naar huis kunnen nemen. Daarnaast verdient het aanbeveling de mondelinge informatieverstrekking te ondersteunen met ander materiaal, waaronder:

- Informatieboekje van het schisisteam.
- Pre- and postoperatief beeldmateriaal.
- Ander beeldmateriaal dat de mondelinge informatie ondersteunt, bijvoorbeeld in de vorm van een PowerPoint presentatie.
- Hulpmiddelen bij de voeding, zoals typen zuigfles en speen.

Aanbeveling-4

Wijs de ouders op websites die objectieve informatie verstrekken, waaronder de websites van:

- www.schisis.nl (Nederlandse Vereniging voor Schisis en Craniofaciale Afwijkingen).
- www.schisisnederland.nl (patiëntenvereniging).
- Websites die mogelijkheden bieden voor lotgenotencontact, zoals facebookgroep of sites die door het behandelend team zijn bedoeld hiervoor.

Literature

Berk NW, Marazita ML, Cooper ME. (1999). Medical genetics on the cleft palate-craniofacial team: understanding parental preference. *Cleft Palate Craniofac J*; 36(1):30-35.

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Royal College of Obstetricians and Gynaecologists (RCOG). (2010). Pregnancy for Fetal Abnormality in England, Scotland and Wales. Report of a working party. https://www.rcog.org.uk/globalassets/documents/guidelines/terminationpregnancyreport18may2010.pdf.

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Stock NM, Costa B, Williams JR, Martindale A; VTCT Foundation Research Team at the Centre for Appearance Research. (2019). Breaking the News: Parents' Experiences of Receiving an Antenatal Diagnosis of Cleft Lip. *Cleft Palate Craniofac J*;56(9):1149-1156.

Validity and Maintenance

Module[1]	Responsible party[2]	Year of autorisation	Next assessment of actuality guideline[3]	Frequency of assessement of actuality[4]	Supervisor of actuality[5]	Relevant factors for changes in recommendations[6]
Prenatal medical counselling	NVPC	2021	2026	every 5 years	NVPC	None

[1] Name of module
[2] Responsible party for the module
[3] maximum of 5 years
[4] half a year, every (other, ..) year
[5] supervising party or parties
[6] Current reseach, changes in organizations/restitions, new available rescourses

Appendixes with module 2

Knowledge gaps

What are the needs and expectations of medical counselling of parents expecting a child with a cleft lip and/or palate?

Implementation plan

Recommendation	Timeline for implementation: < 1 year, 1 to 3 years or > 3 years	Expected effects on costs	Preconditions for implementation (within specified timeframe)	Possible barriers for implementation[1]	Supposed actions for implementation[2]	Who is responsible for the action(s)[3]	Other comments
1	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC	Mainly recommended in previous version of the guideline
2	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC	Already recommended in previous version of the guideline
3	**< 1 year**	nil	Mainly current practice	Availability information booklet, images and tools	Publication of the guideline	NVPC	Mainly recommended in previous version of the guideline
4	**< 1 year**	nil	Mainly current practice	Availability of peer contact/support	Publication of the guideline	NVPC	Mainly recommended in previous version of the guideline

[1] Barriers can exist at the level of the professional, at the level of the organization (the hospital) or at the level of the system (outside the hospital). Consider, for example, disagreement with regard to the recommendation in different organizations, insufficient motivation or knowledge of the specialist, insufficient facilities or personnel, necessary concentration of care, costs, poor cooperation between disciplines, necessary rearrangement of tasks, et cetera.

[2] Actions that are necessary for implementation, but also actions that are possible to encourage implementation. Consider, for example, checking the recommendation during a quality review, publication of the guideline, developing implementation tools, informing hospital administrators, arranging proper reimbursement for a certain type of treatment, making cooperation agreements.

[3] Who is responsibilities for implementation of the recommendations will also depend on the level of barriers. Barriers at the level of the professional will often have to be resolved by the professional association. Organizational barriers will often be the responsibility of hospital administrators. Other parties, such as the NZA and health insurers, are also important in resolving barriers at system level.

Table of excluded studies

Author and year	Reason for exclusion

Aslan, 2018	About the importance of counselling (variables affecting family functions and life quality of parents), not about counselling itself
Dabadie, 2016	Prospective study comparison of MRI and ultrasound in diagnosing CL/P
De Cuyper, 2019	Cross sectional study about the effect of CL/P on quality of life of parents supported by a multidisciplinary cleft team
Greives, 2017	Survey study about factors influencing the choice of parents of their cleft team
James, 2016	Descriptive study about the importance of cleft teams
Laifer-Narin, 2019	Retrospective study of a fetal MRI database examining the accuracy of fetal MRI for prenatal diagnosis
Loozen, 2015	Retrospective cohort study to the accuracy of prenatal transabdominal ultrasound
Maarse, 2018	Survey study about psychosocial and moral considerations of prospective parents
Nidey, 2016	Study about predictors of psychosocial wellbeing and compared fathers and mothers
Shibui, 2016	Description of the counselling protocol in Japan
Sreejith, 2018	Descriptive review about psychological aspects of prenatal diagnosis
Steinberg, 2015	Comprehensive review about what have been changed in the last 30 years in counselling
Stock, 2019	Mixed method online survey to explore the decision-making process from the parents' perspective
Tang, 2016	Centre's experience in providing one-stop multidisciplinary antenatal counselling service to parents of fetus with cleft lip/palate deformity on termination.
Zeytinoglu, 2015	Thesis
Zeytinoglu, 2017	Descriptive qualitative interview study about CL/P diagnosis on couples' relational adjustment and coping

Literature search strategy

Algemene informatie

Richtlijn: Schisis	
Uitgangsvraag: Wat is de effectiviteit van counseling bij ouders van patiënten met een schisis?	
Database(s): Medline, Embase	Datum: 14-4-2020
Periode: 2014 - april 2020	Talen: Engels, Nederlands
Literatuurspecialist: Miriam van der Maten	
Toelichting en opmerkingen: Dit is een update van de eerder uitgevoerde search op 17-12-2014. Het opgegeven artikel van Sreejith (2018) wordt gevonden in de update.	

5 Zoekopbrengst

	OVID/MEDLINE	Psychinfo	Embase	Ontdubbeld
SRs	16	-	13	16
RCT	20	-	15	21
Observationele studies	89	-	99	113
Overige studies	161	-		167
Totaal	286	123	127	**317**

Zoekverantwoording

Database	Zoektermen
Medline (OVID)	1 exp Cleft Lip/ or exp Cleft Palate/ or ((cleft* or fissum or hare or schi*is) adj5 (palat* or lip* or cheilo* or oral or orofacial or facial)).ti,ab,kf. or palat*schi*is.ti,ab,kf. or cheilo*schi*is.ti,ab,kf. or labioschi*is.ti,ab,kf. or harelip*.ti,ab,kf. (30545) 2 exp Parents/ed, px or exp Family/ed, px or exp Psychotherapy/ or exp Family Therapy/ or exp Counseling/ or exp Parent-Child Relations/ or (Psychosocial or "patient education" or counse*ling).ti,ab. (514063) 3 1 and 2 (1160) 4 limit 3 to (yr="2014 -Current" and (dutch or english)) (286) 5 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (441020)

	6 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1970026) 7 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies) (3408080) 8 4 and 5 (16) 9 (4 and 6) not 8 (20) 10 (4 and 7) not (8 or 9) (89) 11 4 not (8 or 9 or 10) (161) 12 8 or 9 or 10 or 11 (286)
Psychinfo	1 cleft lip/ or Cleft Palate/ or ((gnatho* or cheilo* or palato) adj10 schisis).ti,ab. or ((Alveolar adj3 cleft*) or (Orofacial adj3 cleft*) or (cleft adj3 lip*) or (cleft adj3 palate*) or (cleft adj3 maxilla*) or (oral adj3 cleft)).ti,ab. (815) 2 exp psychotherapy/ or exp family therapy/ or exp Counseling/ or parent child communication/ or parent child relations/ or attachment behavior/ or attachment disorders/ or attachment theory/ or authoritarian parenting/ or authoritative parenting/ or exp childrearing practices/ or exp parent child communication/ or parent training/ or exp parental characteristics/ or parental expectations/ or parental investment/ or parental involvement/ or parental role/ or parenting skills/ or exp parenting style/ or permissive parenting/ or (Psychosocial or "patient education" or counse*ling).ti,ab. or exp Social Adjustment/ or exp Adaptation, Psychological/ or exp Health Knowledge, Attitudes, Practice/ or (coping or "social behavio?r").ti,ab. (544151) 3 1 and 2 (123)

Embase (Elsevier)

No.	Query	Results
#10	#5 OR #7 OR #9	127
#9	#3 AND #8 NOT (#5 OR #7)	99
#8	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	5205774
#7	#3 AND #6 NOT #5	15
#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3019867
#5	#3 AND #4	13
#4	'meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de	491364
#3	#1 AND #2 AND (english)/lim AND (1-12-2014)/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	345
#2	'counseling'/exp/mj OR 'psychotherapy'/exp/mj OR counsel*ing:ti,ab,kw OR psychosocial:ti,ab,kw OR 'patient education':ti,ab,kw OR psychotherap*:ti,ab,kw OR socioenvironmental:ti,ab,kw	452505
#1	'cleft lip with or without cleft palate'/exp OR 'cleft palate'/exp OR 'cleft lip face palate'/exp OR (((cleft* OR fissum OR hare OR schi*is) NEAR/5 (palat* OR lip* OR cheilo* OR oral OR orofacial OR facial)):ti,ab,kw) OR palat*schi*is:ti,ab,kw OR cheilo*schi*is:ti,ab,kw OR labioschi*is:ti,ab,kw OR harelip*:ti,ab,kw	37642

Module 3 Timing repairing cleft lip and palate

Clinical question

What considerations are important (advantages and disadvantages) in the determing the best moment to close the cleft lip and/or palate?

Welke overwegingen (voor- en nadelen) spelen een rol bij het bepalen van het moment van het sluiten van de gehemeltespleet en de lipspleet bij kinderen met een (cheilognatho)palatoschisis?

Introduction

In case of a cleft of the palate there is a (abnormal) connection between the nasal and oral cavities, which are normally fully separated. The posterior part of the nasal and oral cavities merge in the oropharynx. Under normal conditions the soft palate functions as a valve, actively closing of the nasal cavity from the oral cavity on demand. This is an essential function to build up pressure for speech and to create a vacuum, for example for feeding. As a consequence, a cleft palate - even if it is minor- causes functional impairment in drinking and speech.

Closure of the (soft and/or hard) palate intents to create a separation between the oral and nasal cavities and to solve these problems. Early closure aims to solve these problems faster compared to later closure, which is evident. The plea for early closure is logic from a pure functional point of view. The problem with early closure relates to scar formation. Some degree of scar formation during surgical closure of the palate is inevitable, even with the best techniques and an experienced surgeon. Scar formation however can cause disturbance of growth of the upper jaw. It is thought that especially scar formation during closure of the hard palate is responsible for most of the noted growth disturbance. Early closure (<18 month) of the hard palate causes scar formation at a younger age and has therefore more time to affect growth of the maxilla compared with later closure.

Disturbed growth of the maxilla is not benign and leads to midface underdevelopment, class 3 malocclusion, and less prominence of the nose. Even the width of the upper jaw might stay small causing cross bite. These problems may require extra and sometimes complex surgical interventions, such as a le Fort I osteotomies etc. after growth has been completed around 18 years of age.

In summary: the classic teaching tells us that early closure favors function, late closure (especially of the hard palate) is better for growth, the holy grail being early closure without growth disturbance.

In view of the issues raised above the timing of (partial) palatal closure seems important. Timing of closure of the cleft lip is less subject to debate. Lip closure does not seem to impair growth. Due to the esthetic importance the cleft lip is usually repaired in the first year of life, mostly in the first trimester after birth, frequently combined with primary correction of the nose (see chapter on cleft nose correction). Nevertheless, it is important to substantiate timing of lip closure with current literature.

Search and select

A systematic review of the literature was performed to answer the following question:

What is the effect of the timing of repairing cleft lip and palate on maxillary and midface growth, speech, hearing, feeding capability, postoperative complications (fistulae), and esthetics (patient, parent and/or doctor satisfaction)?

P: patients with cleft lip and/or palate;
I: closing hard palate before 18 months/ closing lips before 3 months;
C: closing hard palate after 18 months/ closing lips after 3 months;
O: maxillary and midface growth, speech, hearing, feeding capability, postoperative complications (fistulae), and esthetics (patient, parent and/or doctor satisfaction).

Relevant outcome measures

The guideline development group considered the following outcome measures as critical for decision making: maxillary and midface growth, velopharyngeal insufficiency, and esthetics. The outcomes speech, hearing, feeding capability, and postoperative complications were considered as important outcome measures.

Studies should report at least one of the outcomes of interest: esthetics (patient, parent and/or doctor satisfaction), maxillary and midface growth, and velopharyngeal insufficiency. For the outcome measure speech, a follow-up until at least the age of 4 years was deemed sufficient, and for outcome measure hearing. A follow-up length of at least 1 year after surgery was deemed sufficient. When papers reported a shorter follow-up time they were excluded.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the criteria for minimal clinically (patient) important difference for the dichotomous outcome measures; RR < 0.80 of > 1.25)

No a priori criteria were set for the continuous outcome measures because it largely depends on its context. If no information was available about the clinically important difference of the outcome measure, a difference of ten percent between the groups was defined as a minimally clinically important difference.

Search and select (Methods)

A previous systematic search was performed for the 2018 edition of the guideline in the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and December 3rd, 2014. The initial search identified 516 references of which 40 were assessed on full text. After assessment of full text, 22 studies were excluded, and 18 studies were included. To update the previous search, the databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 15th of January 2020. The detailed search strategy is depicted under the tab Methods. The updated systematic literature search resulted in 529 hits. Studies were selected based on the following criteria: studies investigated patients with cleft lip and palate were selected if they compared two different moments in time for repairing cleft lip and palate. A total 22 studies (2 reviews and 20 randomized controlled trials (RCTs)) were initially selected based on title and abstract screening. After reading the full text, the 2 review studies were excluded (see the table with reasons for exclusion under the tab Methods), and 9 RCTs were included and added to the results of the RCTs from the previous search. RCT's provide a higher level of evidence, therefore the (reviews of) observational studies of the previous search were removed from the analysis (n=15).

Results

Summary of literature

Description of studies

A total of 12 RCT studies was included in this literature summary. Most included studies are part of the Scandcleft trials (Heliövaare (2017); Heliövaare (2019), Karsten (2017); Karsten (2020), Küseler (2019), Lohmander (2017), Rautio (2017), Willardsen (2017)). In these trials, lip and soft palate closure at 3 to 4 months, and hard palate closure at 12 months served as a common method in each trial (Arm A, n= 75).

Trial 1 compared Arm A with hard palate closure at 36 months (Arm B, n=73). Which is of interest for this module.
Trial 2 compared Arm A with lip closure at 3 to 4 months and hard and soft palate closure at 12 months. Which is not included in the PICO.
Trial 3 compared Arm A with lip and hard palate closure at 3 to 4 months and soft palate closure at 12 months. Which is not included in the PICO.

The primary outcomes of the scandcleft trials were speech and dentofacial development, with a series of perioperative and longer-term secondary outcomes perioperative complication rate, operation and hospitalization time, postoperative recovery and feeding, speech at 12 and 18 months and 3 years, symptomatic fistulae, hearing, burden of care, and parent satisfaction at age 5 years (till the age of 5 or 8).

Reddy (2018) describes a blocked RCT (not part of de Scandcleft trials) that compared a one-stage palatoplasty at age 12 to 13 months (group A) with a two-stage palatoplasty patients with soft palatoplasty at age 12 to 13 months and hard palatoplasty at age 24 to 25 months (group B). A total of 100 nonsyndromic unilateral cleft lip and palate patients were included. The two groups were compared on fistula rates at 3 years and hypernasality at 6 years. In addition, both groups were compared with a control group of 20 noncleft controls on hypernasality at 6 years.

Richard (2006) describes an RCT in which the effects of operating the soft palate first (n=23, at follow-up 16) versus operating hard palate first (n=24, at follow-up n=19) on facial growth are studied in unilateral complete cleft lip and palate patients. The anterior operation consisted of a lip repair by Millard rotation advancement, a nasal correction using the McComb procedure and a hard palate repair by a single layer vomerine flap. The posterior operation consisted of a soft palate repair with medial von Langenbeck incisions. The two operations were undertaken three months apart with the first operation at 19 months of age. Preoperative maxillary models, speech and velopharyngeal function and ontological examinations were performed. Patients were followed until the age of four to six years.

Wada (1990) is a RCT that describes the effects of one-stage palatal closure (unilateral cleft n=14, bilateral n=8) versus two-stage palatal closure (unilateral n=16, bilateral n=7) in patients with uni- and bilateral cleft lip and palate. Also, the maxillary growth was compared with 11 healthy controls. Lip repair was performed at five months of age. One-stage repair was performed at 20 months using mucoperiosteal palatal pushback procedure. Two-stage repair was performed with primary veloplasty at 20 month and double overlapping palatal hingeflap procedure at five years ten months. Maxillofacial cast models were examined. The children are followed until the age of ten years.

Williams (2011) describes a RCT in which different surgical techniques and different timings of surgery for cleft palate were compared in terms of speech outcome and risk of palatal fistulae in patients with a complete unilateral cleft lip and palate. A 2x2x2 factorial clinical trial was used in which each subject was randomly assigned to one of eight groups: one of two different lip repairs (Spina versus Millard), one of two different palatal repairs (von Langenbeck versus Furlow) and one of two different ages at time of palatal surgery (9 to 12 months versus 15 to 18 months). All surgeries were performed by the same 4 surgeons. A total of 181 patients were operated at 9 to 12 months (Spina - Furlow = 35, Millard - Furlow = 43, Spina - Langenbeck = 51, Millard - Langenbeck = 52) and 195 at 15-18 months (Spina - Furlow = 48, Millard - Furlow = 47, Spina - Langenbeck = 46, Millard - Langenbeck = 54). Children were followed for at least the age of four years.

Results

1. Hard palate

1.1 Maxillary and midface growth (critical)

The dental arch relationship, measured with GOSLON Yardstick score, in children at five and eight years old is showed in the studies of Heliövaara (2017) and Heliövaara (2019), respectively. Children at five years of age (n=74) receiving the repairing of hard palate at 12 months (arm A) had a mean index score of 2.86 (SD 0.94) and 5-years old children (n=68) receiving the repairing of hard palate at 36 months (arm B) had a mean score of 2.58 (SD 0.87). This difference was not significant (p=0.06). At the age of 8 years, children in arm A (n=72) had a mean score of 3.03 (SD 0.85) and children in arm B (n=73) had a mean score of 2.82 (SD 0.81), p=0.137.

Karsten (2017) and Karsten (2020) present the occlusion as outcome of hard palate closure, measured with the Modified Huddart and Bodenham index (MHB), in children at five and eight years old. The total MHB score is sum of the anterior score and two posterior scores (cleft and non-cleft side) and ranges from +2 to -18). Children at the age of 5 in Arm A (n=75) had a mean total MHB score of -6.80 (SD 4.02) compared to 5-years old in Arm B (n=68) who had a mean total MHB score of -5.95 (SD 4.17). There was no significant difference between the groups: MD -0.86 (95% CI -2.21-0.50), p =0.21. Children at the age of 8 in Arm A (n=74) had a mean total MHB score of -9.57 (SD 5.53) compared to 8-years old in Arm B (n=73) who had a mean total MHB score of -8.51 (SD 5.67). There was no significant difference between the groups: MD -1.06 (95% CI -2.90-0.78), p =0.26.

Maxillary growth in 8 years old children is reported by Küseler (2020). Maxillary growth was assessed by cephalometric angles SNA (angle between selle, nasion, and subspinal point) and ANB (angle between maxilla and mandible) using lateral cephalograms. The mean ANB was 2.88 (95% CI 1.68 to 4.07) in the 8 years old children of Arm A (n=74) and the mean ANB was 3.55 (95% CI 2.44 to 4.67) in the 8 years old children of Arm B (n=72), p=0.12 (95%CI −0.19 to 1.66). The mean SNA was 78.42 (95% CI 76.63 - 80.20) in the 8 years old children of Arm A (n=74) and the mean SNA was 78.90 (95% CI 77.28 - 80.52) in the 8 years old children of Arm B (n=72), p=0.41 (95% CI −0.69 to 1.69).

Richard (2006) describes that there was no significant difference in overall facial growth between the different types of palatal closure sequencing.

Wada (1990) reports that in unilateral cleft palate patient's maxillary growth after two-stage palatal closure was comparable to those of non-cleft controls regarding depth and height of the maxilla, while after one-stage closure aberrant maxillary development was observed. For

patients with bilateral clefts, maxillary growth was similar in the one-stage and two-stage palatal closure groups.

Level of evidence of the literature

The level of evidence regarding the outcome maxillary and midface growth started at high as it was based on a RCT but was downgraded by three levels to very low due to study limitations (risk of bias, -1), the small study populations (imprecision, -1), and indirectness (-1).

1.2 Speech (velopharyngeal insufficiency) (critical)

Lohmander (2017) shows the effects of timing on the speech outcome hypernasality. Hypernasality was measured using two different methods: nasometry (nasalance score) and perceptual analysis in the study of Reddy (2018). The one-stage palatoplasty group (group A, n=50) had a mean nasalance score of 20.61 ± 9.23 percent and group B (two-stage palatoplasty, n=50) had a mean score of 16.77 ± 2.15 percent, which is a significant difference between the groups (p = 0.006; 95% CI 1.16 to 6.53). The perceptual analysis of hypernasality did not show significant difference between the groups: group A had 18 patients with hypernasality on single words versus 20 patients in group B (p=0.837 and p = 1.000 for single words and sentences respectively). Compared to the noncleft control group, group A had a significant higher score on hypernasality (p=0.001, 95% CI 2.05 to 7.52). There was virtually no difference in the mean nasalance scores for patients in group B and subjects in group C (p=0.088, 95%CI −0.14 to 2.02).

Richard (2006) reports that there was hypernasal resonance significant enough to warrant surgery in five patients in the posterioir-anterior group and four in the anterior-posterior group. This difference was not statistically significant.

Willardsen (2017) evaluates the effect of timing on speech outcome in terms of consonant production, in children at five years old. The percent consonants correct PCC) score showed a significant difference between the arms; a higher median PCC score in Arm A compared to Arm B (p=0.045). The median number of active cleft speech characteristics (CSCs) was significant higher in Arm B compared to Arm A (p=0.003).

Williams (2011) reports that of the patients operated early (9 to 12 months) 78% had hypernasality and 57% had nasal air emission versus 74% and 55% operated late (15 to 18 months) respectively. The odds ratio for hypernasality was 1.46 (95% CI: -0.84 to 2.54, p=0.12) and for nasal air emission 1.16 (95% CI: 0.72 to 1.85, p=0.49) for patients operated early versus patients operated late.

Level of evidence of the literature
The level of evidence regarding the outcome measure speech started at high as it was based on a RCT but was downgraded by three levels to very low due to study limitations (risk of bias, -1), the small study populations (imprecision, -1), and indirectness (-1).

1.3 Esthetics (patient, parent and/or doctor satisfaction) (critical)
No studies were identified that met the inclusion criteria and reported esthetic results as an outcome measure.

Level of evidence of the literature
The level of evidence regarding the outcome measure feeding capacity was not assessed due to lack of studies.

1.4 Hearing (important)
Richard (2006) reports that there was no significant difference in hearing status between the patients in the posterior-anterior group and the anterior-posterior group.

Level of evidence of the literature
The level of evidence regarding the outcome measure speech started at high as it was based on a RCT but was downgraded by three levels to very low due to study limitations (risk of bias, -2), and the small study populations (imprecision, -1).

1.5 Feeding capability (important)
The outcome feeding capacity was not reported in the included studies.

Level of evidence of the literature
The level of evidence regarding the outcome measure feeding capacity was not assessed due to lack of studies.

1.6 Postoperative complications (important)
Rautio (2017) presents surgical results of the Scandcleft studies, including complications after the surgery; major dehiscence of the palate needing fistula repair and number of patients who needed VPI surgery at the age of 5 years and extended to the moment that the youngest patient in the study was 5 years old (with updating until 9 years). In arm A a total of 6 patients (8%) had major dehiscence of the palate compared to a total of 4 patients (6%) in arm B (p=0.10). The number of patients who needed VPI surgery was 2 (3%) in arm A compared to 1 patient (1%) in arm B at the age of 5 years. After the extended period, a total of 18 patients (24%) needed VPI surgery in arm A compared to 18 patients (26%) in arm B.

Reddy (2018) reports four patients with fistula in the one-stage palatoplasty at age 12 to 13 months (group A, n=50), whereas in the two-stage palatoplasty two patients had fistulas: OR 2.1 (p = 0.409; 95% CI, 0.365 to 11.9).

Richard (2006) reports that there were 10 symptomatic fistulae in the anterior-posterior group and six in the posterior-anterior group (p> 0.05).

Williams (2011) describes that 44/181 patients operated early (9 to 12 months) developed a fistula, versus 37/195 in the late (15 to 18 months) operation group. The odds ratio for fistula formation in the early versus late group was 1.37 (95% CI: 0.84 to 2.22, p=0.21).

Level of evidence of the literature

The level of evidence regarding the outcome measure speech started at high as it was based on a RCT but was downgraded by three levels to very low due to study limitations (risk of bias, -2), and the small study populations (imprecision, -1).

2. Lip closure

No studies were found that compared lip closure before and after 3 months.

Level of evidence of the literature

The level of evidence was not assessed due to lack of studies.

Conclusions

1. Hard palate

1.1 Maxillary and midface growth (critical)

Very low GRADE	The evidence is very uncertain about the effect of timing of hard palate closure on maxillary and midface growth. *Sources: (Heliövaara, 2017; Heliövaara, 2019; Karsten, 2017; Karsten, 2020; Küseler, 2020; Richard, 2006; Wada, 1990.)*

1.2 Speech (velopharyngeal insufficiency) (critical)

Very low GRADE	The evidence is very uncertain about the effect of timing of hard palate closure on speech. *Sources: (Lohmander, 2017; Richard, 2006; Willardsen, 2017; Williams, 2011)*

1.3 Esthetics (patient, parent and/or doctor satisfaction) (critical)

- GRADE	There is no GRADE assessment possible due to lack of studies.

1.4 Hearing (important)

Very low GRADE	The evidence is very uncertain about the effect of timing of hard palate closure on hearing. *Sources: (Richard, 2006)*

1.5 Feeding capability (important)

- GRADE	There is no GRADE assessment possible due to lack of studies.

1.6 Postoperative complications (important)

Very low GRADE	The evidence is very uncertain about the effect of timing of hard palate closure on postoperative complications. *Sources: (Rautio, 2017; Reddy, 2018; Richard, 2006; Williams, 2011)*

2. Lip closure

- GRADE	There is no GRADE assessment possible due to lack of studies.

Considerations

Level of evidence (timing of closure)

The overall level of evidence regarding the timing of lip and palate closure is very low. The literature about the timing of palate closure is fragmented, and studies report different outcomes measures. No studies were found that compared different moments of lip closure.

Advantages and disadvantages of the different protocols

Unfortunately, no conclusions can be drawn from literature regarding the timing of lip and (hard) palatal closure. The literature does not answer the vivid discussion among professionals concerning the disadvantage of late palatal closure on speech development or the disadvantage of early palatal closure on maxillary growth. So, unfortunately, an optimal or uniform protocol on timing of palatal closure cannot be proposed based on literature. A complicating factor to study the effects of timing of repairing cleft lip and/or palate is the fact that the skills of the surgeon are hard to measure but it is likely that these skills - including education, personal training, experience, workload, and working environment - of the surgeon are an important factor in the final outcome. Also, a uniform and validated method to assess, quantify and document VPI is not available. Moreover, reliable, reproducible assessment of speech remains a challenging field. Comparable speech assessment requires both validated tools and systematic consensus training, which is not always available. Therefore, calibration is a key element for possible future studies and trials, including the surgical part of any multicenter study.

In addition to timing there are two other factors relevant for lip and palatal closure, i.e. the technique of closure and the sequence of closure. The technique of closure is reviewed in chapter Technique of lip and/or palate closure. The sequence of closure was for this guideline not regarded as a key factor for long term outcome, but it is undeniable an important variable in many of the protocols of Dutch Cleft teams. It therefore deserves attention.

The Scancleft studies show the most common used sequences of palatal closure. In Arm A and Arm B the lip and soft palate are closed first followed by the hard palate a later stage (in arm A within 12 months). In Arm C the lip is closed first and the whole palate is closed in one operation within 12 months of age. In Arm D the lip and hard palate (with a vomerine flap) are closed first, and the soft palate closed at a later stage but within 12 months after births. Another option is to close the soft palate first (as this is functionally the most important part of a full CL/P) and to close the hard palate and lip together in the second operation, also within 12 months of age. This sequence was popularized in France under guidance René Malek of and forms one Arm in a RCT published by Richard (2006).

To make it more complex there is very limited evidence that it may be beneficial to adjust the protocol to the type of cleft, for example the width of the cleft. A study by Botticelli (2020) on a subgroup of the Scandcleft trials suggests that - from an orthodontic point of view - a wide posterior cleft might benefit from later hard palate closure. The thought of adjusting your protocol to the local situation sounds logic and surgeons do sometimes adjust the protocol in an individual case intuitively, but this is a complex area for research. Numbers for trials become extremely small in most centers when adjusting to sub phenotyping the cleft and/or calculating relative dimensions, such as the width of the cleft in relation to the available tissue on the palatal shelve. This is an interesting field, but it has no implications for this guideline at present.

The velopharyngeal competence composite score (VPC-sum) as used in the study of Lohmander (2017) provides an indication of the velopharyngeal function by hypernasality, audible nasal air leakage, weakness of pressure consonants, and posterior nonoral articulation. No statistically significant differences in VPC-Sum or in hypernasality were found between the arms (Arm A versus Arm B).

The Scandcleft trials are of interest regarding possible difference in outcome due to variation in the sequence of closure of the palate during the first year of life. Although it was not a clinical question, the sequence of closure was part of the literature search. The working group has looked critically at the results of the Scandcleft trials regarding differences between Arm A, Arm C and Arm D and the RCT published by Richards in 2006. Kuseler (2020) did not find significant differences in facial growth between Arm A, C and D at age 8 years and Edwards (2006) did not find differences between the two arms in his study regarding speech and growth age 4 to 7 years. Therefore, sequence of closure of a full CLP during the first year of life does not seem to affect speech and or growth at a later age.

Timing in the Netherlands:
According to the NVSCA website the treatment protocols of the Dutch cleft-teams can be summarized:

- All teams except 1 close the lip at 3-4 months of age, one team closes the lip at 6 months of age.
- All teams close the soft palate mostly in the second half of the first year of life.

Closure of the hard palate diverges from 3 months to 12 years of age and shows the largest discrepancy.

Even in 2021 there remains scarcity of good studies. The available literature does not provide evidence for one single optimal/ best protocol to treat CLP during the first year of life. The current revision of this module in the guideline therefore will not solve the practice variation between different cleft teams regarding the closure of clefts of the lip and palate. As a consequence, we are unremittingly faced with different philosophies in examination and treatment of CL/P. Lack of consensus is most evident in the timing hard palate closure. However, modesty should suit the (Dutch) cleft-teams regarding their local protocols, customs of preferences due to this lasting knowledge deficit. Based on the literature there is no evidence one cleft team can state they have better protocol compared to another team. Cleft teams should support parents in offering a clear explanation of their treatment protocol. Furthermore, we should share our knowledge and experience among the Dutch cleft teams to make progress in cleft care.

Therefore, the working group advises each cleft team to develop and present a team preferred treatment protocol and to document the results carefully and systematically for internal quality control and external comparison.

Although not supported by clinical research:

1. The working group advises to close the cleft lip in the first 6 months of life, as it is common practice in the Netherlands. Then the lip is in good condition when the child starts babbling in the second half of the first year of life.
2. The working group advises to close the soft palate before 12 months to allow velum function to develop normally as babbling progresses to words around 1 year of age.

<u>Values and preferences of patients and their parents or guardians</u>

Parents can be confused by the variety of surgical protocols and (sometimes strong) opinions on cleft lip and palate treatment by teams or surgeons. They need unambiguous information and advice. Unfortunately, literature does not provide us with enough scientific evidence to support one of the protocols of timing of lip and palate closure over the other. Adversely the experience of a surgeon and his/her preferences for a certain technique is essential for optimal results. We advise that each team presents clearly what their vision on timing of cleft lip and palate closure is, elaborated in a straightforward protocol.

Costs/Finances

In general, good results should be achieved in as little surgeries as possible in order to keep the burden on the child, the parents as low as possible, and to keep the health care system within acceptable finances. It is important to properly lay the surgical base in the first year of life, and to keep intermediate interventions during growth to a minimum. The final corrections can be made when the patient has grown out, whereby the patient can then assess and decide for himself or herself what he or she needs or what he or she considers to be desirable.

Acceptance, feasibility and implementation

There is still a lot of variation in surgical practice between the cleft teams, although thereseems to be a trend towards early closure of the hard palate. Special interest groups within the NVSCA try to tackle this point. Within these groups, knowledge is shared, and appointments are made to standardize clinical practise as much as possible. In the Netherlands everyone has equal access to the cleft teams, so there will be no variation in accessibility of care. The different protocols of timing of lip and palate closure exist due to the experience, expertise and preferences of each surgeon and each cleft team. is important that the surgeon uses the (combination of different) technique(s) and the timing protocol in which he or she is most experienced in order to achieve the best result.

Recommendations

Rationale

The literature did not show a clear preference for timing of lip and palate closure, nor clear advantages and disadvantages of early or late closure of the palate. There is no medical indication for early lip closure (before 6 months), it is the preference of parents and social acceptance to close the lip early, to allow proper function closure should be performed within the first year of life. A broad recommendation is given, partly due to the lack of scientific evidence, taking into account the experience and expertise of the cleft team.

Aanbeveling-1

Sluit bij voorkeur de lip operatief in de eerste 6 maanden van het leven.

Aanbeveling-2

Sluit bij voorkeur het palatum durum en het palatum molle in het eerste levensjaar als optimale spraak wordt nagestreefd.

Aanbeveling-3

Sluit bij voorkeur alleen het palatum molle in het eerste levensjaar en het palatum durum pas later als optimale groei van de maxilla wordt nagestreefd.

Aanbeveling-4

Definieer een voorkeursaanpak binnen het schisisteam voor lipsluiting en palatumsluiting om ouders te adviseren in de besluitvorming.

Literature

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Validity and Maintenance

Module[1]	Responsible party[2]	Year of autorisation	Next assessment of actuality guideline[3]	Frequency of assessement of actuality[4]	Supervisor of actuality[5]	Relevant factors for changes in recommendations[6]
Timing repearing cleft lip and palate	NVPC	2021	2026	every 5 years	NVPC	None

[1] Name of module
[2] Responsible party for the module
[3] maximum of 5 years
[4] half a year, every (other, ..) year
[5] supervising party or parties
[6] Current reseach, changes in organizations/restitions, new available rescourses

Appendixes with module 3

Knowledge gaps

What is the effect of the timing of repairing cleft lip and palate on maxillary and midface growth, speech, hearing, feeding capability, postoperative complications (fistulae), and esthetics (patient, parent and/or doctor satisfaction)?

P: patients with cleft lip and/or palate;
I: closing hard palate before 18 months / closing lips before 3 months;
C: closing hard palate after 18 months / closing lips after 3 months;
O: maxillary and midface growth, speech, hearing, feeding capability, postoperative complications (fistulae), and esthetics (patient, parent and/or doctor satisfaction).

Implementation plan

Recommendation	Timeline for implementation: < 1 year, 1 to 3 years or > 3 years	Expected effects on costs	Preconditions for implementation (within specified timeframe)	Possible barriers for implementation[1]	Supposed actions for implementation[2]	Who is responsible for the action(s)[3]	Other comments
1	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC	Already recommended in previous version of the guideline
2	**1 to 3 years**	nil	Mainly current practice		Publication of the guideline	NVPC	
3	**1 to 3 years**	nil	Mainly current practice		Publication of the guideline	NVPC	
4	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC	Already recommended in previous version of the guideline

[1] Barriers can exist at the level of the professional, at the level of the organization (the hospital) or at the level of the system (outside the hospital). Consider, for example, disagreement with regard to the recommendation in different organizations, insufficient motivation or knowledge of the specialist, insufficient facilities or personnel, necessary concentration of care, costs, poor cooperation between disciplines, necessary rearrangement of tasks, et cetera.

[2] Actions that are necessary for implementation, but also actions that are possible to encourage implementation. Consider, for example, checking the recommendation during a quality review, publication of the guideline, developing implementation tools, informing hospital administrators, arranging proper reimbursement for a certain type of treatment, making cooperation agreements.

[3] Who is responsibilities for implementation of the recommendations will also depend on the level of barriers. Barriers at the level of the professional will often have to be resolved by the professional association. Organizational barriers will often be the responsibility of hospital administrators. Other parties, such as the NZA and health insurers, are also important in resolving barriers at system level.

Evidence tables

Research question: What is the effect of the timing of repairing cleft lip and palate on maxillary and midface growth, speech, hearing, feeding capability, postoperative complications (fistulae), and esthetics (patient, parent and/or doctor satisfaction)?

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Heliövaare, 2017	Type of study: Three parallel group, randomised clinical trials in international multicenter study Setting: 10 cleft teams Country: five countries: Denmark, Finland, Norway, Sweden, and the UK Source of funding: n.r.	Inclusion criteria: Caucasian, born with a non-syndromic complete UCLP (a soft tissue bridge of 5mm or less was accepted), and one caregiver had the national language as the mother tongue and spoke it with the child. Exclusion criteria: - N total at baseline: 148 Included in the Scandcleft trial: Arm A n=75 Arm B n=73	Describe intervention (treatment/procedure/test): Lip and soft palate closure at 3–4 months, and hard palate closure at 12 months	Describe control (treatment/procedure/test): Lip and soft palate closure at 3–4 months, and hard palate closure at 36 months	Length of follow-up: 5 years Loss-to-follow-up: I: 1 C: 5 Incomplete outcome data: n.r.	Outcome measures and effect size (include 95%CI and p-value if available): Maxillary and midface growth: Mean index score Arm A: 2.86 (SD 0.94) Arm B: 2.58 (SD 0.87) P=0.06	

		Important prognostic factors[2]: *n.r.* Groups comparable at baseline? n.r.					
Heliövaare, 2019	See Heliövaare, 2017 Source of funding: Finnish Association of Woman Dentists	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	Length of follow-up: 8 years Loss-to-follow-up: I: 3 C: 0 Incomplete outcome data: n.r.	Outcome measures and effect size (include 95%CI and p-value if available): Maxillary and midface growth: Mean index score Arm A: 3.03 (SD 0.85) Arm B: 2.82 (SD 0.81) P=0.137	
Karsten, 2017	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	Length of follow-up: Loss-to-follow-up: I: 0 C: 5 Incomplete outcome data: n.r.	Outcome measures and effect size (include 95%CI and p-value if available): Maxillary and midface growth: Modified Huddart and Bodenham index I: -6.80 (SD 4.02) C: -5.95 (SD 4.17)	

						MD -0.86 (95% CI -2.21-0.50) P =0.21	
Karsten, 2020	See Heliövaare, 2017 Source of funding: grant from the Freemasons, Stockholm, Sweden	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	<u>Length of follow-up</u>: 8 years <u>Loss-to-follow-up</u>: I: C: <u>Incomplete outcome data</u>:	Outcome measures and effect size (include 95%CI and p-value if available): <u>Maxillary and midface growth:</u> Modified Huddart and Bodenham index I: -9.57 (SD 5.53) C: -8.51 (SD 5.67) MD: −1.06 (−2.90–0.78) P=0.26	
Küseler, 2019	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	<u>Length of follow-up</u>: 8 years <u>Loss-to-follow-up</u>: I: 1 C: 1 <u>Incomplete outcome data</u>:	Outcome measures and effect size (include 95%CI and p-value if available): <u>Maxillary and midface growth:</u> cephalometric angles SNA: Arm A: 78.42 (95% CI 76.63 - 80.20) Arm B: 78.90 (95% CI 77.28 - 80.52) p=0.41 (95% CI −0.69 to 1.69)	

						cephalometric angles ANB: Arm A: 2.88 (95% CI 1.68 – 4.07) Arm B: 3.55 (95% CI 2.44 - 4.67) p=0.12 (95%CI −0.19 to 1.66)	
Lohmander, 2017	See Heliövaare, 2017 Source of funding: Swedish Research Council for Health, Working Life and Welfare, No. 2011–1443	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	<u>Length of follow-up</u>: 5 years <u>Loss-to-follow-up</u>: I: 3 C: 2 <u>Incomplete outcome data</u>:	Outcome measures and effect size (include 95%CI and p-value if available): <u>Speech:</u> VPC SUM score: Non-significant difference between groups: p=0.96 Hypernasality: Non-significant difference between groups: p=0.62	
Rautio, 2017	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	<u>Length of follow-up</u>: 5-9 years' Rates of fistula and surgery for VPI were assessed until the youngest patient of the study had	Outcome measures and effect size (include 95%CI and p-value if available): <u>Maxillary and midface growth:</u> <u>Speech:</u>	

					reached the age of 5 years with updating until 9 years for the latter. <u>Loss-to-follow-up</u>: n.r. <u>Incomplete outcome data</u>: n.r.	<u>Hearing:</u> <u>Feeding capacity:</u> <u>Postoperative complications:</u> <u>Esthetics</u>:	
Reddy, 2018	Type of study: randomized controlled trial Setting: high-volume center that performs more than 700 primary cleft lip and palate operations every year Country: GSR Institute of Craniofacial and Facial Plastic Surgery, India Source of funding: partly funded by the former World	<u>Inclusion criteria</u>: patients with nonsyndromic complete unilateral cleft lip and palate with a previously repaired cleft lip <u>Exclusion criteria</u>: patients with bilateral cleft lip and palate, patients with isolated cleft palate, patients younger than 12 months and older than 13 months, and patients with associated syndromic conditions.	Describe intervention (treatment/procedure/test): The Bardach two-flap technique20 with optimal muscle dissection or levator myoplasty was performed for patients in group A (at age 12 to 13 months) as a single procedure. The levator myoplasty was performed by relieving the levator muscle from the posterior border of the hard palate and repositioning it medially to be sutured to the contralateral levator veli palatini muscle. The tensor veli palatini muscle was not disturbed from its attachment. We did not dissect the tensor veli palatini muscle in the soft palate. In noncleft palates, the tensor veli palatini is inserted into the	Describe control (treatment/procedure/test): Soft palatoplasty with levator myoplasty (at age 12 to 13 months) and two-flap hard palatoplasty (at age 24 to 25 months) as a separate procedure.	<u>Length of follow-up</u>: fistula at 3 years and speech at 6 years <u>Loss-to-follow-up</u>: none <u>Incomplete outcome data</u>:	Outcome measures and effect size (include 95%CI and p-value if available): <u>Speech:</u> mean nasalance score I: 20.61 ± 9.2 C: 16.77 ± 2.15 p = 0.006 (95% CI 1.16 - 6.53) Hypernasality (perceptual): I: 18 patients C: 20 patients p = 0.837 <u>Postoperative complications</u>: Fistula	

	Health Collaborating Centre, Radboudumc, Nijmegen, The Netherlands	N total at baseline: 100 Important prognostic factors[2]: *Sex:* *I: 70% M* *C: 60% M* Groups comparable at baseline? n.r.	palatine aponeurosis and the surface behind the transverse ridge on the horizontal part of the palatine bone. In patients with cleft palate, the tensor veli palatini muscle is also attached in the same area and therefore does not require any dissection.			I: 4 patients C: 2 patients OR: 2.1 (p=0.409, 95% CI, 0.365 - 11.9)	
Richard 2006	Type of study: randomized controlled trial Setting: outpatients Country: United Kingdom Source of funding: non-commercial	Inclusion criteria: 1) children with non-syndromic unilateral cleft palate 2) age 3-60 months Exclusion criteria: - N total at baseline: I: Posterior-anterior (P-A): 23 C: Anterior-posterior (A-P): 24	Describe intervention (treatment/procedure/test): Posterior – anterior order of palate closure (The anterior operation consisted of a lip repair by Millard rotation advancement, a nasal correction using the McComb procedure and a hard palate repair by a single layer vomerine flap. The posterior operation consisted of a soft palate repair with medial von Langenbeck incisions. The two operations were undertaken 3	Describe control (treatment/procedure/test): Anterior-posterior order of palate closure: (The anterior operation consisted of a lip repair by Millard rotation advancement, a nasal correction using the McComb procedure and a hard palate repair by a single layer vomerine flap. The posterior operation consisted of a soft palate repair with medial von Langenbeck incisions. The two operations were undertaken 3	Length of follow-up: Until the age of 4-6 years Loss-to-follow-up: I: 6/23 (26%) 1 died, 5 lost contact C: 4/24 (17%) 1 syndromic, 3 lost contact	Outcome measures and effect size (include 95%CI and p-value if available): Maxillary growth: No significant differences in cephalometric measurements between groups Speech:	No power analysis for sample size is presented. Bias due to imprecision?

		Important prognostic factors[2]: *For example age* *I: 18.7 months* *C: 18.8 months* *Sex:* *I: 67% M* *C: 46% M* Groups comparable at baseline? Yes	months apart with the first operation at 19 months of age.)	months apart with the first operation at 19 months of age.)	Incomplete outcome data: Not reported	No significant differences in speech between groups. Hearing loss: No significant differences in hearing status between groups. Fistula formation: No significant differences in prevalence of symptomatic fistulae between groups.	
Wada 1990	Type of study: randomized controlled trial Setting: outpatients Country: Japan Source of funding: no funding	Inclusion criteria: 1) patients with unilateral or bilateral cleft palate Exclusion criteria: N total at baseline: One stage closure: Unilateral cleft: 14 Bilateral cleft: 8	Describe intervention (treatment/procedure/test): Lip repair at 5 months by Tennison's procedure Mucoperiosteal palatal pushback procedure at 20 months (one-stage closure)	Describe control (treatment/procedure/test): Lip repair at 5 months by Tennison's procedure Primary veloplasty at 20 months Double overlapping palatal hingeflap procedure at 5 years 10 months (two-stage closure)	Length of follow-up: Until the age of 10 years Loss-to-follow-up: Not reported Incomplete outcome data: Not described	Outcome measures and effect size (include 95%CI and p-value if available): Maxillary growth: In the unilateral cleft palate patients the maxillary growth of the patients who underwent the two-stage closure was comparable to those of the non-cleft controls	

		Two stage closure: Unilateral cleft: 16 Bilateral cleft: 7 Important prognostic factors[2]: *Not reported* Groups comparable at baseline? Unclear				regarding depth and height of the maxilla, while the one-stage closure patients had aberrant maxillary development. For the patients with bilateral clefts, the maxillary growth was similar in the one-stage and two-stage palatal closure groups.	
Willardsen, 2017	See Heliövaare, 2017 Source of funding: Swedish Research Council for Health, Working Life and Welfare, No. 2011–1443.	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	Length of follow-up: 5 years Loss-to-follow-up: I: 3 C: 2 Incomplete outcome data: n.r.	Outcome measures and effect size (include 95%CI and p-value if available): Speech: Percent consonants correct score (PCC): Median PCC score was higher in arm A compared with arm B (n=143). p=0.45 Cleft speech characteristics (CSCs). The median number of active CSCs is significant higher in in Arm B	

						compared with Arm A. p=0.03	
Williams 2009	Type of study: RCT Setting: outpatients 91 center) Country: United States of Amerika and Brazil Source of funding: non-commercial	Inclusion criteria: 1) patients with cleft lip at palate, of age and in good health for surgery Exclusion criteria: 1) family and patient did not show up for scheduled surgery date 2) condition that could interfere with speech development N total at baseline: Early surgery (E): 181 Late surgery (L): 195 Important prognostic factors[2]: *Not reported* Groups comparable at baseline? Unclear	Describe intervention (treatment/procedure/test): Palate closure at 9-12 months of age Spina – Furlow=35 Millard – Furlow= 43 Spina – von Langenbeck= 51 Millard – von Langenbeck= 52	Describe control (treatment/procedure/test): Palate closure at 15-18 months of age Spina – Furlow=48 Millard – Furlow= 47 Spina – von Langenbeck= 46 Millard – von Langenbeck= 54	Length of follow-up: Until at least the age of 4 years Loss-to-follow-up: After surgery 31/498 (6%) Reasons not described Incomplete outcome data: Not described	Outcome measures and effect size (include 95%CI and p-value if available): Odds ratio (OR) Speech: Hypernasality: E: 79% L: 73% OR (E versus L): 1.46 (95% CI: 0.84 – 2.54, p=0.12) Nasal air emission: E: 57% L: 54% OR (E versus L): 1.16 (95% CI: 0.72 – 1.85, p=0.49) Fistula formation: E: 44/181 L: 37 / 195 OR (E versus L): 1.37 (95% CI: 0.84 – 12.22, p=0.21)	Method of randomization and (presence or absence of) blinding unclear. Statistical analyses presented very adequately.

BCLP: bilateral cleft lip and palate; CP: cleft palate only; UCLP: unilateral cleft lip and palate

Notes:

1. Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures.
2. Provide data per treatment group on the most important prognostic factors ((potential) confounders).
3. For case-control studies, provide sufficient detail on the procedure used to match cases and controls.
4. For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders.

Risk of bias table for intervention studies (randomized controlled trials)

Research question: What is the effect of the timing of repairing cleft lip and palate on maxillary and midface growth, speech, hearing, feeding capability, postoperative complications (fistulae), and esthetics (patient, parent and/or doctor satisfaction)?

Study reference (first author, publication year)	**Describe method of randomisation[1]**	**Bias due to inadequate concealment of allocation?[2]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?[4]** (unlikely/likely/unclear)	**Bias due to loss to follow-up?[5]** (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?[6]** (unlikely/likely/unclear)
Heliövaara, 2017	The randomisation was done by use of a dice by the trial coordinator. The coordinator then provided an envelope to be opened just before the first surgery containing the group allocation for the child. The envelope was opened on the	Unlikely	Unlikely	Unlikely (operator blinding is not possible, but raters of all outcomes were blinded)	Unlikely Ratings were performed by a blinded panel of 16 orthodontists who scored all models.	Unlikely	Unlikely	Unclear

	morning of the first operation.							
Heliövaare, 2019	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	Unlikely Ratings were performed by a blinded panel of 11 orthodontists who scored all models.	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017
Karsten, 2017	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	Unlikely The raters were blinded for patient and centre.	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017
Karsten, 2020	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	Unlikely Dental casts were blindly assessed by four senior consultants in orthodontics from the participating cleft centres	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017
Küseler, 2019	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	Unlikely Raters of all outcomes were blinded	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017
Lohmander, 2017	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	Unlikely All assessments were performed blinded and individually using a laptop and the same type of headphones	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017
Rautio, 2017	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	Unclear Two surgeons did all of the first surgeries for centre A. The	Unclear	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017

				second operation (hard palate closure) was done by more surgeons than the first operation. The same surgeon did the 1st and 2nd surgery in 47% of the cases				
Reddy, 2018	The randomization sequence was generated by a computer program using blocked randomization in block sizes of 20 in each block. Within each block, participants were randomly assigned numbers by a computerized program to one of the two treatment groups. The randomization was performed by one surgeon who did not perform the surgery	Unlikely	Unlikely The surgical interventions and the randomization procedure were explained to the parent(s) of each eligible patient. If the parents did not agree to be part of the study, the child was excluded from the trial.	Unlikely The surgeon (R.R.R.) was blinded to the randomization process. After assigning the treatment method, each patient's parents were informed of the treatment plan by the surgeon who performed the randomization.	Unlikely The collected speech samples were presented in a random order to two qualified speech-language pathologists who were blinded to the subject's identity and treatment	Unlikely	Unlikely	Unlikely
Richard 2006	"randomly allocated, stratified by block randomization"	Unclear	Unclear	Unlikely	Unclear	Unlikely	Unclear	Unclear
Wada 1990	"randomly assigned"	Unclear	Unclear	Unlikely	Unclear	Unlikely	Unclear	Unclear
Willardsen, 2017	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017	Unlikely The transcribers were blinded to	See Heliövaare, 2017	See Heliövaare, 2017	See Heliövaare, 2017

					the randomisation of the children, and they only evaluated children connected to a cleft palate centre where they did not work.			
Williams 2009	"block randomization plan"	Unclear	Unclear	Unlikely	Unclear	Unlikely	Unclear	Unclear

1. Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.

2. Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules.

3. Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.

4. Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.

5. If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear.

6. Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.

Table of excluded studies

Author and year	Reason for exclusion
Bannister, 2017	Scandcleft study, descriptive study of postoperative nursing care
Bartzela, 2010	Retrospective observational study
Berkowitz, 2005	Does not meet selection criteria
Botticelli, 2019	Subgroup analyses of Scandcleft arm A and B; Velopharyngeal competence (VPC) and hypernasality
Botticelli, 2020	Subgroup analyses of Scandcleft arm A and B; outcome dento-occlusal assessment
Da Silva Filho, 2000	Does not meet selection criteria (follow-up too short)
Deluke 1997	Does not meet selection criteria (case series)
Farronato 2014	Does not meet selection criteria
Feragen, 2017	Scandcleft study, parental report on social and emotional experiences
Feragen, 2017	Scandcleft study, parental report on treatment outcomes
Friede, 2001	Retrospective observational study
Fudalej, 2010	Does not meet selection criteria
Fudalej, 2011	Prospective observational studu
Gerke 2014	Does not meet selection criteria (congress abstract)
Goodacre, 2003	Does not meet inclusion criteria (lip closure)
Grobbelaar, 1994	Observational study
Gundlach, 2013	Retrospective observational study
Hammarström, 2019	Comparison Scandcleft arm A and C
Hudson 1994	Does not meet selection criteria (review, not systematic)
Jørgensen	Subgroup analyses of Scandcleft arm A and B; outcome obstruent correctness and error types
Kirschner, 2000	Retrospective observational study
Klintö, 2014	Does not meet selection criteria (follow-up too short)
Landheer, 2010	Retrospective observational study
Latham 2007	Does not meet selection criteria
Liao, 2006	Systematic review of retrospective and non-randomized studies
Lohmander, 2011	Does not meet selection criteria
Molsted, 2017	Not a comparison study
Nollet, 2005	Meta-analysis of mainly observational studies to assess determinants for treatment outcome
O'Gara, 1994	Does not meet selection criteria (follow-up too short)
Persson, 2020	Comparison Scandcleft arm A and D
Prasad, 2000	Does not meet selection criteria
Randag, 2014	Retrospective observational study
Reddy, 2017	Systematic review with search till 2015, no meta-analysis
Rizell, 2017	Scandcleft study, outcome dental anomalies
Rodrigues, 2019	Systematic review with search till 2018, included 5 cohort studies in qualitative analysis
Rohrich, 1996	Retrospective observational study
Rohrich 2000	Does not meet selection criteria (review, not systematic)
Semb, 2017	Background article about scandcleft studies
Shaw, 2017	Background article about scandcleft studies
Silva, 2001	Included in systematic review Yang, 2010
Tanino, 1997	Does not meet selection criteria
Wada, 1990	Does not meet selection criteria
Westberg	Comparison Scandcleft arm A and C

Willadsen, 2012	Does not meet selection criteria
Willardsen, 2019	Same study as Willardsen, 2017; results presented per center
Williams, 2011	Does not meet selection criteria
Yang, 2010	Systematic review of retrospective nonrandomized studies
Ysunza, 2010	Does not meet selection criteria
Ysunza, 1998	Prospective observational study
Zemann, 2011	Observational study

Literature search strategy

Uitgangsvraag:

- **Timing lip- en palatumsluiting:** welke overwegingen (voor- en nadelen) spelen een rol bij het bepalen van het moment van het sluiten van de gehemeltespleet bij een patiënt met een schisis?
- **Techniek lip- en palatumsluiting:** is er voorkeur voor een chirurgische techniek bij het sluiten van de lip- en/of gehemeltespleet bij een patiënt met een schisis?

Database(s): Medline, Embase	Datum: 15-1-2020
Periode: 2014-heden	Talen: Engels

Zoekverantwoording

Database	Zoektermen	Totaal
Medline (OVID)	1 exp Cleft Lip/ or exp Cleft Palate/ or ((cleft* or fissum or hare or schi*is) adj5 (palat* or lip* or cheilo* or oral or orofacial)).ti,ab,kf. or palat*schi*is.ti,ab,kf. or cheilo*schi*is.ti,ab,kf. or labioschi*is.ti,ab,kf. or harelip*.ti,ab,kf. (29835) 2 exp Cleft Lip/su or Cleft Palate/su or exp "Reconstructive Surgical Procedures"/ or exp general surgery/ or exp surgery, plastic/ or operation*.ti,ab,kf. or surgery.ti,ab,kf. or closure*.ti,ab,kf. or correction.ti,ab,kf. or 'surgical repair'.ti,ab,kf. or palatoplast*.ti,ab,kf. or cheiloplast*.ti,ab,kf. or reconstruction.ti,ab,kf. or millard.ti,ab,kf. or (vomer* adj2 flap*).ti,ab,kf. or langenbeck*.ti,ab,kf. or furlow*.ti,ab,kf. (2059371) 3 1 and 2 (12468) 4 limit 3 to (english language and yr="2014 -Current") (2641) 5 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (428537) 6 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1939003) 7 4 and 5 (137) 8 (4 and 6) not 7 (233) 9 7 or 8 (370) **137 SRs + 233 RCT = 370 in totaal (129 uniek)**	**529**
Embase	'cleft lip'/exp OR 'cleft palate'/exp OR 'cleft lip face palate'/exp OR (((cleft* OR fissum OR hare OR schi*is) NEAR/5 (palat* OR lip* OR cheilo* OR oral OR orofacial)):ti,ab,kw) OR palat*schi*is:ti,ab,kw OR cheilo*schi*is:ti,ab,kw OR labioschi*is:ti,ab,kw OR harelip*:ti,ab,kw **AND** 'surgery'/exp/mj OR 'lip reconstruction'/exp OR 'palatoplasty'/exp OR 'plastic surgery'/exp OR 'reconstructive surgery'/exp OR operation*:ti,ab,kw OR surgery:ti,ab,kw OR closure*:ti,ab,kw OR correction:ti,ab,kw OR 'surgical repair':ti,ab,kw OR palatoplast*:ti,ab,kw OR cheiloplast*:ti,ab,kw OR labioplast*:ti,ab,kw OR reconstruction:ti,ab,kw OR millard:ti,ab,kw OR ((vomer* NEAR/2 flap*):ti,ab,kw) OR langenbeck*:ti,ab,kw OR furlow*:ti,ab,kw **AND**	

	(english)/lim AND (2014-2020)/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) **Gebruikte filters:** *Sytematische reviews* ('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) ***=103*** *RCT's* ('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) ***= 300*** **= 403 totaal (400 uniek)**	

Module 4 Technique repairing cleft lip and palate

Clinical question

Is there a preference for a surgical technique of repairing cleft lip and palate in children with cleft lip and/or palate?

Is er een voorkeur voor een chirurgische techniek bij het sluiten van de gehemeltespeet en de lipspleet bij kinderen met een (cheilognatho-)palatoschisis?

Introduction

The presence of a cleft lip and/or palate causes an abnormal appearance, the inability to close the lip and/or the inability to separate the nasal cavity from the oral cavity. A cleft palate causes nutritional and speech problems. A cleft lip is often associated with abnormalities of the nose affecting appearance and causing functional problems. A cleft in the alveolar arch results in orthodontic and dental abnormalities. The different parts of clefts alone or in combination often cause permanent stigmata. The aim of the multidisciplinary treatment of cleft lip and palate is to efficiently reduce these stigmata to a minimum.

Surgery that closes the lip and/or the palate (soft and/or hard) aims to resolve or prevent complaints, and at the same time to induce as few new problems as possible. Many different techniques have been described over time. It is important to know which technique gives the best results in the short term and the long term. When writing the previous edition of the guideline (2018), it appeared that there was a shortage of prospective and randomized studies.

Search and select

A systematic review of the literature was performed to answer the following question:
What is the effect of different techniques of repairing cleft lip and palate on speech, hearing, feeding capability, maxillary and midface growth, postoperative care and complications and esthetics (patient, parents and/or doctor satisfaction)?

P: patients with cleft lip and/or palate
I: surgical intervention with a specific technique for repairing cleft lip and palate
C: surgical intervention with another surgical technique for repairing cleft lip and palate
O: speech, hearing, feeding capability, maxillary and midface growth, postoperative complications, esthetics (patient, parent and/or doctor satisfaction).

<u>Relevant outcome measures</u>

For cleft palate repair, the guideline development group considered the following outcome measures as critical or important for decision making:
speech, hearing and feeding capability were considered as critical.
maxillary and midface growth, postoperative complications, and esthetics were considered as important.

For cleft lip repair, the guideline development group considered the following outcome measures as critical or important for decision making:
postoperative complications, and esthetics were selected as critical.
Speech, feeding capability, and maxillary and midface growth, were considered as important.

Studies should report at least one of the outcomes of interest: esthetics (patient, parent and/or doctor satisfaction), speech, feeding capability, postoperative complications. For the outcome speech, a follow-up until at least the age of four years. A follow-up length of at least one year was deemed sufficient for the outcome hearing. When papers reported a shorter follow-up time they were excluded.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the criteria for minimal clinically (patient) important difference for the dichotomous outcome measures; RR < 0.80 of > 1.25)

No a priori criteria were set for the continuous outcome measures because it largely depends on its context. If no information was available about the clinically important difference of the outcome measure, a difference of ten percent between the groups was defined as a minimally clinically important difference.

Search and select (Methods)

A systematic search had been performed for the 2018 edition of the guideline in the databases Medline (through OVID), Embase and the Cochrane Library on December 3rd, 2014. This search identified 519 references, and 39 reference were selected after reviewing title and abstracts. After checking eligibility of full text articles, 25 studies were excluded and 14 studies were included in the summary of literature, of which seven RCTs, and seven observational studies. To update the previous search, the databases Medline (via OVID) and Embase (via Embase.com) were searched with previous search terms until January 1st, 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 529 new hits. Studies were selected based on the following criteria: studies including patients with cleft lip and/or palate were selected if they compared two different operative techniques in terms of closure of the soft palate. A total 14 studies (8 reviews and 6 RCTs) were initially selected based on title and abstract screening. After reading the full text, the 8 review studies and 4 RCTs were excluded (see the table with reasons for exclusion under the tab Methods), and 2 RCTs were included and added to the six RCTs of the previous search who met the selection criteria above.

Results

Two studies were added to the 2018 version of the analysis of the literature describing (lip and) palate closure; one study described the closure of palatum molle/soft palate and one study described the closure of palatum durum/hard palate. No studies describing lip closure were added. To distinguish between lip and palate closure and between hard and soft palate, the literature analyses is divided in three parts:

1. Palatum molle / soft palate
2. Palatum durum / hard palate
3. Lip closure

Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

1. Palatum molle/ soft palate

Description of studies

A total of four randomized controlled trials (RCTs) were included: Abdel – Aziz (2011); Henkel, (2004); Ganesh (2015); Williams (2011).

The study of Abdel-Aziz and Ghandour (2011) is a RCT that compares the effects of the Furlow double opposing Z-plasty (n=22) and the Wardill – Kilner V-Y (n=24) pushback technique in terms of velopharyngeal outcome and speech in patients with a cleft of the soft palate and no other congenital anomalies. Age at surgery was 11-36 months. All cases were followed for at least 1 year. Flexible nasopharyngoscopy and perceptual speech resonance evaluation were used to assess the velopharyngeal closure and speech outcome respectively.

The study of Henkel (2004) is a RCT in which the effects of soft palate closure using the wave-line technique in the intravelar veloplasty (n=12) are compared to the classic intravelar veloplasty (n=12) in terms of speech outcomes in patients with complete cleft of the soft palate. Patients were randomly assigned to one or the other group following a previously determined succession. Surgery was performed at the age of 10-12 months. Speech was investigated at the age of 4 years by a speech pathologist blinded for the technique.

Williams (2011) describes a RCT in which different surgical techniques and different timings of surgery for complete cleft palate were compared in terms of speech outcome and risk of palatal fistulae in patients with a complete unilateral cleft lip and palate. A 2x2x2 factorial clinical trial was used in which each subject was randomly assigned to 1 of 8 groups: 1 of 2 different lip repairs (Spina versus Millard), 1 of 2 different palatal repairs (von Langenbeck versus Furlow) and 1 of 2 different ages at time of palatal surgery (9-12 months versus 15-18 months). All surgeries were performed by the same 4 surgeons. A total of 181 patients were operated at 9-12 months (Spina – Furlow = 35, Millard – Furlow = 43, Spina – Langenbeck = 51, Millard – Langenbeck = 52) and 195 at 15-18 months (Spina – Furlow = 48, Millard – Furlow = 47, Spina – Langenbeck = 46, Millard – Langenbeck = 54). Children were followed for at least the age of 4 years.

Ganesh (2015) describes a RCT to evaluate the effects of two different surgical protocols (vomer flap and separate soft palate closure versus two-flap technique) on dental arch relationship, speech outcomes and the occurrence of fistula during mixed dentition (7-10 years). Out of 200 patients recruited only 179 patients completed the treatment for lip and palate repair. Out of those 179 patients, 91 patients were allocated to the VF Group and 88 patients to the TF group. However, only 85 patients in total were seen at the follow up during the period of mixed dentition. In the vomer flap group (n=40), the cleft lip was repaired using the Millard technique along with nose correction. After 6 months, soft palate repair was carried out with sharp separation of the muscle fibers from the enveloping oral and the nasal mucosa and from the hard-palatal shelves. The tensor tendon was released just medial to the hamulus, followed by retro positioning and plication of muscle bundles along the midline. In the two-flap group (n=45), cleft lip was repaired by the Millard technique with nose correction, and anterior palate repair up to the incisor foramen. Six months later, the palate was repaired with two-flap palatoplasty. Both in the two-flap group and the vomer flap group the same technique of soft palate closure was followed. Greater part of the velar muscles (Tensor veli palatini & Levator veli palatini) was dissected free from its abnormal attachments followed by recreation of the muscular sling, retro positioning, and plication of muscle bundles along the midline. All operations were performed by the same plastic surgeon.

Comparison 2. Palatum durum/ hard palate

Description of study

One study is included in this literature summary that described hard palate surgery (Rossell-Perry, 2017).

The article of Rossell-Perry (2017) a prospective, randomized, single-blind controlled trial describes the effect of relaxing incisions on maxillary growth after primary palatoplasty in patients with unilateral cleft lip and palate at the age of five. Cleft lip repair was performed in all patients at approximately 3 months of age using the two-flap (n=72) or one-flap method (n=70) according to their usual surgical protocol: upper rotation advancement plus double unilimb Z-plasty or triple unilimb Z-plasty. The one-flap palatoplasty differed from the two-flap technique by the use of a relaxing incision on the cleft side only. Extension of the subperiosteal dissection was the same in both groups. The soft palate surgical treatment was likewise identical with both techniques. All operations were performed by the same plastic surgeon. Dental arch relationships and maxillary arch dimensions were evaluated at the age of five. The dental arch was rated from 1 ("excellent") to 5 ("very poor") and maxillary arch was evaluated as (1) intercanine distance = distance between the canine mesiobuccal cusp tips, (2) intermolar distance = distance between the second molar mesiobuccal cusp tips, and (3) maxillary length = distance in the midline from a point between the incisors to the posterior border of the maxilla.

Comparison 3. Lip closure

Description of studies

Three randomized studies comparing different lip closure techniques were identified; (Chowdri, 1990; De Silva Amartunga, 2004, Williams. 2011).

Chowdri (1990) is a randomized comparative study performed in India in which rotation advancement lip repair as described by Millard (n=58) is compared to triangular flap lip repair as described by Randall (n=50) in terms of esthetic results and complications. Age at lip repair was 3 years. Patients were followed for 1 to 6 years. Esthetics were evaluated independently by 3 examiners, each scoring surgical results on a 0 to 10 scale for 10 aspects of lip and nose, making a total assessment of 100 points for the 10 components studied.

De Silva Amaratunga (2004) describes an RCT in which the esthetic results of unilateral lip repair are compared for Millard's method (n=18), Cronin's method (n=21) and a combination of the two methods (n=20). Lip repair was performed at the age of 2 to 6 months. The results of the repair were assessed 3 months after surgery. Esthetic results were assessed using the Cleft Lip Component Symmetry Index (0 to 100, with 100 points indicating perfect symmetry).

Williams (2011) describes a RCT which is mentioned in the section on palatal closure above. In this study not only the surgical techniques for closure of palate where compared but also the surgical closure of lips with 2 different techniques. A 2x2x2 factorial clinical trial was used in which each subject was randomly assigned to 1 of 8 groups: 1 of 2 different lip repairs (Spina versus Millard), 1 of 2 different palatal repairs (von Langenbeck versus Furlow) and 1 of 2 different ages at time of palatal surgery (9 to 12 months versus 15 to 18 months). All surgeries were performed by the same 4 surgeons. A total of 181 patients were operated at 9 to 12 months (Spina - Furlow = 35, Millard - Furlow = 43, Spina - Langenbeck = 51, Millard - Langenbeck = 52) and 195 at 15 to 18 months (Spina - Furlow = 48, Millard - Furlow = 47, Spina - Langenbeck = 46, Millard - Langenbeck = 54). Children were followed for at least the age of 4 years.

Results

The different techniques and the different outcomes in the included studies are presented in Table 4.1.

Table 4.1 different comparisons and different techniques in the included studies

Study	Techniques		Results	
	Experimental group	**Control group**	**Experimental group**	**Control group**
1. Soft palate				
Abdel-Azziz, 2011	Furlow double opposing Z-plasty (n=22)	Wardill – Kilner V-Y pushback technique (n=24)	Speech Nasality: 0.88 ± 1.01 Nasal emission: 0.92 ± 1.1 Complications: Fistulae N=2	Speech Nasality: 0.27 ± 0.55 Nasal emission: 0.36 ± 0.73 Complications: Fistulae N=0
Ganesh, 2015	vomer flap (Millard technique for the lip along with nose correction) (n=40)	two-flap technique for the whole palate (Millard technique with nose correction, and anterior palate repair up to the incisor foramen) (n=45)	Speech Hypernasality Normal: 11.8% Mild: 70.6% Moderate: 17.6% Weak oral pressure words (present): 41.2% sentences (present): 41.2% maxillary and midface growth Dental arch relation: 2.15 (0.662)	Speech Hypernasality Normal: 20.5% Mild: 76.9% Moderate: 2.6% Weak oral pressure words (present): 15.4% sentences (present): 15.4% maxillary and midface growth Dental arch relation: 2.49 (0.757)
Henkel, 2004	wave-line technique in the intravelar veloplasty (n=12)	classic intravelar veloplasty (n=12)	Speech Compensatory grimacing when speaking: 1/12 (α-ι) test negative: 12/12 Sounds: /l/, /n/, /d/, /t/ normal: 6/10 Sounds /z/, /s/ normal: 6/10 Complications 1 patient with wound dehiscence in the oral mucosa	Speech Compensatory grimacing when speaking: 8/12 (α-ι) test negative: 8/12 Sounds: /l/, /n/, /d/, /t/ normal: 3/12 Sounds /z/, /s/ normal: 4/12 Complications No complications
Williams, 2011	Spina-Furlow 9-12 months (n=35) Spina – Langenbeck 9-12 months (n=51) Spina-Furlow 15-18 months (n=48) Spina – Langenbeck 15-18 months (n=46)	Millard -Furlow 9-12 months (n=43) Millard – Langenbeck 9-12 months (n=52) Millard - Furlow 15-18 months (n=47) Millard – Langenbeck 15-18 months (n=54)	Speech Hypernasality (Von Langenbeck versus Furlow) OR 0.54 (95% CI: 0.31 – 0.95) p=0.014 Nasal air emission (Von Langenbeck versus Furlow) OR: 0.72 (95% CI 0.45 – 1.15) p=0.12 Complications In total 37/269 (14%) patients operated by von Langenbeck developed fistula, versus 44/190 (23%) in the Furlow operation group. The odds ratio for fistula formation in the von Langenbeck versus the Furlow group was 1.93 (95% CI: 1.12 – 3.14, p=0.008).	
2. Hard palate				

Rossell-Perry, 2017	two-flap upper rotation advancement plus double unilimb Z-plasty or triple unilimb Z-plasty (n=72)	one-flap upper rotation advancement plus double unilimb Z-plasty or triple unilimb Z-plasty and use of a relaxing incision on the cleft side only (n=70)	<u>maxillary and midface growth</u> 5-year-olds' index: 2.57 ± 1.08	<u>maxillary and midface growth</u> 5-year-olds' index: 2.80 ± 1.91
3. Lip closure				
Chowdri, 1990	Millard (n=58)	triangular flap lip repair as described by Randall (n=50)	Esthetics Lip: 38 ± 5 Nose: 34 ± 4 Lip + Nose: 71 ± 10	Esthetics Lip: 39 ± 5 Nose :34 ± 4 Lip + Nose: 73 ± 12
De Silva Amartunga, 2004	Millard's method (n=18)	Cronin's method (n=21) combination of the two methods (n=20)	Esthetics Cupid's bow height 77 Vermillion height: 87 Nostril height symmetry: 93 Nostril width: 96	Esthetics Cupid's bow height Cronin 86 Combined: 87 Vermillion height: Cronin: 97 Combined: 97 Nostril height symmetry: Cronin: 93 Combined: 92 Nostril width: Cronin: 99 Combined: 95
Williams, 2011	See above			

1. Palatum molle/ soft palate

1.1 Outcome measure speech (critical)

Four studies (Abdel-Azziz and Ghandour (2011); Ganesh (2015); Henkel (2004); Williams (2011)) assessed speech. Due to heterogeneity of the different techniques evaluated in the studies and the different outcome measures, it was not possible to pool the data.

Abdel-Azziz and Ghandour (2011) described in 46 patients that velopharyngeal closure and speech outcome were statistically better after Furlow Z-plasty than after the V-Y pushback procedure. Auditory perceptual assessment for nasality was 0.88 ± 1.01 in the Furlow group and 0.27 ± 0.55 in the V-Y pushback group (p=0.035). Nasal emission was 0.92 ± 1.1 in the Furlow group versus 0.36 ± 0.73 in the V-Y pushback group (p=0.049). Glottal articulation was 1.13 ± 1.04 in the Furlow group and 0.50 ± 0.74 in the V-Y pushback group (p=0.029). There was no statistically significant difference in pharyngealization of fricatives and speech intelligibility between the groups.

Ganesh (2015) reported speech outcomes of patients receiving vomer flap (VF) technique or two-flap technique (TF). In the VF group of 91 patients 36 needed releasing incisions. It was observed that the researchers were able to achieve less posteriorization of the velum in VF group when compared to the TF group (personal comment author upon e-mail request from working group May 2020). The results of the speech outcomes were obtained from only 34 patients in the VF group and 39 in the TF group, for various reasons. The results showed that 11.8% of patients in the vomer-flap group had normal resonance and 17.6% had moderate hypernasality. In the two-flap group 20.5% of patients had normal resonance and 2.6% showed moderate hypernasality, resulting in a RR of 6.88 (95% CI 0.87 to 54.35) for moderate hypernasality. Weak oral pressure consonants were perceived in 41% and 15% of the vomer flap and two-flap group, respectively (RR 2.68 (95% CI 1.16 to 6.19)).

Henkel (2004) showed in 24 patients that compensatory grimacing when speaking was observed in 1/12 patients in the wave-line veloplasty group versus 8/12 in the classic intravelar veloplasty group (p<0.05). A sound difference was observed in speech with a closed and open nose in 12/12 of the wave-line veloplasty group and 8/12 in the classic intravelar veloplasty group (p<0.05). Articulation of alveolar sounds was judged normal in significantly more subjects in the wave-line veloplasty group (6/10 (2 children too playful for examination)) versus the classic intravelar veloplasty group (3/12, p<0.05). They concluded that the waveline technique seems to be superior, however group size is small.

Williams (2011) reports in 376 subjects that patients operated using the Von Langenbeck technique had an 0.54 OR (95% CI 0.31 to 0.95, p=0.014) for hypernasality and a 0.72 OR (95% CI: 0.45 to 1.15, p=0.12) for nasal air emission when compared to the Furlow technique.

Level of evidence of the literature

The level of evidence regarding the outcome measure speech started at high as it was based on randomized controlled trials. The level of evidence was downgraded by three levels to very low due to the risk of bias (-1, concealment allocation) and limited number of included patients (-2, imprecision).

1.2 Outcome measure hearing (critical)

The outcome hearing was not reported in the included studies.

Level of evidence of the literature
The level of evidence regarding the outcome measure hearing was not assessed due to lack of studies.

1.3 Outcome feeding capability (critical)
The outcome feeding capacity was not reported in the included studies.

Level of evidence of the literature
The level of evidence regarding the outcome measure feeding capacity was not assessed due to lack of studies.

1.4 Outcome measure maxillary and midface growth (important)
The dental arch relationship was measured by Ganesh (2015) with GOSLON scores; 1: good growth - 5: very poor growth. GOSLON scores of the 40 patients in the vomer flap group and 45 patients in the two-flap group were based on the intraoral digital photographs examined by a surgeon and an orthodontist, who were not members of the cleft team. These photographs were taken during regular follow-up through the period of mixed dentition (age range 7 to 9 years old). The mean GOSLON score in the vomer flap group was lower than the GOSLON score in the two-flap group (mean difference = -0.34 (95%CI -0.64 to -0.04). In the vomer flap group, 70% of the patients demonstrated good growth (GOSLON scores 1 and 2) and 30% revealed adequate growth (GOSLON score 3). In the TF group, 54% of the patients displayed good growth, 37.7% had the adequate growth category, and 8.8% had poor growth (GOSLON score 4). None of the patients from either group were found to have very poor GOSLON scores (GOSLON score 5).

Level of evidence of the literature
The level of evidence regarding the outcome maxillary and midface growth started at high as it was based on a randomized controlled trial. The level of evidence was downgraded by three levels to low due to loss to follow up (-1, risk of bias), and the small study population and crossing the borders of clinical relevance (-2, imprecision).

1.5 Outcome measure postoperative complications (important)
Four studies (Abdel-Azziz and Ghandour (2011); Ganesh (2015); Henkel (2004); Williams (2011)) assessed postoperative complications. Due to heterogeneity of the different techniques evaluated in the studies, it was not possible to pool the data.

Abdel-Azziz (2011) reports that in total 0/22 fistulas were found in the Furlow group versus 2/24 in the V-Y pushback procedure group (no p-value reported).

Ganesh (2015) reported that palatal fistula appeared only in one patient in the vomer flap group (n=40) and did not appear in the two-flap group (n=45).

Henkel (2004) reports that 1 patient in the wave-line group developed wound dehiscence in the oral mucosa that healed secondarily without complications (p-value not reported). All other patients healed without complications.

In Williams (2011) only fistula rates were compared and were found not to be different between the Spina and Millard repair technique. In total 37/269 (14%) patients operated by von Langenbeck developed fistula, versus 44/190 (23%) in the Furlow operation group. The odds ratio for fistula formation in the von Langenbeck versus the Furlow group was 1.98 (95% CI: 1.16 to 3.07, p=0.010).

Level of evidence of the literature
The level of evidence regarding the outcome postoperative complications started at high as it was based on randomized controlled trials. The level of evidence was downgraded by three levels to very low due to the risk of bias (-1, concealment allocation) and limited number of included patients (-2, imprecision).

1.6 Outcome measure esthetics (important)
The outcome esthetics was not reported in the included studies.

Level of evidence of the literature
The level of evidence regarding the outcome measure esthetics was not assessed due to lack of studies.

2. Palatum durum / hard palate
2.1 Outcome measure speech (critical), 2.2 Outcome measure hearing (critical), 2.3 Outcome feeding capability (critical), and 2.6 Outcome measure esthetics (important)
These outcome measures were not reported in the included studies.

Level of evidence of the literature
The level of evidence regarding the outcome measures speech, hearing, feeding capability, and esthetics were not assessed due to lack of studies.

2.4 Outcome measure maxillary and midface growth (important)
Rossell-Perry (2017) reported dental arch relationships and maxillary arch dimensions after 5 years. Dental arch relationships were assessed using the 5-year-olds' index ranging from 1 (excellent dental arch relationship) to 5 (very poor dental arch relationship). The mean score for the 5-year-olds' index was 2.57±1.09 in the two-flap technique group (n=72) and 2.80±1.91 in the one-flap technique group (n=70); these scores were not significantly different between the groups. None of the patients developed a very poor dental arch relationship.

Maxillary arch dimensions were measured on the maxillary arch casts (1) intercanine distance = distance between the canine mesiobuccal cusp tips, (2) intermolar distance = distance between the second molar mesiobuccal cusp tips, and (3) maxillary length = distance in the midline from a point between the incisors to the posterior border of the maxilla. The intercanine distance was 27.64±1.57, the intermolar distance was 35.32±1.32 and the maxillary length was 29.63±2.14 in the two-flap group. In the one-flap group the intercanine distance was 27.32±1.87, the intermolar distance was 35.92±1.21 and the maxillary length was 30.02±2.04. These difference between the groups were not significant.

Level of evidence of the literature
The level of evidence regarding the outcome maxillary and midface growth started at high as it was based on a randomized controlled trial. The level of evidence was downgraded by two levels due to risk of bias (-1, incomplete accounting of patients loss to follow up) and due to the small study population (-1, imprecision).

2.5 Outcome measure postoperative complications (important)
Rossell-Perry (2017) reported an equal number of postoperative palatal fistulas in both the two-flap and one-flap group (n = 2; 2.85%). All fistulas were asymptomatic and located in the middle third of the palate.

Level of evidence of the literature
The level of evidence regarding the outcome postoperative complications was nog graded due to the small number of events.

3. Lip closure

3.1 Outcome measure speech (important), 3.2 Outcome feeding capability (important), 3.3 Outcome measure maxillary and midface growth (important), 3.4 Outcome measure postoperative complications (critical)

These outcome measures were not reported in the included studies.

Level of evidence of the literature
The level of evidence regarding the outcome measures speech, hearing, and feeding capability, maxillary and midface growth, and postoperative complications were not assessed due to lack of studies.

3.5 Outcome measure esthetics (critical)

Three studies (Chowdri (1990); De Silva Amaratunga (2004); Williams (2011)) assessed esthetics. Due to heterogeneity of the different techniques evaluated in the studies, it was not possible to pool the data.

Chowdri (1990) report that the esthetic scores were similar in the patients treated with rotation advancement repair (71 ± 10) and triangular flap repair (73 ± 12, p> 0.50). There was also no significant difference for the lip-scores alone (p>0.10) or the nose-scores alone (p>0.80) between the two surgical techniques. Regarding postoperative complications, this study reports that 5/58 (9%) of the patients in the rotation flap advancement group developed scar hypertrophy compared to 2/50 (4%) in the triangular flap group (p>0.10). Furthermore, 4 patients in the rotation advancement group developed wound dehiscence, compared to 0 patients in the triangular flap group (p-value not reported).

De Silva Amaratunga (2004) reports that the Cleft Lip Component Symmetry Index score of philtral height, vermillion height, and Cupid's bow height achieved with the combined method was comparable to that achieved with Cronin's method and was superior to that obtained with Millard's method (p< 0.01). Further, the combined method achieved a Cleft Lip Component Symmetry Index score for the philtral width that was not significantly different from that of Millard's method and better than that of Cronin's method (p< 0.01).

In Williams (2011) only fistula rates were compared and were found not to be different between the Spina and Millard repair techniques. The esthetic result of the different lip-closure techniques was not compared in this study.

Level of evidence of the literature
The level of evidence regarding the outcome esthetics started at high as it was based on randomized controlled trials. The level of evidence was downgraded by three levels due to due to risk of bias (-1, incomplete accounting of patients loss to follow up) and limited number of included patients (-2, imprecision).

Conclusions

1. Soft palate

1.1 Outcome measure speech (critical)

Very low GRADE	The evidence is uncertain about the effect of different techniques of soft palate repair on speech related outcomes like hypernasality and nasal emission. *Sources: (Abdel-Azziz, 2011; Ganesh, 2015; Henkel, 2004; Williams, 2011)*

1.2 Outcome measure hearing (critical), 1.3 Outcome feeding capability (critical) and 1.6 Outcome measure esthetics (important)

- GRADE	There is no GRADE assessment due to lack of randomized studies.

1.4 Outcome measure maxillary and midface growth (important)

Very low GRADE	The evidence is uncertain about the effect of the vomer flap technique (one-layer closure) compared to the two-flap technique on dental arch relationship (measured at the age of mixed dentition). *Sources: (Ganesh, 2015)*

1.5 Outcome measure postoperative complications (important)

Very low GRADE	Postoperative complications, in the sense of fistulae, may appear using different techniques, however, the evidence is uncertain about the effects of the techniques on the appearance of fistulae. *Sources: (Abdel-Azziz, 2011; Ganesh, 2015; Henkel, 2004; Williams, 2011)*

2. Hard palate

2.1 Outcome measure speech (critical), 2.2 Outcome measure hearing (critical) 2.3 Outcome feeding capability (critical) and 2.6 Outcome measure esthetics (important)

- GRADE	There is no GRADE assessment due to lack of studies.

2.4 Outcome measure maxillary and midface growth (important)

Very low GRADE	The evidence is uncertain about the effect of one-flap versus the two-flap techniques for closing the hard palate at approximately 3 months of age on dental arch relationships and maxillary arch dimensions after 5 years. *Sources: (Rossell-Perry, 2017)*

2.5 Outcome measure postoperative complications (important)

- GRADE	There is no GRADE assessment due to events. *Sources: (Rossell-Perry, 2017)*

3. Lip closure

3.1 Outcome measure speech (important), 3.2 Outcome feeding capability (important), 3.3 Outcome measure maxillary and midface growth (important), 3.4 Outcome measure postoperative complications (critical)

- GRADE	There is no GRADE assessment due to lack of studies.

3.5 Outcome measure esthetics (critical)

Very low GRADE	The evidence is very uncertain about the effect of different techniques of lip repair on esthetics. *Sources: (Chowdri, 1990; De Silva Amaratunga, 2004; Williams, 2011)*

Overwegingen - van bewijs naar aanbeveling

Level of evidence

The level of evidence regarding different techniques of lip and palate repair is limited. Overall, the literature is fragmented due to the amount of different techniques and different outcomes measures. Summarizing it can be stated that hard and soft palate repair with perfect unhampered growth and optimal speech without VPI remains the holy grail for which no perfect solution has been found so far.

For the future the choice of surgical technique ideally should take into account sub phenotyping of the cleft, relevant genetic information and an estimate of the potential growth of the maxilla for each individual, but this has not reached clinical practise so far.

For lip closure, the evidence is uncertain about the effect the different techniques on esthetics and the other outcome measures were not described in the studies. In addition, the level of evidence is hampered by the fact that the skill and experience of the surgeon plays an important role in all surgery related studies and no doubt also in CLP closure techniques. Small – but perhaps important - technical variations between centres and surgeons performing the same operation do exist (and are the driving force behind innovation). As a result, a von Langenbeck closure in the hand of surgeon or centre A might differ from the same operation by surgeon or centre B. Even within centres true calibration between surgeons is not something commonly done. This all makes measuring outcome and comparison of studies in this field quite complex and lowering evidence levels.

Voor- en nadelen van de technieken

Palatal closure techniques

This module concerns the techniques of lip and palate closure. There is a close relation to the chapter “Timing of lip and palate closure”. Unfortunately, literature does not show enough evidence to support certain techniques of palatal closure. However, we will do some suggestions and give some tips in selecting a type of surgical technique.

The main used techniques of soft palate closure are straight midline closure of the mucosa with or without lateral relaxing incisions versus double opposing z-plasty according to Furlow. Both techniques are performed by experienced surgeons with acceptable results but every technique has a learning curve. The advantage of the straight-line closure is its relative ease and has the opportunity to do a second correction through the same scars. The advantage of the Furlow technique is transposition of mucosa increasing the length of the soft palate but at the expense of tissue in width. Therefore, the Furlow technique is less favorite for wider palatal clefts with a higher rate of fistula formation (Williams, 2011). Position of the scars make second surgery more complicated in the Furlow technique.

Attention should be payed to reconstruction of the muscular sling of the levator veli palatini muscle. Sommerlad (2002) describes many details of this muscular repositioning. The Furlow double opposing z-plasty automatically creates the muscular sling. When a straight midline closure technique of the mucosa is used, separate attention for muscle positioning is indispensable.

In closing the hard palate most used techniques are the vomer flap (nasal layer only closure), mucoperiosteal flaps axially based on the great palatinal artery or anteriorly and posteriorly based leaf-flaps (Von Langenbeck) and buccal transposition flaps. The advantage of the vomer flap technique is that no scar tissue is made on the palatal bone, which may impair outgrowth of the maxilla. However only the relative thin nasal mucosa is closed and therefore more fragile. The mucoperiosteal flaps are thicker and firmer, but require an extensive dissection from the bone which might inhibit full growth of the palatal bone. When the mucoperiosteal flaps are used simultaneous closure of the nasal palatal mucosa can be performed, resulting in a more secure double layer closure. The mucoperiosteal flap technique enables simultaneous closure of soft and hard palate. The advantage of the buccal flap technique is adding of tissue and therefore less dissection of the palatal bone. It can be used for nasal and oral layer closure. Disadvantage is scar formation of the buccal mucosa, it is more time consuming and might need additional surgery on the pedicle of the flap.

Lip closure techniques

Many lip closure techniques are described. Millard, Fisher and straight-line closure are more favorite. Unfortunately, literature does not show enough evidence to support certain techniques of lip closure. However, we will do some suggestions and give some tips in selecting a type of surgical technique. The straight-line technique gives good position of the scar in the -line but lengthening is limited. Straight line closure seems more applicable to incomplete clefts of the lip. Fisher and Millard give better lengthening but a more extensive scar due to z-plasties. Many surgeons have their own variations on those basic techniques.

In conclusion, none of the mentioned surgical techniques surpasses each other, but experience of a surgeon with a certain technique is essential for optimal results.

<u>Values and preferences of patients and their parents or guardians</u>

Parents can be confused by the variety of surgical techniques and (sometimes strong) opinions on cleft lip and palate treatment by teams or surgeons. They need unambiguous information and advice. Unfortunately, literature does not provide us with enough scientific evidence to support one techniques of surgical treatment of cleft lip and palate over the other. Adversely the experience of a surgeon with certain techniques is essential for optimal results. We advise that each team presents clearly what their vision on cleft lip and palate treatment is, elaborated in a straightforward protocol. Each protocol preferably illustrated by instructive photos and comprehensive movies.

<u>Costs/Finances</u>

In general, good results should be achieved in as little surgeries as possible in order to keep the burden on the child, the parents as low as possible, and to keep the health care system within acceptable finances. It is important to properly lay the surgical base in the first year of life, and to keep intermediate interventions during growth to a minimum. The final corrections can be made when the patient has grown out, whereby the patient can then assess and decide for himself or herself what he or she needs or what he or she considers to be desirable.

<u>Acceptance, feasibility and implementation</u>

There is still a lot of variation in surgical practice between the cleft teams, although a change seems to take place. Special interest groups within the NVSCA try to tackle this point. Within these groups, knowledge is shared, and appointments are made to standardize clinical practise as much as possible. In the Netherlands everyone has equal access to the cleft teams, so there will be no variation in accessibility of care. The different techniques are also equally feasible to perform, each surgeon has his own experience and expertise. It is

important that the surgeon uses the (combination of different) technique(s) in which he or she is most experienced in order to achieve the best result.

Recommendations/aanbevelingen

Rationale

Uit de literatuur blijkt dat er geen duidelijke voorkeur voor een techniek is, meerder technieken zouden gebruikt kunnen worden voor lip en palatumsluiting. Er zijn geen duidelijke voor- en nadelen van de diverse technieken. Er wordt een brede aanbeveling gegeven, mede door het gebrek aan wetenschappelijk bewijs, waarbij de ervaring en deskundigheid van de chirurg in acht wordt genomen.

Positioneer tijdens palatumsluiting de palatummusculatuur naar een meer anatomische positie (verbinding in de mediaan en meer naar posterieur geplaatst) voor een beter resultaat op de spraak, bijvoorbeeld zoals bij een Furlow of Langenbeck met transpositie van de spieren.

Gebruik geen originele Furlow verlengingsplastiek bij een brede palatale schisis in verband met verhoogde kans op fistel vorming.

Gebruik een (combinatie van) techniek(en) voor palatumsluiting waarin de chirurg het meest ervaren is zodat het risico op complicaties minimaal is.

Gebruik een (combinatie van) techniek(en) voor lipsluiting waarin de chirurg het meest ervaren is voor een optimaal resultaat wat betreft functie en esthetiek met een minimaal risico op complicaties.

Stimuleer de discussie over de techniek(en) bij de schisis-chirurgen (special interest groups NVSCA).

Literature

Abdel-Aziz, M., & Ghandour, H. (2011). Comparative study between VY pushback technique and Furlow technique in cleft soft palate repair. European Journal of Plastic Surgery, 34(1), 27-32.

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de Silva Amaratunga, Nihal Asoka. "Combining Millard's and Cronin's Methods of Unilateral Cleft Lip Repair - a Comparative Study." Asian Journal of Oral and Maxillofacial Surgery 16.1 (2004): 5-9.

Ganesh P, Murthy J, Ulaghanathan N, Savitha VH. (2015) A randomized controlled trial comparing two techniques for unilateral cleft lip and palate: Growth and speech outcomes during mixed dentition. *J Craniomaxillofac Surg*;43(6):790-5.

Henkel KO, Dieckmann A, Dieckmann O, Lenz JH, Gundlach KK. (2004). Veloplasty using the wave-line technique versus classic intravelar veloplasty. *Cleft Palate Craniofac J*;41(1):1-4.

Rossell-Perry P, Cotrina-Rabanal O, Figallo-Hudtwalcker O, Gonzalez-Vereau A. (2017). Effect of Relaxing Incisions on the Maxillary Growth after Primary Unilateral Cleft Palate Repair in Mild and Moderate Cases: A Randomized Clinical Trial. *Plast Reconstr Surg Glob Open.*16;5(1):e1201.

Sommerlad BC, Mehendale FV, Birch MJ, Sell D, Hattee C, Harland K. (2002). Palate Re-Repair Revisited. *The Cleft Palate-Craniofacial Journal*;39(3):295-307.

Williams, W. N., Seagle, M. B., Pegoraro-Krook, M. I., Souza, T. V., Garla, L., Silva, M. L., ... & Whitaker, M. E. (2011). Prospective clinical trial comparing outcome measures between Furlow and von Langenbeck palatoplasties for UCLP. Annals of plastic surgery, 66(2), 154-163.

5

Validity and Maintenance

Module[1]	**Responsible party[2]**	**Year of autorisation**	**Next assessment of actuality guideline[3]**	**Frequency of assessement of actuality[4]**	**Supervisor of actuality[5]**	**Relevant factors for changes in recommendations[6]**
Technique repairing cleft lip and palate	NVPC	2021	2026	every 5 years	NVPC	None

[1] Name of module
[2] Responsible party for the module
[3] maximum of 5 years
[4] half a year, every (other, ..) year
[5] supervising party or parties
[6] Current reseach, changes in organizations/restitions, new available rescourses

Appendixes with module 4

Knowledge gaps

What is the effect of different techniques of repairing cleft lip and palate on speech, hearing, diet, maxillary growth, postoperative care and complications and esthetical outcome complications and (patient, physician, and parents' satisfaction)?

P: patients with cleft lip and/or palate;
I: surgical techniques for repairing cleft lip and palate;
C: other surgical technique for repairing cleft lip and palate;
O: speech, hearing, feeding capability, maxillary and midface growth, postoperative complications, esthetics (patient, parent and/or doctor satisfaction).

Implementation plan

Recommendation	Timeline for implementation: < 1 year, 1 to 3 years or > 3 years	Expected effects on costs	Preconditions for implementation (within specified timeframe)	Possible barriers for implementation[1]	Supposed actions for implementation[2]	Who is responsible for the action(s)[3]	Other comments
1	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC	Mainly recommended in previous version of the guideline
2	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC	Already recommended in previous version of the guideline
3	**< 1 year**	nil	Mainly current practice		Publication of the guideline	NVPC	Already recommended in previous version of the guideline

[1] Barriers can exist at the level of the professional, at the level of the organization (the hospital) or at the level of the system (outside the hospital). Consider, for example, disagreement with regard to the recommendation in different organizations, insufficient motivation or knowledge of the specialist, insufficient facilities or personnel, necessary concentration of care, costs, poor cooperation between disciplines, necessary rearrangement of tasks, et cetera.

[2] Actions that are necessary for implementation, but also actions that are possible to encourage implementation. Consider, for example, checking the recommendation during a quality review, publication of the guideline, developing implementation tools, informing hospital administrators, arranging proper reimbursement for a certain type of treatment, making cooperation agreements.

[3] Who is responsibilities for implementation of the recommendations will also depend on the level of barriers. Barriers at the level of the professional will often have to be resolved by the professional association. Organizational barriers will often be the responsibility of hospital administrators. Other parties, such as the NZA and health insurers, are also important in resolving barriers at system level.

Evidence tables

Research question: What is the effect of different techniques of repairing cleft lip and palate on speech, hearing, diet, postoperative esthetical complications (patient, parent and/or doctor satisfaction)?

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Palatum molle							
Abdel-Aziz, 2011	Type of study: randomized controlled trial Setting: outpatients Country: Egypt Source of funding: not reported	Inclusion criteria: 1) patients with cleft soft palate without any other congenital anomalities 2) treated at participating hospital Exclusion criteria: - N total at baseline: Intervention: 24 Control: 22 Important prognostic factors[2]: *For example age ± SD:* *total group: 1 year 4 months (range 11 months – 3 years)*	Describe intervention (treatment/procedure/test): V-Y pushback technique for cleft palate repair	Describe control (treatment/procedure/test): Furlow double-oppsing Z-plasty for cleft repair	Length of follow-up: At least 1 year Until the age of 4 years Loss-to-follow-up: 60 patients included in total (number per group not mentioned) Speech assessment performed in I: 24, C: 22 Reasons for this not reported Incomplete outcome data: See above	Outcome measures and effect size (include 95%CI and p-value if available): Means and standard deviations of the auditory perceptual assessment in both treatment groups Nasality I: 0.88 ± 1.01 C: 0.27 ± 0.55 P=0.035 Glottal Articulation I: 1.13 ± 1.04 C: 0.5 ± 0.74 P=0.029 Pharyngealization of fricatives: I: 1.00 ± 1.18 C: 0.55 ± 1.1 P=0.10 Nasal emission: I: 0.92 ± 1.1 C: 0.36 ± 0.73	Author's conclusion: The Furlow Z-plkasty is better than the V-Y pushback technique in repair of clefts involving the soft palate as it has a higher success rate regarding speech outcome and velopharyngeal closure; also it has a lower operative tima and blood loss.

		Sex: *Total group: 45% M* Groups comparable at baseline? unclear				P=0.049 Speech intelligibility I: 1.08 ± 1.25 C: 0.59 ± 1.1 P=0.14 Fistulae: I: n=2 C: n=0 p-value not reported	
Ganesh, 2015	Type of study: randomized controlled trial Setting: not reported Country: India Source of funding: not reported	Inclusion criteria: patients with nonsyndromic UCLP Exclusion criteria: children operated on by more than one surgeon were excluded N total at baseline: 200 Intervention: 100 Control: 100 Important prognostic factors[2]: *Mean age lip repair* *I: 5.2 mo* *C: 6.3 mo*	Describe intervention (treatment/procedure/test): Protocol 1 consisted of the vomer flap (VF), whereby patients underwent primary lip nose repair and vomer flap for hard palate single-layer closure, followed by soft palate repair 6 months later	Describe control (treatment/procedure/test): Protocol 2 consisted of the two-flap technique (TF), whereby the cleft palate (CP) was repaired by two-flap technique after primary lip and nose repair	Length of follow-up: 7-10 years Loss-to-follow-up: 115 Of the 200 randomized patients, 179 completed the protocol. However, only 85 patients presented for follow-up (I: 40 and C: 45) Incomplete outcome data: For various reasons, speech samples were obtained from	Outcome measures and effect size (include 95%CI and p-value if available): Dental arch relation (mean GOSLON Yardstick) I: 2.15 ± 0.662 C: 2.49 ± 0.757 P=0.032 Speech outcomes Hypernasality I: Normal: 11.8% Mild: 70.6% Moderate: 17.6% C: Normal: 20.5% Mild: 76.9% Moderate: 2.6% P=0.05 Weak oral pressure words (present)	Author's conclusion: Our results showed marginally better growth outcome in the VF group compared to the TF group. However, the speech outcomes were better in the TF group.

		Mean age palate repair *I: 12.3 mo* *C: 12.9 mo* *Mean age follow up* *I: 7.8 y* *C: 8.1 y* *Sex:* *I: 60% M* *C: 51% M* Groups comparable at baseline? Yes			only 34 patients in the VF group and 39 in the TF group.	I: 41.2% C: 15.4% P=0.014 Weak oral pressure sentences (present) I: 41.2% C: 15.4% P=0.014	
Henkel, 2003	Type of study: randomized trial Setting: outpatients Country: Germany Source of funding: not reported	Inclusion criteria: 1) patients with complete cleft of the soft palate Exclusion criteria: - N total at baseline: Intervention: 12 Control: 12 Important prognostic factors[2]: *For example age ± SD: NR*	Describe intervention (treatment/procedure/test): Wave-line technique for intravelar veloplasty Age: 12 months Labioplasty: 6 months Repair of hard palate: 4-5 years Primary bone grafting: 11-13 years	Describe control (treatment/procedure/test): Classic intravelar veloplasty Age: 12 months Labioplasty: 6 months Repair of hard palate: 4-5 years Primary bone grafting: 11-13 years	Length of follow-up: Until the age of 4 years Loss-to-follow-up: No loss to follow-up reported Incomplete outcome data: In wave-line technique group 2/12 (17%) were too playful for	Outcome measures and effect size (include 95%CI and p-value if available): Mouth breathing: I: 4/12 C: 8/12 p-value not reported Compensatory grimacing when speaking I: 1/12 C: 8/12 P<0.05 (α-ι) test negative I: 12/12	Author's conclusion: Primary repair of clefts of the soft palate using the wave-line is straightforward, safe and easy. On the basis of the present results, this technique seems superior to the classic intravela veloplasty.

		Sex: *NR* Groups comparable at baseline? Unclear			examination on sound tests	C: 8/12 P<0.05 Sounds: /l/, /n/, /d/, /t/ normal I: 6/10 C: 3/12 P<0.05 Sounds /z/, /s/ normal I: 6/10 C: 4/12 P<0.05	
Rossell-Perry, 2017	Type of study: prospective, randomized, double-blind controlled trial study Setting: Surgical Center Program Lima Country: Peru Source of funding: not reported	Inclusion criteria: Peruvian infants with nonsyndromic complete unilateral cleft lip and palate who were otherwise healthy. Only children with mild or moderate unilateral cleft lip and palate were included in this study because severe cases require a relaxing incision on the cleft side.	Describe intervention (treatment/procedure/test): The two-flap palatoplasty group underwent Bardach's two-flap palatoplasty plus the Sommerlad type of intravelar veloplasty and unilateral uvuloplasty. 31% upper rotation advancement + double unilimb Z-plasty 69% triple unilimb Z-plasty All operations were performed by the same plastic surgeon	Describe control (treatment/procedure/test): One flap technique. The one-flap palatoplasty differed from the two-flap technique by the use of a relaxing incision on the cleft side only. 33% upper rotation advancement + double unilimb Z-plasty 67% triple unilimb Z-plasty All operations were performed by the same plastic surgeon	Length of follow-up: 5 years Loss-to-follow-up: I: 6 C: 8 Incomplete outcome data: -	Outcome measures and effect size (include 95%CI and p-value if available): evaluation of maxillary arch dimensions and dental arch relationships using the 5-year-olds' index, rating from 1 ("excellent") to 5 ("very poor"). I: 2.57 ± 1.08 C: 2.80 ± 1.91 P=0.71	Author's conclusion: The results arising from this clinical trial do not provide statistical evidence that one technique let us obtain better maxillary development than the other at 5 years. The use of relaxing incisions was not associated with maxillary growth impairment. A technique with limited relaxing incisions does not has better maxillary growth.

		Exclusion criteria: Patients with severe unilateral cleft lip and palates were excluded. N total at baseline: I: 78 C: 78 Important prognostic factors[2]: *Sex (male):* *I: 54%* *C: 61%* *Cleft severity (moderate)'* *I: 72%* *C: 67%* Groups comparable at baseline? Yes					
Williams, 2009	Type of study: randomized controlled trial Setting: outpatients	Inclusion criteria: 1) patients with complete unilateral cleft lip and palate Exclusion criteria:	Describe intervention (treatment/procedure/test): Furlow	Describe control (treatment/procedure/test): Von Langenbeck	Length of follow-up: Until the age of 4 years Loss-to-follow-up: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Hypernasality: Odds ratio (OR) Von Langenbeck versus Furlow	Author's conclusion: In this study the Furlow double opposing Z-palatoplasty resulted in significantly better velopharyngeal function for speech than the von Langenbeck procedure

	Country: United States of America / Brazil Source of funding: non-commercial	1) failure of family to return to the hospital at assigned operation date 2) conditions impairing speech development (hearing problems, mental retardation) <u>N total at baseline</u>: Intervention: 134 Control: 201 <u>Important prognostic factors</u>[2]: *Furlow:* *Spina: 83,* *Millard: 90* *Operation at 9-12 months: 78* *Operation at 15-18 months: 95* *Von Langenbeck* *Spina: 97,* *Millard: 106* *Operation at 9-12 months: 103* *Operation at 15-18 months:100*			<u>Incomplete outcome data</u>: Not reported	0.54 (95% CI: 0.31 – 0.95) p=0.014 Nasal air emission Odds ratio (OR) Von Langenbeck versus Furlow 0.72 (95% CI 0.45 – 1.15) p=0.12	as determined by the perceptual cul-de-sac test of hypernasality.

		Groups comparable at baseline? Unclear					
Lip adhesion							
Chowdri, 1990	Type of study: randomized trial Setting: outpatients Country: India Source of funding: not reported	Inclusion criteria: 1) patients with unilateral cleft lip Exclusion criteria: - N total at baseline: Intervention: 58 Control: 50 Important prognostic factors[2]: *For example ag:* *I: 3.1* *C: 2.9* *Sex: NR* *Complete cleft:* *I: 38/58 (73%)* *C: 30/50 (60%)* *Associated cleft palate:* *I: 39/58 (67%)*	Describe intervention (treatment/procedure/test): Rotation advancement	Describe control (treatment/procedure/test): Triangular flap repair	Length of follow-up: 6 years Loss-to-follow-up: Follow-up period (years) and number of patients per period (reasons for dropout not described: 1-2: 11 2-3: 22 3-4: 35 4-5: 29 5-6: 11 Incomplete outcome data: As above	Outcome measures and effect size (include 95%CI and p-value if available): Comparison scores (esthetic results) Lip I: 38 ± 5 C: 39 ± 5 p>0.10 Nose I: 34 ± 4 C: 34 ± 4 p>0.80 Lip + Nose I: 71 ± 10 C: 73 ± 12 p>0.50	Author's conclusion: No significant difference was found in overall postoperative appearance of lip and nose between rotation-advancement and triangular flap repair. As a result we recommend either technique for unilateral cleft lip repair.

		C: 32/50 (64%) Groups comparable at baseline? yes					
De Silva Armatunga, 2004	Type of study: randomized trial Setting: outpatients Country: Sri Lanka Source of funding: not reported	Inclusion criteria: 1) patients with unilateral cleft lip Exclusion criteria: - N total at baseline: Millard: 18 Cronin: 21 Combined: 20 Important prognostic factors[2]: *For example age ± SD: unclear (age distribution reported)* *Sex:* *Millard: 61% M* *Cronin: 62% M* *Combined: 65% M* Groups comparable at	Describe intervention (treatment/procedure/test): Millard procedure Cronin procedure	Describe control (treatment/procedure/test): Method combining Millard an Cronin Procedure	Length of follow-up: 3 months Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Cleft Lip Component Symmetry Index score Cupid's bow height Millard: 77 Cronin 86 Combined: 87 P<0.01 for Millard versus other 2 groups Vermillion height: Millard: 87 Cronin: 97 Combined: 97 P<0.01 for Millard versus other 2 groups Nostril height symmetry: Millard: 93 Cronin: 93 Combined: 92 P>0.05, reduced in all groups	Author's conclusion: The advantages of Millard's and Cronin's methods, which are the most widely used methods of cleft lip repair; could be retained and the disadvantages eliminated to a degree by combining the 2 methods. A basic muscle repair could also be included in the new combined method.

		baseline? Unclear				Nostril width: Millard: 96 Cronin: 99 Combined: 95 p>0.05 for Cronin versus other 2 groups	
Williams, 2009	See above						

BCLP: bilateral cleft lip and palate; CP: cleft palate only; UCLP: unilateral cleft lip and palate

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures.**
2. **Provide data per treatment group on the most important prognostic factors ((potential) confounders).**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls.**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders.**

Risk of bias table for intervention studies (randomized controlled trials)

Research question: What is the effect of different techniques of repairing cleft lip and palate on speech, hearing, diet, postoperative esthetical complications (patient, parent and/or doctor satisfaction)?

Study reference (first author, publication year)	**Describe method of randomisation[1]**	**Bias due to inadequate concealment of allocation?[2]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?[4]** (unlikely/likely/unclear)	**Bias due to loss to follow-up?[5]** (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?[6]** (unlikely/likely/unclear)
Palatum molle								
Abdel-Aziz, 2011	"randomly classified into two equal groups	Likely	Likely	Likely	Likely	Unlikely	Likely	Unlikely
Ganesh, 2015	Randomization was done by allocation concealment, whereby 200 chits were put in a box (100 for each group) and the parent or guardian was asked to pick one chit 1 day before the surgery.	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear, it is unclear what the consequences are of the large group that was lost to follow-up.	Unclear
Henkel, 2003	Each patient was assigned to one of the two groups following a previously determined succession	Likely	Likely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely
Williams, 2009	Block randomization plan for 4 surgeons:	Likely	Likely	Unlikely	Unlikely	Unlikely	Unclear	Unlikely

	each sequential set assigned to a surgeon was assigned to the 8 study groups at random							
Palatum durum								
Rossell-Perry, 2017	Blockrandomization: Sequence generation for the randomized group allocation was accomplished through the use of computer-generated random numbers. A block size of 6 and allocation ratio of 2:1 were used. The group assignment was protected in a sealed envelope, which was opened by the surgeon just before surgery.	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unclear	Unclear
Lip adhesion								
Chowdri, 1990	"simple random sampling procedure"	Likely	Likely	Unlikely	Likely	Unlikely	Unclear	Unclear
De Silva Armatunga, 2004	"randomly allocated"	Likely	Likely	Unlikely	Likely	Unlikely	Unclear	Unclear
Williams, 2009	See above							

1. Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.

2. 8Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules.

3. **Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.**
5. **If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear.**
6. **Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.**

Table of excluded studies

Author and year	Reason for exclusion
Adetayo, 2018	RCT does not meet selection criteria (follow-up too short)
Adetayo, 2019	RCT does not meet selection criteria (follow-up too short)
Bartzela, 2011	Does not meet selection criteria (does not answer research question, compares center protocols, not surgical techniques).
Bichara, 2015	Review does not meet selection criteria (does not answer research question, compares lip surgery versus lip and palate surgery)
Carroll, 2013	Excluded on study design (observational study)
Deshmukh, 2018	RCT does not meet selection criteria (follow-up too short)
Enemark, 1993	Does not meet selection criteria (palatum durum)
Flinn, 2005	Does not meet selection criteria (does not answer research question, compares center protocols, not surgical techniques).
Flores, 2008	Does not meet selection criteria (none of the relevant outcome measures reported)
Gilleard, 2014	Included RCT of this review is already described in previous version of this guideline
Grobbelaar, 1994	Does not meet selection criteria (does not answer research question).
Grobbelaar, 1995	Excluded on study design (observational study)
Halli, 2012	Excluded on study design (observational study)
Hardwicke, 2014	Descriptive review included studies before 2014
Hassan, 2005	Does not meet selection criteria (follow-up too short)
Hassan, 2007	Excluded on study design (observational study)
Holtmann, 1984	Does not meet selection criteria (follow-up too short)
Kappen, 2018	Review of cohort and cross-sectional studies
Karling, 1998	Does not meet selection criteria (does not answer research question).
Kitagawa, 2003	Does not meet selection criteria (palatum durum)
Latham, 2007	Does not meet selection criteria (more of a timing than technique issue)
Lee, 2013	Does not meet selection criteria (palatum durum)
Leenstra, 1996	Does not meet selection criteria (follow-up too short)
Maggiuli, 2014	Does not meet selection criteria (outcome: maxillary growth, follow-up: 6 months postoperatively; too short to draw conclusions regarding maxillary growth)
McWilliams, 1995	Excluded on study design (observational study)
Meazzini, 2008	Does not meet selection criteria (does not answer research question, compares center protocols, not surgical techniques).
Miachon, 2014	Narrative review
Minatel, 2019	Review included only 1 RCT (Ganesh, 2015) which is described in the guideline
Mølsted, 1993	Does not meet selection criteria (palatum durum)
Nasser, 2008	Does not meet selection criteria (palatum durum)
Nollet, 2007	Does not meet selection criteria (does not answer research question, compares center protocols, not surgical techniques).
Reddy, 2010	Excluded on study design (observational study)
Rose, 2001	Does not meet selection criteria (none of the relevant outcome measures reported)
Rossell-Perry, 2014	Does not meet selection criteria (describes uvular repair, not palatal repair)
Shaw, 1992	Does not meet selection criteria (not an original article)
Sommerlad, 2001	Does not meet selection criteria (does not answer research question, does not compare different surgical techniques).
Stein, 2019	Included RCTs in this review are already described in previous version of this guideline
Syafrudin Hak, 2011	Does not meet selection criteria (compares orthopaedic treatment not surgical techniques)
Tahir, 2017	RCT does not meet selection criteria (follow-up too short)
Tanino, 1997	Number of participants too low (<10 per group)
Timbang, 2014	Included RCT of this review is already described in previous version of this guideline
Trotman, 1996	Does not meet selection criteria (palatum durum)
Wada, 1990	Does not meet selection criteria (palatum durum)
Wermker, 2013	Does not meet selection criteria (study includes adult patients)

Witt, 1999	Excluded on study design (observational study)

Literature search strategy

Uitgangsvraag:

- **Timing lip- en palatumsluiting:** welke overwegingen (voor- en nadelen) spelen een rol bij het bepalen van het moment van het sluiten van de gehemeltespleet bij een patiënt met een schisis?
- **Techniek lip- en palatumsluiting:** is er voorkeur voor een chirurgische techniek bij het sluiten van de lip- en/of gehemeltespleet bij een patiënt met een schisis?

Database(s): Medline, Embase	Datum: 15-1-2020
Periode: 2014-heden	Talen: Engels

Database	Zoektermen	Totaal
Medline (OVID)	1 exp Cleft Lip/ or exp Cleft Palate/ or ((cleft* or fissum or hare or schi*is) adj5 (palat* or lip* or cheilo* or oral or orofacial)).ti,ab,kf. or palat*schi*is.ti,ab,kf. or cheilo*schi*is.ti,ab,kf. or labioschi*is.ti,ab,kf. or harelip*.ti,ab,kf. (29835) 2 exp Cleft Lip/su or Cleft Palate/su or exp "Reconstructive Surgical Procedures"/ or exp general surgery/ or exp surgery, plastic/ or operation*.ti,ab,kf. or surgery.ti,ab,kf. or closure*.ti,ab,kf. or correction.ti,ab,kf. or 'surgical repair'.ti,ab,kf. or palatoplast*.ti,ab,kf. or cheiloplast*.ti,ab,kf. or reconstruction.ti,ab,kf. or millard.ti,ab,kf. or (vomer* adj2 flap*).ti,ab,kf. or langenbeck*.ti,ab,kf. or furlow*.ti,ab,kf. (2059371) 3 1 and 2 (12468) 4 limit 3 to (english language and yr="2014 -Current") (2641) 5 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (428537) 6 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1939003) 7 4 and 5 (137) 8 (4 and 6) not 7 (233) 9 7 or 8 (370) **137 SRs + 233 RCT = 370 in totaal (129 uniek)**	**529**
Embase	'cleft lip'/exp OR 'cleft palate'/exp OR 'cleft lip face palate'/exp OR (((cleft* OR fissum OR hare OR schi*is) NEAR/5 (palat* OR lip* OR cheilo* OR oral OR orofacial)):ti,ab,kw) OR palat*schi*is:ti,ab,kw OR cheilo*schi*is:ti,ab,kw OR labioschi*is:ti,ab,kw OR harelip*:ti,ab,kw **AND** 'surgery'/exp/mj OR 'lip reconstruction'/exp OR 'palatoplasty'/exp OR 'plastic surgery'/exp OR 'reconstructive surgery'/exp OR operation*:ti,ab,kw OR surgery:ti,ab,kw OR closure*:ti,ab,kw OR correction:ti,ab,kw OR 'surgical repair':ti,ab,kw OR palatoplast*:ti,ab,kw OR cheiloplast*:ti,ab,kw OR labioplast*:ti,ab,kw OR reconstruction:ti,ab,kw OR millard:ti,ab,kw OR ((vomer* NEAR/2 flap*):ti,ab,kw) OR langenbeck*:ti,ab,kw OR furlow*:ti,ab,kw **AND** (english)/lim AND (2014-2020)/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) **Gebruikte filters:** <u>*Sytematische reviews*</u> ('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de)	

	=103 *RCT's* ('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) ***= 300*** **= 403 totaal (400 uniek)**	

Module 5 Postoperative nutritional care

Clinical question

What are the nutritional advices that can be given to children with cleft lip an/or palate after surgery (cleft palate repair, pharyngoplasty and bone grafting procedure)?

Welke postoperatieve voedingsadviezen kunnen worden gegeven aan kinderen met een schisis na diverse operaties aan de lip en het gehemelte?

Introduction

After a cleft operation (palate repair or palatoplasty or pharyngoplasty) or alveolar bone grafting the patient is advised to drink fluid or eat soft food. The most important reason for this is avoidance of mechanical damage to wound bed. Following an alveolar bone graft procedure, the idea is to avoid chewing force to the premaxilla bone or front elements. Following a palatal repair procedure, the patient is also advised to avoid citrus fruits.

Currently, there is no clear evidence for these nutritional instructions, such as the relation between nutrition and disturbance of the soft tissues and bone. Meanwhile, the effort for the child and his/her parents seems to be considerable. There is also no clear evidence for the duration of the nutritional instructions.

Next to the discussion about the food consistence, there is a discussion about whether or not tube feeding is effective after a palatal repair procedure and pharyngoplasty. This discussion is mainly between surgeon and paediatric nurse or paediatrician and a decision that is mainly made on individual (patient) basis. This is a sub question which could be interesting to take into account.

Search and select

A systematic review of the literature was performed to answer the following question: What is the effect of consuming soft food (e.g. liquid food, mashed food or tube feeding) versus solid/normal food after cleft palate repair, pharyngoplasty and bone grafting procedure for children with cleft lip-nose deformities?

P: patients after cleft palate repair, pharyngoplasty and bone grafting procedure between 6 months and 11 years old;
I: liquid food, mashed food or tube feeding (until 6 weeks post procedure);
C: solid/normal food (until 6 weeks post procedure);
O: no disturbed wound healing, enough food intake, no moving premaxilla, no fistulas.

Because of the fact that lip closure and closure of the soft palate are usually performed in young infants who are bottle or breast fed, these procedures were not included in the research question.

<u>Relevant outcome measures</u>

The guideline development group considered surgical wound healing and amount of food intake/nutritional status as critical outcome measures for decision making; and moving premaxilla and fistulas as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the criteria for minimal clinically (patient) important difference for the dichotomous outcome measures; RR < 0.80 of > 1.25)

No a priori criteria were set for the continuous outcome measures because it largely depends on its context.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until August 20th, 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 331 hits. Studies were selected based on the following criteria:

- Involving patients with a cleft palate procedure or bone graft procedure between 6 months and 11 years old.
- Comparing liquid food, mashed food or tube feeding with solid/normal food 3-6 weeks postoperatively.
- Assessing surgical wound healing and/or the amount of food intake or nutritional status.

A total of 25 studies were initially selected based on title and abstract screening. After reading the full text, 25 studies were excluded (see the table with reasons for exclusion under the tab Methods) and no studies were included.

Results

No studies were found that answered the question: What is the effect of offering soft food versus solid/normal food after a cleft palate or bone graft procedure for children with cleft lip-nose deformities? In the justifications a descriptive overview can be found of indirect studies.

Conclusions

No conclusions could be drawn based on the literature.

Considerations

No studies were found that directly compared thin, fluid, soft food or tube feeding with normal/solid food until 6 weeks after palatoplasty, pharyngoplasty or bone graft procedure in children with cleft lip/nose deformities between 6 months and 11 years old, on the outcomes: wound healing, amount of food intake/nutritional status, moving premaxilla and fistulas.

We will provide an overview of indirect studies that assessed feeding methods and/or nutritional status in children following cleft palate or bone graft procedure.

Palate repair and different feeding methods

A systematic review by Duarte (2015) compared different feeding methods in children with cleft lip and palate, such as breast feeding, bottle feeding, syringe-, tube-, spoon- or paladai-feeding. For the purpose of our question only studies that compared feeding methods for soft food (cup, syringe, tube or paladai) with feeding methods for solid food (spoon) in palate repair (associated or not associated with lip repair) were assessed. Bone graft procedures were not included by Duarte (2015). Studies comparing breast feeding/bottle feeding methods were not assessed.

Two studies, included and analysed by Duarte (2015), could be assessed: Hughes (2013) compared tube feeding versus oral food intake and Trettene (2013) compared cup versus spoon feeding. Unfortunately, the studies were focused on the immediate hospital period following palate repair within 24 hours, and not the period 3 to 6 weeks post-surgery.

An overview of study characteristics, taken from the systematic review by Duarte (2015):

Table 5.1 Study description Hughes (2013) and Trettene (2013) by systematic review of Duarte (2015)

Author (year)	Study design	Age range	Isolated cleft palate repair, cleft palate and lip (n, n)	Comparison	Assessed period after procedure	Assessed parameters
Hughes (2013)	Pilot study of an RCT	5 to 10 months	32, 9	Feeding tube (n=18) versus. Oral feeding (n=23)	Until 24 hours after procedure	Analgesia/pain; number of painful episodes, intravenous fluids and enteral feeding.
Trettene (2013)	Prospective cross-sectional study	11 to 18 months	Not reported	Cup (n=88) versus. spoon (n=88)	Until 24 hours after procedure; at 4 different time points	Coughing, choking, escape; accepted volume.

Tube versus oral food and cup versus spoon during the postoperative feeding period following surgical repair of cleft palate associated or not associated with lip repair
Source: Duarte (2015)

Table 5.2 Tube versus oral food during the 24-hour postoperative feeding period following surgical repair of cleft palate

	Nasogastric feeding (n=18)	Oral feeding (n=23)	Test statistic
Analgesia/pain: 1) post operative morphine, mean mg/kg (range) 2) paracetamol, mean mg/kg (SD*) 3) ibuprofen, mean mg/kg (SD*)	1) 0.16 (0.04 to 0.31) 2) 64.4 (13.3) 3) 13.2 (8.23)	1) 0.16 (0.024 to 0.4) 2) 61.9 (14) 3) 14.6 (4.7)	1) >0.1 (Mann-Whithney test) 2) >0.1 (Student's t-test) 3) >0.1 (Student's t-test)
Number of painful episodes (median, range)	4.5 (0-13)	5 (0 to 14)	> 0.1 (Mann-Whithney test)
Post operative fluids: 1) postoperative fluid and feed in first 24 hours, mean ml/kg (SD*) 2) number requiring post-operative fluids	1) 147 (55) 2) 9	1) 59 (33) 2) 0	1) Difference of means (95% CI*) 88 (61.3 to 114.9) 2) Not assessable

SD= standard deviation, CI=confidence interval
Source: Hughes (2013)

Table 5.3 Cup versus spoon during the 24-hour postoperative feeding period following surgical repair of cleft palate

	Cup feeding	Spoon feeding	Test statistic
Variables related to feeding technique: 1) coughing episodes during food administration (n Yes, %) 2) choking during food administration (n Yes, %) 3) food escape by the commissure (n Yes, %)	1) 4 (5%) 2) 5 (6%) 3) 67 (76%)	1) 0 2) 1 (1%) 3) 52 (59%)	1) 0.121 (Fisher exact test) 2) 0.211 (Fisher exact test) 3) 0.024* (Fisher exact test)
Accepted volume, ml (median, range)	140,0	150,0	0.029* (Mann-Whitney test)

*** Significant association (p<0.05)**
Source: Trettene (2013)

Hughes (2013) showed that use of analgesia and the number of painful episodes was similar among the tube group (n=18) and the oral food group (n=23) within 24 hours post-surgery. However, the received amount of fluid food volume was higher in the tube feeding group, with less often need for intravenous fluid (Duarte, 2015).

Trettene (2013) showed that the spoon technique (n=88) caused less food escape and a higher volume of food received than the cup technique (n=88) within 24 hours post-surgery. It is unclear from this study if the food given with the cup was a different (thinner) consistency than the food with the spoon (Duarte, 2015).

From these studies it remains unclear which food consistence is most effective in week 3 tot 6 post surgery, because this was not assessed (the studies did not meet the PICO). It also remains unclear if the food consistence differed among the nasogastric/oral feeding and cup/spoon feeding.

When nasogastric and oral feeding are compared in the first 24 hours, the nasogastric tube led to a higher postoperative fluid volume, however the amount of painful episodes and need for analgesia was comparable. How often the tube itself led to pain, discomfort or damage to the repair was not assessed, but one case in which the tube had to be removed due to discomfort was described. It is unclear which infants are at risk as poor feeders and could benefit from nasogastric feeding (Hughes 2013).

When cup and spoon feeding are compared, spoon feeding led to a higher amount of volume accepted and less food escape through the commissure. It could be hypothesized that soft food with the spoon is easier to consume, with less chances for leakage, swallowing or processing problems, than fluid food.

Both studies had a low methodological quality and a small sample size, so results should be interpreted with caution.

Palate repair and the influence on eating function

One retrospective single center study from Japan (Fujikawa, 2016) was found that assessed the impact of palatal repair surgery on eating function: the amount of a whole meal that was consumed and the food type (fluid food, paste food, soft food and others). Nurses recorded the amount of food intake during the hospital period, and the data was retrieved from medical records. The protocol was made so that patients began with drinking water and taking fluid food and work towards eating food pastes and soft food by postoperative day 7.

A total of 19 patients participated in the study. All patients underwent push back palatoplasty.

The results show that the eating rate increased during the first 6 post-operative days and then stayed more or less constant. The amount of fluid foods and pastes decreased over time, and the amount of soft foods and other foods increased. Unfortunately, the study did not assess the 3 to 6 weeks post-surgery period. However, because palatoplasty greatly influences eating function, it could be expected that the energy intake is still lower than 100%.

If soft food is encouraged, it could be predicted the amount of fluid food and pastes keeps decreasing and the amount of soft food increasing, however this is largely speculative. From this analysis it is also difficult to predict which food types are benefitting patients most in the 3 to 6 weeks post procedure. Because of the lower amount of food intake, and the lower nutritional value of fluid food and food pastes, it could be recommended to develop a new soft food type which minimizes palatal stress for postoperative cleft management, according to the authors (Fujikawa, 2016). This study had a low methodological quality and limited amount of study participants, so results should be taken with caution.

Bone graft

No studies were found that assessed bone graft and the impact of different food types or feeding methods.

Advantages and disadvantages of the feeding methods

Infants and children are very susceptible to problems of nutrition. In comparison with adults, they have lower percentages of muscle mass and fat and therefore have fewer reserves and a higher resting energy metabolism. Children are in a growth- and developmental phase, with nutritional requirements that are greater and clearly differentiated from those of adults and that vary according to the stage of growth. In sick and hospitalized children, malnutrition is associated with increased risk of infection, delayed wound healing, longer hospital stay, and increased morbidity and mortality. (Joosten, 2017) In children with cleft lip/palate, feeding is an immediate concern. There is evidence of delay in growth of these children as compared to those without clefts, especially if these were associated with a syndrome or anomaly (Bessell, 2011). For example: Pandya (2001) found an incidence of failure to thrive in Pierre Robin patients of 100%. Therefore, in these children it is very important to evaluate the nutritional status and achieve optimal growth prior to and after surgery. If needed, a dietitian or paediatrician should be consulted.

Operations in the mouth such as in cleft surgery might have considerable repercussions in the intake of food and sometimes even fluids. Apart from the effect on general wellbeing of the child and his or her parents, food and drinks are crucial for proper wound healing. A balanced and clear protocol for post-operative feeding and feeding methods is therefore important. Unfortunately, the literature shows very little to no evidence for the proper postoperative food (soft versus solid) or feeding methods. What we do know is that changes in food or feeding methods, either because the patient cannot or may not eat the food he or she is accustomed to, can lead to stress and loss of weight (Matsunaka, 2015; Madhoun, 2020).

Especially in young children minimizing crying has been considered to be the most important factor in avoiding tension on the surgical wound. For this reason the use of a pacifier - to prevent crying - should be allowed. Changes in feeding methods seems to stress the infants and may cause them to cry, which places tension on the wound (Matsunaka, 2015).

It is assumed that normal feeding with solid food may cause mechanical damage to the wound, but no evidence was found in the literature that endorses this. Cohen (1992) conclude in a retrospective analysis of two non-solid food feeding protocols, i.e. tube and syringe feedings versus unrestricted bottle or breast feeding, that there were no wound complications in the unrestricted group. They conclude that immediate unrestricted feeding may be instituted safely, thus improving and simplifying postoperative management after cleft lip and/or palate repair.

In a prospective randomized study (Kim, 2009) the effect of bottle-feeding versus spoon feeding on early postoperative course after palatoplasty was evaluated. They concluded that bottle-feeding had no adverse effect on wound disruption or fistula formation. Although statistically insignificant, infants in the spoon-feeding group ingested a larger amount of food during the first 3 days and the need for sedatives was lower as compared to the bottle-feeding group. For this reason, it would be wise to encourage parents to introduce spoon feeding as normally advised from the age of 4 months on, to ensure that children can eat well from a spoon after surgery.

The large variation in feeding protocols in the Netherlands after cleft surgery seems to be based on assumptions rather than on scientific evidence. It is evident that a thorough oral hygiene post-surgery, a subject closely related to eating, is very important too. Cleaning the mouth and teeth after feeding might have a positive influence on the possible negative effects of certain food or fluids on the wound. Because this subject was not part of the clinical question, we did not investigate the role of oral hygiene but because of its importance and relation to feeding we want is to be mentioned here.

Values and preferences of patients and their parents or guardians

In our experience a stringent feeding protocol which states soft food for a couple of weeks after cleft surgery seems to be a rather big burden for the cleft patients and their parents. Especially after the cleft bone graft procedure the most important question for the children is all too often when they can start their normal food again. One of the Dutch cleft teams created therefore a cookbook, written by and for children with a cleft and supervised by students of dietetics. The aim was to create tasty recipes in accordance with a soft diet protocol (https://www.radboudumc.nl/expertisecentra/expertisecentra-zeldzame-aandoeningen/schisis/masterkoekies-kookboek).

One study included in the review of Duarte states that (little) children who got a gastric feeding tube for 24 hours post-operative needed less pain medication and were dismissed faster. Also, their parents seemed to be more relaxed because they had the feeling their child received enough food and pain medication (Kent, 2009). The possible adverse events of gastric feeding tube are problems with reintroducing oral intake, need for replacement, infections and it might be a burden for the child in itself. In general, the nasogastric feeding tube does not seem to be standard practice in the Netherlands unless the oral feeding methods are not successful after a certain amount of time. To prevent mechanical damage to the wound by fingers of the child, it is common to provide arm splints in some countries (The USA for example). This is not common in The Netherlands because it is believed to discomfort the child by the use of splints.

Costs/Finances

A soft feeding protocol in general does not lead to extra costs. In some occasions supplementary food (i.e. Nutridrink) or a nasogastric feeding tube at home can lead to extra costs which are usually covered by the health care insurance.

Acceptance, feasibility and implementation

The working group created support from all cleft teams through the questionnaire, which increases the feasibility of the recommendations.

If necessary, adjust nutritional advice to the preferences of the patient within the possibilities of the various protocols used, which are important for recovery and well-being.

The large variation in feeding protocols in the Netherlands after cleft surgery seems to be based on assumptions rather than on scientific evidence. Because no scientific evidence was found to advise a stringent soft food protocol versus a normal diet after cleft surgery the working group collected the feeding protocols after cleft surgery (especially palate and bone graft procedure) of all the cleft teams in the Netherlands. Table 5.4 shows a summary of the feeding protocols after cleft surgery of all cleft teams in the Netherlands. The results are shown for: closure of hard palate (palatoraphia anterior), pharyngeoplasty, and bone grafting procedure in cleft patients. Only the common recommendations of the different teams are shown.

Table 5.4 Overview feeding protocols post cleft surgery of Dutch cleft teams (lip surgery excluded)

General recommendations post cleft surgery			
Always start with drinking water post-surgery			day of surgery
Always rinse with water after eating			3 weeks post-surgery
Don't use a straw for drinking			3 weeks post-surgery
Do not put hard object into the mouth such as fork, fingers, hard / sharp food such as chips			3-4 weeks post-surgery
No indications to apply nasal gastric feeding tube as standard of care			
Surgery	**Age child at operation**	**Common recommendations for post-surgical feeding protocol**	**Duration of the advice**
Bone grafting procedure	9 to 12 years	Start with drinking water, then only fluid drinking (tea, apple juice, milk etc.)	day 1 post-surgery
		Thicker fluids: like yogurt, oatmeal, soup	day 2-7 days post-surgery
		Soft food: like bread without crusts, mashed food, pasta	week 2- 6 post-surgery
		Do not bite or chew with front teeth	first 6 weeks post-surgery
Palatorafia anterior	variation 3 months to 3 years	fluids (like apple juice, milk, water)	day 1
		smooth grinded food (yoghurt, smoothies, Olvarit 4 months)	day 2 t/m 7
		mashed food (like bread without crusts, pasta)	week 2 and 3 postoperatively
		no fingers or pacifier or thumb sucking	until 3 weeks postoperatively
		avoid orange juice and grapefruit juice	until 3 weeks postoperatively
Pharynxplastiek	4 to 7years	fluids (like apple juice, milk, water)	day 1
		mashed food (like bread without crusts, pasta)	day 2 - 3 weeks
		avoid orange juice and grapefruit juice	until 3 weeks postoperatively

Recommendations/Aanbevelingen

Rationale

5 Based on the literature summary, the working group is unable to make a statement about the effect of soft food versus normal / solid food after cleft surgery. Our recommendations are therefore mainly based on the corresponding recommendations in postoperative nutrition of the various cleft teams in the Netherlands and on the expert opinion of the working group members.

Aanbeveling-1

Probeer zoveel mogelijk wijzigingen in voedingswijze te voorkomen postoperatief na schisis operaties.

Aanbeveling-2

Pas de voedingsadviezen, zoals omschreven in de overzichtstabel, zoveel mogelijk toe.

Aanbeveling-3

Adviseer patiënten na een bot in gnatho (BIG) procedure het voedsel gedurende 6 weken niet af te happen met het front.

Aanbeveling-4

Overweeg een beetverhoging aan te brengen (door de orthodontist) indien er contact is tussen boven - en onderfront na een bot in gnatho BIG procedure.

Aanbeveling-5

Evalueer de groei en voedingstoestand zowel pre- als postoperatief en consulteer zo nodig een kinderarts of diëtist.

Literature

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Validity and Maintenance

Module[1]	Responsible party[2]	Year of autorisation	Next assessment of actuality guideline[3]	Frequency of assessement of actuality[4]	Supervisor of actuality[5]	Relevant factors for changes in recommendations [6]
Postoperative nutritional care	NVPC	2021	2026	every 5 years	NVPC	None

[1] Name of module
[2] Responsible party for the module
[3] maximum of 5 years
[4] half a year, every (other, ..) year
[5] supervising party or parties
[6] Current reseach, changes in organizations/restitions, new available rescourses

Appendixes with module 5

Knowledge gap

Is breastfeeding or bottle feeding preferred with patients aged 3 to 9 months after lip closure or soft palate closure?

P: patients after a lip closure or soft palate closure, between 3 and 9 months of age;
I: breastfeeding;
C: bottle feeding (included use of a pacifier), Spoon feeding;
O: no disturbed wound healing, enough food intake, no fistulas.

Implementation plan

Recommendation	Timeline for implementation: < 1 year, 1 to 3 years or > 3 years	Expected effects on costs	Preconditions for implementation (within specified timeframe)	Possible barriers for implementation[1]	Supposed actions for implementation[2]	Who is responsible for the action(s)[3]	Other comments
1	**< 1 year**	nil	Mainly current practice	The will and mindset of the cleft team to actually apply the recommendations in the guideline.	Publication of the guideline	NVPC	
2	**< 1 year**	nil	Mainly current practice	Idem	Publication of the guideline	NVPC	
3	**< 1 year**	nil	Mainly current practice	Idem	Publication of the guideline	NVPC	
4	**1 tot 3 jaar**	minor	Consultation orthodontist of cleft team	Idem	Publication of the guideline	NVPC	

[1] Barriers can exist at the level of the professional, at the level of the organization (the hospital) or at the level of the system (outside the hospital). Consider, for example, disagreement with regard to the recommendation in different organizations, insufficient motivation or knowledge of the specialist, insufficient facilities or personnel, necessary concentration of care, costs, poor cooperation between disciplines, necessary rearrangement of tasks, et cetera.

[2] Actions that are necessary for implementation, but also actions that are possible to encourage implementation. Consider, for example, checking the recommendation during a quality review, publication of the guideline, developing implementation tools, informing hospital administrators, arranging proper reimbursement for a certain type of treatment, making cooperation agreements.

[3] Who is responsibilities for implementation of the recommendations will also depend on the level of barriers. Barriers at the level of the professional will often have to be resolved by the professional association. Organizational barriers will often be the responsibility of hospital administrators. Other parties, such as the NZA and health insurers, are also important in resolving barriers at system level.

Table of excluded studies

Author and year	Reason for exclusion
Augsornwan, 2013	Wrong comparison: breast feeding/bottle versus spoon/syringe after lip repair

Assunção, 2005	Wrong comparison: bottle versus spoon/syringe after cheiloplasty
Bannister, 2017	Wrong comparison: description of postoperative care following first stage cleft closure
Beluci, 2012	Wrong comparison: nutritional status before and after mandibular surgery. Comparison between nutritional status before surgery and 5 days after surgery.
Bessell, 2011	Studies on feeding methods, e.g. breast, bottle, spoon, maxillary plate etc. No direct comparison solid versus soft food. More recent SR = Duarte 2016. Wrong comparison: breastfeeding versus spoon feeding, rigid versus squeezable bottle and maxillary plate versus no maxillary plate
Blough, 2019	Wrong intervention: risk factor analysis for wound complications during palatoplasty
Burianova, 2017	Wrong participants: baby's in first 2 weeks of life.
De Vries, 2014	Wrong intervention: analysis of occurrence of feeding difficulties in cleft palate children
Duarte, 2016	Wrong comparison: different methods of feeding, not soft versus solid food. This study was used for the justifications.
Farronato, 2014	Wrong design: narrative review/background article
Fujikawa, 2016	No comparison: no comparison soft versus solid food. But a description how the amount of fluid, paste and soft food increased over the time course of one-week post operation palatoplasty
Gopinath, 2013	Wrong comparison: nutritional intake of CLP children versus children without CLP
Harris, 2010	Wrong comparison: safety of cleft lip repair in babies
Hughes, 2013	Wrong comparison: nasogastric feeding versus oral feeding after palate repair. N.B. This study was used for the justifications.
Kaye, 2019	Wrong comparison: differences in weight loss and recovery between CLP (lip) and CP (palate) repair children
Kim, 2009	Wrong comparison: breast feeding/bottle versus spoon/syringe after palatoplasty
Kent, 2009	Wrong comparison: nasogastric feeding versus bottle feeding after palate repair
Matsunaka, 2015	Wrong design: protocol of Matsunaka 2019 (see under)
Matsunaka, 2019	Wrong participants: cleft lip repair, exclusion of cleft palate repair. Wrong comparison: breast/bottle feeding versus other feeding methods after cleft lip repair
Onyekwelu, 2016	Wrong comparison: omitting intravenous fluids as a postoperative routine versus no intravenous fluids after lip/palate repair
Prahl, 2005	Wrong comparison: maxillary plate versus no maxillary plate in first year of life in infants with complete unilateral cleft lip and palate
Rajamani, 2007	Wrong comparison: nerve block versus intravenous fentanyl during cleft lip surgery in children
Robin, 2006	Wrong study design: narrative review. No information on feeding after palate repair or bone surgery.
Selber, 2014	Wrong participants: Pharyngoesophageal (PE) reconstruction.
Worley, 2018	Wrong design: narrative review/background article

Literature search strategy

Algemene informatie

Richtlijn: Schisis	
Uitgangsvraag: Wat is het effect van het aanbieden van zachte voeding na schisisoperaties m.n. na de sluiting van het palatum durum en de BIG procedure?	
Database(s): Embase, Medline	Datum: 20-8-2020
Periode: 2000 – augustus 2020	Talen: Engels
Literatuurspecialist: Miriam van der Maten	
Toelichting en opmerkingen: In overleg met de adviseur is besloten te zoeken op de P (patiënten na cleft-lip/palatum operatie) in combinatie met een zoekblok over voeding (bij kinderen)/voedingsmethoden/sondevoeding. Term 'palatorafia' werd niet gevonden in de databases	

5 Zoekopbrengst

	Embase	OVID/MEDLINE	Ontdubbeld
SRs	19	18	24
RCT	77	40	85
Observationeel	159	171	222
Totaal	255	229	**331**

Zoekverantwoording

Database	Zoektermen		
Embase	**No.**	**Query**	**Results**
	#12	#9 OR #10 OR #11	255
	#11	#5 AND #8 NOT (#9 OR #10)	159
	#10	#5 AND #7 NOT #9	77
	#9	#5 AND #6	19
	#8	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	5381878
	#7	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3100761
	#6	'meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de	516647
	#5	#3 AND #4 AND (english)/lim AND (2000-2020)/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	640
	#4	'nutrition'/de OR 'child nutrition'/exp OR 'feeding behavior'/exp OR 'food intake'/exp OR nutrition*:ti,ab,kw OR diet*:ti,ab,kw OR feed*:ti,ab,kw OR food*:ti,ab,kw OR 'feeding tube'/exp OR 'enteric feeding'/exp OR ((feeding NEAR/2 (tube* OR catheter OR enteral OR enteric)):ti,ab,kw) OR peg:ti,ab,kw	2117738
	#3	#1 OR #2	22922
	#2	('cleft lip with or without cleft palate'/exp OR 'cleft palate'/exp OR 'cleft lip face palate'/exp OR (((cleft* OR fissum OR hare OR schi*is) NEAR/5 (palat* OR lip* OR cheilo* OR oral OR orofacial OR facial)):ti,ab,kw) OR palat*schi*is:ti,ab,kw OR cheilo*schi*is:ti,ab,kw OR labioschi*is:ti,ab,kw OR harelip*:ti,ab,kw OR 'palate'/exp OR palate:ti,ab,kw OR palatum:ti,ab,kw) AND ('bone graft'/exp OR 'bone graft*':ti,ab,kw OR 'bone flap*':ti,ab,kw OR 'bone transplant*':ti,ab,kw OR 'bone autograft*':ti,ab,kw OR 'bone allograft*':ti,ab,kw OR 'osseous flap*':ti,ab,kw OR 'osseous graft*':ti,ab,kw OR 'plastic surgery'/exp OR 'reconstructive surgery'/exp OR surgery:ti,ab,kw OR surgeries:ti,ab,kw OR operation*:ti,ab,kw OR operative:ti,ab,kw OR reconstruct*:ti,ab,kw OR plastic:ti,ab,kw OR corrective:ti,ab,kw OR correction*:ti,ab,kw OR repair*:ti,ab,kw OR closure:ti,ab,kw OR 'postoperative period'/exp OR 'postoperative care'/exp OR postoperat*:ti,ab,kw OR postsurg*:ti,ab,kw)	21776
	#1	'palatoplasty'/exp OR 'pharynx reconstruction'/exp OR pharyngoplast*:ti,ab,kw OR palatoplas*:ti,ab,kw	3971
Medline (OVID)	1 (Pharyngoplasty* or palatoplas*).ti,ab,kf. (1657) 2 (exp Cleft Lip/ or exp Cleft Palate/ or ((cleft* or fissum or hare or schi*is) adj5 (palat* or lip* or cheilo* or oral or orofacial)).ti,ab,kf. or palat*schi*is.ti,ab,kf. or cheilo*schi*is.ti,ab,kf. or labioschi*is.ti,ab,kf. or harelip*.ti,ab,kf. or exp Palate/ or palate.ti,ab,kf. or palatum.ti,ab,kf.) and (exp Bone Transplantation/ or 'bone graft*'.ti,ab,kf. or 'bone flap*'.ti,ab,kf. or 'bone transplant*'.ti,ab,kf. or 'bone autograft*'.ti,ab,kf. or 'bone allograft*'.ti,ab,kf. or 'osseous flap*'.ti,ab,kf. or 'osseous graft*'.ti,ab,kf. or exp Reconstructive Surgical Procedures/ or exp Surgery, Plastic/ or (surgery or surgeries or operation* or operative or reconstruct* or plastic or		

	corrective or correction* or repair* or closure or postoperat* or postsurg*).ti,ab,kf. or exp Postoperative Period/ or exp Postoperative Care/) (16866) 3 1 or 2 (17339) 4 "diet, food, and nutrition"/ or exp "Infant nutritional physiological phenomena"/ or exp Feeding behavior/ or exp Feeding methods/ or (nutrition* or diet* or feed* or food*).ti,ab,kf. or exp Enteral Nutrition/ or (feeding adj2 (tube* or catheter or enteral or enteric)).ti,ab,kf. or peg.ti,ab,kf. (1567057) 5 3 and 4 (656) 6 limit 5 to (english language and yr="2000 -Current") (465) 7 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (461384) 8 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2017394) 9 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies) (3502520) 10 6 and 7 (18) 11 (6 and 8) not 10 (40) 12 (6 and 9) not (10 or 11) (171) 13 10 or 11 or 12 (229)

Appendix 1 Implementation plan

Introduction

This plan has been drawn up with the aim of advancing the implementation of these guidelines. In order to compile this plan, an inventory of factors that could either facilitate or hinder the recommendations was carried out. The guideline working group has made recommendations concerning the timeline for implementation, the preconditions necessary for this and the actions that should be taken by various parties.

Methodology

In order to arrive at this plan, the working party has applied the following to each recommendation in the guidelines:

- the time point by which the recommendations should have been nationally implemented;
- the expected impact of implementation of the recommendation on healthcare costs;
- preconditions necessary to be able to implement the recommendation;
- possible barriers to the implementation of the recommendation;
- possible actions to advance the implementation of the recommendation;
- the party responsible for the actions to be undertaken.

Readers of this implementation plan should take the differences between 'strong' recommedations and 'weak' recommendations into account. In the former case, the working group clearly states what should or should not be done. In the latter case, the recommendation is less strong and the working party expresses a preference but leaves more room for alternatives. One reason for this could be that there is insufficient research evidence to support the recommendation. A weak recommendation can be recognised by its formulation and may begin with something like 'Consider the…(Overweeg)'. The working group has considered the implementation of both weak and strong recommendations.

Implementation plan

Recommendation	Timeline for implementation: < 1 year, 1 to 3 years or > 3 years	Expected effects on costs	Preconditions for implementation (within specified timeframe)	Possible barriers for implementation[1]	Supposed actions for implementation[2]	Who is responsible for the action(s)[3]	Other comments

[1] Barriers can exist at the level of the professional, at the level of the organization (the hospital) or at the level of the system (outside the hospital). Consider, for example, disagreement with regard to the recommendation in different organizations, insufficient motivation or knowledge of the specialist, insufficient facilities or personnel, necessary concentration of care, costs, poor cooperation between disciplines, necessary rearrangement of tasks, et cetera.

[2] Actions that are necessary for implementation, but also actions that are possible to encourage implementation. Consider, for example, checking the recommendation during a quality review, publication of the guideline, developing implementation tools, informing hospital administrators, arranging proper reimbursement for a certain type of treatment, making cooperation agreements.

[3] Who is responsibilities for implementation of the recommendations will also depend on the level of barriers. Barriers at the level of the professional will often have to be resolved by the professional association. Organizational barriers will often be the responsibility of hospital administrators. Other parties, such as the NZA and health insurers, are also important in resolving barriers at system level.

Actions to be undertaken by each party

Below is a list of actions that in the opinion of the guideline working group should be undertaken to facilitate the implementation of the guidelines.

All academic and professional organisations that are directly involved

- Tell members about the guidelines. Publicise the guidelines by writing about them in journals and disseminating news of them at congresses.
- Provide professional education and training to ensure that the expertise required to follow the guidelines is available.
- Where relevant and possible, develop resources, instruments and/or digital tools to facilitate the implementation of the guidelines.
- Monitor the way in which the recommendations are put into practice by means of audits and quality inspections.
- Include indicators developed for these guidelines in quality registrations and indicator sets.
- Make interprofessional agreements about implementing continuous modular maintenance of the guidelines.

Initiatives to be undertaken by the professional organisation

- Hospital management boards and other system stakeholders (where applicable), should be kept informed of recommedations that could have an effect on the organisation of care and on costs, and on what may be expected by the party concerned.
- Publicise the guidelines to other interested academic and professional bodies.

Local professional groups/ individual medical professionals

- Discuss the recommendations at meetings of professional groups and local working parties.
- Tailor local protocols to fit the recommendations from the guidelines.
- Follow the continuing professional education on these guidelines (yet to be developed).
- Modify local information for patients using the materials that the professional bodies will make available.
- Make agreements with other disciplines involved to ensure the implementation of the recommedations in practice.
- Register pre- and postoperative factors and, as far as is possible, include important considerations for decision-making in existing protocols and the electronic dossier.

The system stakeholders (including health insurers, NZA, hospital managers and their associations, IGZ)

In relation to the financing of care for patients with open fracture of the lower limb, it is expected that hospital management boards will be prepared to make the investments necessary to enable the implementation of these guidelines (see impact on healthcare costs above). In addition, hospital managers are expected to monitor those medical professionals concerned and ascertain how familiar they are with the new guidelines and how they are putting them into practice.

Health insurers are expected to reimburse the costs of the care that is prescribed in these guidelines. When the time frames for implementation have elapsed, health insurers can use the strong recommendations in these guidelines for purposes of purchasing care.

Researchers and subsidy providers

Initiate research into the knowledge gaps, preferably in a European setting.

Knowledge Institute Federation of Medical Specialists
Publicise these guidelines among the staff and contect to development of related guidelines, for example on ankle fractures and post-osteosynthesis infection.
Add guidelines to guideline database. Incorporate this implementation plan in a place where all parties will be able to find it.

Appendix 2 Knowledge gaps

In order to acquire an evidence base for this guideline, systematic literature searches were carried out which gave a comprehensive picture of the evidence base for various treatment options. In summary, it can be contended that the evidence concerning treatment options is limited. In many cases recommendations were supported on the basis of a very low level of evidence, augmented by the expertise of the working group and patient preferences. The most important knowledge gaps that were identified are listed below.

Module Genetic testing

As already mentioned, the actual benefit and cost-effectiveness of genetic testing cannot be determined until the yield of genetic testing has been determined in an unbiased population, and follow-up studies have been performed to analyse the effect of a specific diagnosis, taking into account the quality of life of people with CL/P and their parents.

What is the effect of different genetic tests in isolated clefts of the lip and palate on the diagnostic yield in isolated clefts of the lip and palate?

P: patients with isolated cleft lip and/or palate or pregnant women undergoing prenatal screening for cleft lip and/or palate in their child;
I: diagnostic genetic tests (copy number variant (CNV) analysis (e.g. array comparative genomic hybridization (CGH), SNP array, CMA), next generation sequencing, e.g. gene panels, whole exome sequencing);
C: comparison of the tests above;
R: long term follow-up of children with apparently isolated cleft to identify late onset features an underlying genetic/ syndrome diagnose;
O: yield, sensitivity, specificity, diagnostic accurateness.

Future prospective studies are recommended to resolve these issues.

Module Prenatal medical counselling

What are the needs and expectations of medical counselling of parents expecting a child with a cleft lip and/or palate?

Module Timing repairing cleft lip and palate

What is the effect of the timing of repairing cleft lip and palate on maxillary and midface growth, speech, hearing, feeding capability, postoperative complications (fistulae), and esthetics (patient, parent and/or doctor satisfaction)?

P: patients with cleft lip and/or palate;
I: closing hard palate before 18 months / closing lips before 3 months;
C: closing hard palate after 18 months / closing lips after 3 months;
O: maxillary and midface growth, speech, hearing, feeding capability, postoperative complications (fistulae), and esthetics (patient, parent and/or doctor satisfaction).

Module Technique repairing cleft lip and palate

What is the effect of different techniques of repairing cleft lip and palate on speech, hearing, diet, maxillary growth, postoperative care and complications and esthetical outcome complications and (patient, physician, and parents' satisfaction)?

P: patients with cleft lip and/or palate;
I: surgical techniques for repairing cleft lip and palate;
C: other surgical technique for repairing cleft lip and palate;
O: speech, hearing, feeding capability, maxillary and midface growth, postoperative complications, esthetics (patient, parent and/or doctor satisfaction).

Module Postoperative (nutritional) care

Is breastfeeding or bottle feeding preferred with patients aged 3 to 9 months after lip closure or soft palate closure?

P: patients after a lip closure or soft palate closure, between 3 and 9 months of age;
I: breastfeeding;
C: bottle feeding (included use of a pacifier), Spoon feeding;
O: no disturbed wound healing, enough food intake, no fistulas.