Overige delen van de richtlijn astma van de Nederlandse Vereniging voor Kindergeneeskunde

zoals nu gepubliceerd op http://www.nvk-richtlijnen.nl/astma/index.php/Achtergrondinformatie_over_deze_richtlijn

Inhoud:

Achtergrondinformatie over deze richtlijn

De richtlijn 'Astma bij kinderen' is een herziening van de richtlijn uit 2007. In deze richtlijn komen diagnostiek en behandeling, als ook controle, van kinderen met (verdenking op) astma aan de orde.

Aanleiding

De commissie 'Richtlijnen en indicatoren' van de Nederlandse Vereniging voor Kindergeneeskunde heeft opdracht gegeven voor de herziening van een beperkt aantal knelpunten ten opzichte van de richtlijn uit 2007. Enerzijds was deze richtlijn niet geheel volgens de moderne regels van evidence-based richtlijnontwikkeling opgesteld, anderzijds waren er nieuwe inhoudelijke knelpunten die om evidence-based beantwoording vroegen.

Deze richtlijn sluit aan op andere actuele ontwikkelingen op het gebied van professionele kwaliteit inzake astma bij kinderen, namelijk:

- Zorgstandaard 'Astma voor kinderen en adolescenten'. Deze is recent verschenen onder auspiciën van de Long Alliantie Nederland.
- Multidisciplinaire richtlijn astma. Deze wordt eveneens ontwikkeld door een werkgroep van de Long Alliantie Nederland. Hierin komen ook uitgangsvragen op het terrein van de kindergeneeskunde aan bod.
- Herziening van de Standaard 'Astma bij kinderen' van het Nederlands Huisartsen Genootschap.

De ontwikkeling van de zorgstandaard 'Astma bij volwassenen' (Long Alliantie Nederland), de herziening van de standaard 'Astma bij volwassenen' (Nederlands Huisartsen Genootschap) en de ontwikkeling van de richtlijn 'Diagnostiek en behandeling van ernstig astma' (Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose) zijn zijdelings van belang voor deze richtlijn.

Doel

Het doel van deze richtlijn is het bieden van ondersteuning aan kinderartsen bij het realiseren van een uniform en zoveel mogelijk evidence-based beleid bij kinderen van 0 tot 18 jaar met (verdenking op) astma. Deze richtlijn is primair geschreven voor de doelgroep kinderartsen. Zorgprofessionals kunnen deze richtlijn tevens gebruiken voor het bijhouden van kennis, voor onderwijs- en nascholingsdoeleinden en voor het opstellen van samenwerkingsafspraken.

Werkwijze en samenstelling werkgroep

Deze richtlijn is ontwikkeld door een werkgroep, bestaande uit een kerngroep van drie personen, aangevuld met andere experts op het gebied van astma. De kernwerkgroep bereidde de werkgroepvergaderingen voor, deed het literatuuronderzoek en schreef conceptteksten en de evidence rapporten. Deze werden door de overige leden van de werkgroep becommentarieerd.

De ontwikkeling van deze richtlijn is gefinancierd door de Stichting Kwaliteitsgelden Medisch Specialisten (SKMS). De financier had geen invloed op de inhoud van de richtlijn.

Samenstelling van de werkgroep

De kernwerkgroep 'Astma bij kinderen' bestond uit de volgende leden:

- Dhr. drs. E.J. (Erik-Jonas) van de Griendt, kinderarts-pulmonoloog, Flevoziekenhuis en De Kinderkliniek Almere / Emma Kinderziekenhuis - AMC Amsterdam, projectleider
- Mw. dr. N. (Nicole) Boluyt, kinderarts, Emma Kinderziekenhuis - AMC Amsterdam, adviseur, tot juni 2012
- Dhr. dr. J.J.E. (Jannes) van Everdingen, dermatoloog, Nederlandse Vereniging voor Dermatologie en Venereologie Utrecht / Regieraad Kwaliteit van Zorg Den Haag, adviseur, vanaf juni 2012
- Mw. drs. M.K. (Mariska) Tuut, epidemioloog, PROVA, Varsseveld

De overige leden van de werkgroep waren:

- Dhr. prof. dr. P. (Patrick) Bindels, huisarts, Erasmus Medisch Centrum Rotterdam
- Mw. dr. A. (Annemie) Boehmer, kinderarts-pulmonoloog, Maasstadziekenhuis Rotterdam
- Dhr. dr. R. (René) van Gent, kinderarts, Maxima Medisch Centrum Veldhoven

- Dhr. dr. H. (Hans) de Groot, allergoloog, Reinier de Graaf Gasthuis Delft (sinds maart 2012)
- Mw. dr. H.M. (Hettie) Janssens, kinderarts-pulmonoloog, Sophia Kinderziekenhuis Erasmus Medisch Centrum Rotterdam
- Mw. S. (Saeeda) Lone Latif, longfunctieanalyst, Academisch Medisch Centrum Amsterdam
- Dhr. drs. J. (Jurgen) ter Rijdt, KNO-arts, Isala Klinieken Zwolle (sinds maart 2012)
- Mw. M. (Margareth) Siemons-Wokke, verpleegkundig specialist kinderlongziekten, Medisch Centrum Alkmaar
- Mw. drs. R. (Renee) van Tuyll, jeugdarts, STMR Rivierenland, Tiel
- Mw. dr. J.L.E. (Elianne) Vrijlandt, kinderarts-pulmonoloog, Beatrix Kinderziekenhuis / Universitair Medisch Centrum Groningen
- Mw. dr. E. (Els) Weersink, longarts, Academisch Medisch Centrum Amsterdam
- Mw. dr. J. (Judit) Wesseling, kinderarts, Rijnstate Ziekenhuis Arnhem

De werkgroepleden hebben onafhankelijk gehandeld en zijn gemandateerd door hun beroepsverenigingen. Bij de samenstelling van de werkgroep werd rekening gehouden met een evenredige afspiegeling van academisch versus perifeer werkende kinderartsen en kinderlongartsen. De leden werden verder zo gekozen dat er connecties waren met het bestuur van de sectie kinderlongziekten van de Nederlandse vereniging voor Kindergeneeskunde, de werkgroep van de Standaard astma bij kinderen van het Nederlands Huisartsen Genootschap, de Long Alliantie Nederland en de commissie Richtlijnen en Indicatoren van de Nederlandse vereniging voor Kindergeneeskunde. Na het vaststellen van de uitgangsvragen werden 2 andere relevante disciplines toegevoegd (allergologie en KNO), eveneens met mandaat van hun beroepsvereniging. De leden van de werkgroep hebben allen een belangenverklaring ingevuld, waarin zij mogelijke belangenverstrengeling konden aangeven. De werkgroepleden hebben bij elkaar geen belangenverstrengeling geconstateerd met betrekking tot de uitgewerkte uitgangsvragen. De belangenverklaringen zijn ter inzage bij de NVK.

Ontwikkeling conceptrichtlijn

De werkgroep heeft gedurende een periode van 12 maanden 4 maal vergaderd. De kernwerkgroep heeft reeds bestaande internationale richtlijnen over astma bij kinderen beoordeeld middels het AGREE-instrument. De richtlijn van de British Thoracic Society (BTS) scoorde hierop het beste. De werkgroep concludeerde dat de richtlijn van de BTS kwalitatief goed, recent (juni 2011) en voor een groot deel op de Nederlandse situatie van toepassing kan zijn. De Quick Reference Guide van deze richtlijn is vertaald, geadapteerd voor de Nederlandse situatie en vormt de basis van deze richtlijn. Voor achtergrondinformatie over de totstandkoming van de BTS-richtlijn wordt verwezen naar:

- Quick Reference Guide BTS richtlijn
- Fulltekst BTS richtlijn
- Levels of evidence SIGN richtlijnen

Verschillen tussen de Britse richtlijn en de Nederlandse situatie werden geïdentificeerd. Daarna werden knelpunten geïdentificeerd, vervolgens geprioriteerd. De 5 belangrijkste knelpunten werden via uitgangsvragen, evidence-based beantwoord.

In 2011 werden door de sectie Kinderlongziekten van de Nederlandse Vereniging voor Kindergeneeskunde reeds vier controversiële vragen omtrent behandeling van astma bij kinderen beantwoord. Het ging om de volgende uitgangsvragen:

- Leidt het titreren van de behandeling bij kinderen met astma op basis van de concentratie van stikstofmonoxide in de uitademingslucht FeNO vergeleken met conventioneel monitoren op symptomen en longfunctie tot betere astmacontrole?
- Zijn leukotriëen receptor antagonisten (LTRAs) effectiever (en veiliger) dan inhalatiesteroïden bij jonge kinderen met recidiverend piepen op basis van virale luchtweginfecties?
- Zijn inhalatiesteroïden met extrafijne deeltjes effectiever (en veiliger) dan inhalatiesteroïden met normale deeltjes bij kinderen met astma?
- Wat is bij kinderen met astma die ondanks het gebruik van inhalatiesteroïden nog klachten hebben de meest effectieve en veilige behandeling ('stap 3 dilemma')?

Deze vier vragen zijn opgenomen in deze nieuwe richtlijn.

In 2012 werden als onderdeel van '5 acute problemen in de kindergeneeskunde' tevens een nieuwe richtlijn voor de behandeling van acuut astma geautoriseerd door de Nederlandse Vereniging voor Kindergeneeskunde gepubliceerd. Dit onderdeel wordt eveneens opgenomen in deze richtlijn.

Daarnaast werden vijf nieuwe uitgangsvragen opgesteld door de werkgroep:

- Meten van de fractionele excretie van stikstofmonoxide (FeNO) in uitademingslucht:
    - Draagt de niet-invasieve meting van de ontstekingsverschijnselen in de luchtwegen d.m.v. FeNO, in aanvulling op of in de plaats van de standaardmethode van diagnostiek bij kinderen met astma bij aan een verbetering van de aandoening?
    - Draagt het omlaag brengen van de dosis van inhalatiesteroïden o.b.v. FeNO i.p.v. de standaarddiagnostiek van astma (symptomen, longfunctie, etc) bij kinderen die hoge doseringen inhalatiesteroïden gebruiken bij aan de preventie van exacerbaties
- Wat is de bijdrage van familietherapie aan de standaardbehandeling van kinderen met (moeilijk behandelbare) astma?
- Ademdysregulatie (dysfunctional breathing):
    - Wat is the incidentie van ademdysregulatie (ADR) bij kinderen die zich presenteren met de symptomen van astma?
    - Wat is de beste vorm van diagnostiek (of per exclusionem) om bij kinderen die zich presenteren met de symptomen van astma ademdysregulatie (ADR) vast te stellen?
    - Wat is de beste vorm van behandeling van kinderen met ademdysregulatie (ADR)?
- Draagt immuuntherapie (A: subcutaan; B: sublinguaal) bij kinderen (6-12 jr.) en adolescenten (>12 jr.) met stabiel astma en inhalatie allergie voor pollen, gras of huisstofmijt bij aan een verbetering van hun astma?
- Zelfmanagement:
    - Wat is de bijdrage van zelfmanagement educatie aan de standaardbehandeling van kinderen met (moeilijk behandelbaar) astma, ondanks een normale ICS dosering?
    - Welke onderdelen van zelfmanagement educatie dragen het meest bij aan verbetering van astma bij kinderen?

Deze vragen werden evidence-based beantwoord door leden van de kernwerkgroep en becommentarieerd door de overige leden van de werkgroep. Bij de uitwerking van de vragen werd een systematische werkwijze gevolgd, waarbij literatuur volgens tevoren afgesproken criteria werd gezocht, geselecteerd en beoordeeld. De precieze werkwijze per uitgangsvraag staat vermeld in de desbetreffende evidence rapporten:

- Evidence rapport FeNO
- Evidence rapport gezinstherapie
- Evidence rapport dysfunctioneel ademhalen
- Evidence rapport SCIT/SLIT
- Evidence rapport zelfmanagement

Waar mogelijk en relevant werd gebruik gemaakt van de GRADE-methode voor het wegen van de waarde van de evidence. Hierbij werden aan het begin van het richtlijntraject uitkomstmaten gedefinieerd, zie hiervoor de evidence rapporten. Resultaten werden per uitkomstmaat samengevat, waarbij tevens de 'overall' kwaliteit van de onderliggende bewijslast (evidence) werd aangegeven.

GRADE kent vier niveaus: 'high', 'moderate', 'low' en 'very low'. Per uitkomst werd een GRADE niveau toegekend. Wanneer een uitkomst als 'high' geclassificeerd werd, wil dit zeggen dat het onwaarschijnlijk is dat toekomstig onderzoek de schatting van de uitkomst zal veranderen. Met andere woorden, er is veel vertrouwen in de juistheid van de schatting van de uitkomst. Een 'very low' classificatie wil zeggen dat er veel onzekerheid is over de juistheid van de uitkomst. De niveaus moderate en low zitten tussen high en very low in, qua vertrouwen in de resultaten.

Het onderzoeksdesign is een belangrijke factor binnen GRADE. Gerandomiseerde en gecontroleerde studies krijgen daarom in beginsel de kwalificatie 'high'. Er zijn vijf factoren die kunnen zorgen voor een lagere kwalificatie:

1. Beperkingen in de onderzoeksopzet.

2. Inconsistentie: onverklaarde heterogeniteit van de resultaten.
3. Indirectheid: de populatie, interventie, controle en uitkomst (PICO) waarop de evidence gebaseerd is wijken op een of meer punten af van de PICO die men wil onderzoeken. Ook het gebruik van surrogaatmarkers valt onder indirectheid.
4. Imprecisie: wijde betrouwbaarheidintervallen rond een geschat effect duiden op onzekerheid in de grootte van het effect. Er is sprake van imprecisie bij een te kleine steekproef (lage statistische power), weinig events en een betrouwbaarheidsinterval dat wel statistisch significant is maar zowel in het gebied van klinische relevantie als in het gebied van een verwaarloosbaar effect ligt.
5. Publicatiebias.

Observationele studies daarentegen krijgen in beginsel de kwalificatie 'low'. Er zijn drie factoren die kunnen zorgen voor een hogere kwalificatie:

1. Groot effect
2. Aanwezigheid van dosisresponsrelatie
3. Vermindering van het effect door plausibele indirectheid van bewijs confounders

Iedere beperkende (of bevorderende) factor kan leiden tot het verlagen (of verhogen) van de classificatie met een of twee niveaus. Indien de resultaten niet gepoold konden worden, werd volstaan met een globale inschatting van de kwaliteit van de onderliggende bewijslast. Aan de hand van de algehele kwaliteit van bewijs, grootte en zekerheid over het netto gunstig effect van een interventie, waarden en voorkeuren van patiënten, middelenbeslag, professioneel perspectief, organisatie van zorg en maatschappelijk perspectief, wordt vervolgens bepaald of een sterke en zwakke (conditionele) aanbeveling wordt geformuleerd.

Voor een uitgebreidere beschrijving van GRADE wordt verwezen naar www.gradeworkinggroup.org.

Kostenimplicaties

Er is geen complete kosteneffectiviteitsanalyse of budgetimpactanalyse gedaan. Kostenaspecten zijn bij de 5 evidence reviews die voor deze richtlijn door de werkgroep zijn geschreven voor zover relevant beschreven in de 'overwegingen (considerations)' in de paragraaf voor de aanbevelingen.

Commentaar en autorisatie

De uiteindelijke tekst van de richtlijn is op 19-12-2012 ter commentaar voorgelegd aan de leden van sectie kinderlongziekten (SKL), overige leden van de Nederlandse Vereniging voor Kindergeneeskunde en aan overige wetenschappelijke verenigingen.

In de definitieve richtlijn, die ter autorisatie is aangeboden aan de Nederlandse Vereniging voor Kindergeneeskunde op 3 mei 2013, is het commentaar verwerkt van de volgende personen/organisaties:

- Leden van de sectie kinderlongziekten van de Nederlandse Vereniging van Kindergeneeskunde: dr. W.A. Balemans, kinderarts-pulmonoloog, prof. dr. J.C. de Jongste, kinderarts-pulmonoloog, prof. dr. P.L. Brand, kinderarts-pulmonoloog, mw. dr. M.W. Pijnenburg, kinderarts-pulmonoloog, dr. B.L. Rottier, kinderarts-pulmonoloog, prof. dr. G.H. Koppelman, kinderarts-pulmonoloog, Dr. F.G.A. Versteegh, kinderarts
- Mw. dr. S.G. Pasmans, kinderdermatoloog
- Mw. T. Dauven, verpleegkundig specialist
- Dr. R.M.M. Geijer, huisarts, namens het Nederlands Huisartsen Genootschap
- Dr. W.J. de Waal, namens het Nederlands Instituut voor Psychologen
- Dr. H.M. Blom, namens de Nederlandse Vereniging voor Keel-Neus-Oorheelkunde en Heelkunde van het Hoofd-Halsgebied
- Dr. G.J. Braunstahl en dr. N. ten Hacken, namens de Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose

Publicatie en implementatie

In de verschillende fasen van de ontwikkeling van het concept van de richtlijn is zoveel mogelijk rekening gehouden met de implementatie van de richtlijn en de daadwerkelijke uitvoerbaarheid van de aanbevelingen. De definitieve richtlijn

is onder de verenigingen verspreid en via de website van de NVK (www.nvk.nl) elektronisch beschikbaar gesteld. Op wetenschappelijke bijeenkomsten van de betrokken wetenschappelijke verenigingen zijn de aanbevelingen van de richtlijn gepresenteerd. Verder zal er patiëntenvoorlichtingsmateriaal worden ontwikkeld ter ondersteuning van de richtlijn.

Om de implementatie en evaluatie van deze richtlijn te stimuleren, zijn interne indicatoren ontwikkeld aan de hand waarvan de implementatie steekproefsgewijs kan worden gemeten.

Kwaliteitsindicatoren

Indicatoren geven in het algemeen de zorgverleners de mogelijkheid te evalueren of zij de gewenste zorg leveren. Zij kunnen daarmee ook onderwerpen voor verbeteringen van de zorgverlening identificeren. Er werd een beperkt aantal kwaliteitsindicatoren opgeleverd ten behoeve van deze richtlijn. Zie hiervoor de paragraaf indicatoren.

Herziening

De richtlijn wordt 1x per 3 jaar gereviseerd. De verantwoordelijkheid hiervoor ligt primair bij de initiatiefnemer voor deze richtlijn, de Nederlandse Vereniging voor Kindergeneeskunde. Uiteraard kunnen de (leden van) wetenschappelijke en beroepsverenigingen die deelnamen aan de ontwikkeling van deze richtlijn en ook andere zorgverleners aan de Nederlandse Vereniging voor Kindergeneeskunde kenbaar maken dat de richtlijn niet (meer) adequaat of actueel is.

Juridische betekenis

Richtlijnen zijn geen wettelijke voorschriften, maar op 'evidence' gebaseerde inzichten en aanbevelingen waaraan zorgverleners moeten voldoen om kwalitatief goede zorg te verlenen. Na autorisatie van de richtlijn door een beroepsvereniging, wordt de richtlijn gezien als deel van de 'professionele standaard'.

Aangezien de aanbevelingen hoofdzakelijk gebaseerd zijn op de 'gemiddelde patiënt', kunnen zorgverleners op basis van hun professionele autonomie waar nodig afwijken van de richtlijn. Afwijken van richtlijnen kan in bepaalde situaties zelfs noodzakelijk zijn. Wanneer van de richtlijn wordt afgeweken, dient dit beargumenteerd en gedocumenteerd te worden.

Publicatie en implementatie

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Herziening

De richtlijn wordt 1x per 3 jaar gereviseerd.

Overzicht belangenverklaringen

Naam	Hoofdfunctie	Nevenwerkzaamheden	Persoonlijke financiële belangen	Persoonlijke relaties	Reputatiemanagement	Extern gefinancierd onderzoek	Kennisvalorisatie	Overige Belangen
KERNGROEP								
Erik-Jonas v.d. Griendt	Kinderarts-pulmonoloog, Flevoziekenhuis en de Kinderkliniek, Almere (0,8 FTE)	Projectleider NVK richtlijn astma bij kinderen (0,2 FTE)	_	_	_	_	_	_

Nicole Boluyt	Kinderarts-epidemioloog	Bestuurslid Stichting Astma Bestrijdingsfonds (SAB, onbetaald) en redacteur nascholingstijdschrift Praktitsche Pediatrie (kleine vergoeding)	-	-	-	-	-	-
Jannes van Everding en	Algemeen secretaris Regieraad Kwaliteit van Zorg	Directeur NVDV/Huidfonds	_	_	_	_	_	_
Mariska Tuut	Eigenaar PROVA (adviesbureau op het gebied van kwaliteit van zorg, voert diverse projecten uit, met name evidence-based richtlijnontwikkeling)	_	_	_	_	_	_	_
OVERIGE WERKGROEPLEDEN								
Patrick Bindels	Hoogleraar huisartsgeneeskunde, hoofd afdeling huisartsgeneeskunde, Erasmus MC Rotterdam (0,8 FTE) Huisarts, praktijk Buitenhof, Amsterdam (0,2 FTE)	Lid Gezondheidsraad Lid RGO Lid autorisatie commissie (plv lid) NHG Lid Wetenschappelijk advies raad Astmafonds Lid wetenschappelijk raad Geneesmiddelen bulletin Alle nevenwerkzaamheden onbetaald (behoudens vacatiegeld bij RGO en NHG)	-	-	Tot december 2011 voorzitter NHG verenigingsraad	Tot 2011 is binnen de afdeling huisartsgeneeskunde van het Erasmus MC te Rotterdam onderzoek gedaan naar de effectiviteit van SLIT bij kinderen met een huisstofmijtallergie of een graspollenallergie. Dit onderzoek werd gefinancierd door Artu (farmaceut). De uitvoering van het onderzoek is gedaan volgens de criteria van good clinical practice. Inmiddels is dit onderzoek afgerond en zal leiden tot 2 promoties in 2012. Via afdeling huisartsgeneeskunde AMC-UvA nog betrokken bij wetenschappelijk onderzoek gefinancierd door Astmafonds naar de diagnostiek van	-	-

						astma bij jonge kinderen. In 2012 is, bij de afdeling huisartsgeneeskunde van het Erasmus MC, gestart met een door het Astmafonds gefinancierd onderzoek naar de behandeling van allergische rhinitis bij kinderen uit de huisartsenpraktijk.		
Annemie Boehmer	Kinderarts-pulmonoloog	Redacteur kindergeneeskundig nascholings tijdschrift (kleine vergoeding)	-	-	-	-	-	-
René van Gent	Kinderarts	APLS instructeur (vrijwilligers vergoeding) Instructeur teach the teacher cursus (detachering)	-	-	-	-	-	-
Hans de Groot	Allergoloog		-	-	-	-	-	-
Hettie Janssens	Kinderarts-pulmonoloog	Lid werkgroep inhalatie instructie LAN (onbetaald) Lid adviesgroep neonatale screening CF van NVK (onbetaald) Lid werkgroep kinderformularium (onbetaald) Co-chair pediatric networking group ISAM (onbetaald)	-	-	-	Ontwikkeling benchmark testing voor gezichtsmasker voorzetkamer (2012-2013; Philips Respironics (hoofdonderzoeker); 25.000,-) Perifere targeting van inhalatie antibiotica bij CF (2012-2016; Chiesi (mede-onderzoeker) 300.000,-) Studie naar effectiviteit en veiligheid van astma onderhoudstherapie bij kinderen met astma (2011-2015; ZonMW (mede-aanvrager) 600.000,-) Studie naar adherence bij kinderen met		

						astma (2011-2013; ZonMW (mede-aanvrager) 150.000,-)		
Saeeda Lone-Latif	Longfunctieanalist		-	-	-	-	-	-
Jurgen ter Rijdt	KNO-arts		-	-	-	-	-	-
Margareth Siemons-Wokke	Verpleegkundig specialist kinderlongziekten							
Renee van Tuyll	Jeugdarts KNMG Stafarts STMR afd. jeugdgezondheidszorg		-	-	-	-	-	-
Elianne Vrijlandt	Kinderarts-pulmonoloog	Bestuurslid sectie kinderlongziekten NVK (onbetaald) Commissie richtlijnontwikkeling BPD (SKMS, betaald)	-	-	-	-	-	-
Els Weersink	Longarts		-	-	-	-	-	-
Judit Wesseling	Kinderarts	Lid Commissie richtlijnen en indicatoren NVK						

Evidence reviews

Evidence review dysfunctional breathing

Erik-Jonas van de Griendt, kinderlongarts, Flevoziekenhuis & De Kinderkliniek Almere / Emma Kinderziekenhuis – AMC Amsterdam
Mariska Tuut, epidemioloog, PROVA Varsseveld

namens de werkgroep NVK-richtlijn astma

- Link to evidence review vocal cord dysfunction

Definition and delimitation

Dysfunctional Breathing DB) is a respiratory disorder, psychologically or physiologically based, involving breathing too deeply and/or too rapidly (hyperventilation syndrome (HVS)) or erratic breathing interspersed with breathholding (dysfunctional breathing (DB)) or sighing (sighing dyspnoea) [Brashear, 1983; Morgan, 2002].
We choose to use the term DB (in Dutch: dysfunctionele ademhaling) for the forms of breathing abnormalities mentioned before.

Vocal cord dysfunction (VCD) is a respiratory disorder involving paradoxal movements of the vocal cords (i.e. adduction instead of abduction during inspiration). VCD is well known to asthma specialists as a common mimic of asthma. This is a closely linked disorder, however distinct and diagnosed by flexible laryngoscopy, and therefore

described in part 2. Treatment of VCD, for example with speech therapy, is preferably coordinated by an ENT-specialist [KNO-arts].

Description of the condition

Hyperventilation is defined as a state of alveolar ventilation in excess of metabolic requirements, leading to a decreased arterial partial pressure of carbon dioxide (PaCO2) and respiratory alkalosis. If sustained, these physiological changes may result in a wide range of clinical symptoms which characterise DB, including breathlessness, chest tightness, dizziness, tremor and paraesthesia.

In many children, DB is not a continuously symptomatic state but a syndrome of episodic symptoms which occur with or without recognisable provocation. Not all patients with DB present with hyperventilation and hypocapnia. As such, the term dysfunctional breathing encompasses a complex set of behaviour and symptoms with no obvious physiological explanation. Either way, DB can result in significant patient morbidity and an array of symptoms. The presence of these symptoms can themselves result in anxiety which can provoke further breathing irregularity.

Clinical considerations and all-day practise

In children presenting with symptoms of asthma, breathlessness and chest tightness are also often present. The child with asthma may confuse different origins of breathlessness, for example 'real asthmatic' breathlessness versus breathlessness due to DB. Asthma specialists frequently recognise the co-incidence of the two, with a trend towards more problems of the combination of asthma and DB in the age of puberty and more in girls. Patients seem to experience huge difficulties in separating differences in symptoms, thus facing difficulties in selfmanagement and the execution of their written action plan.

If presuming DB in a patient with asthma, the patient is often send to a chest physiotherapist or remedial therapy for additional confirmation and treatment. The physiotherapist will treat with breathing exercises in accordance with local or international protocols.

No gold standard is known for DB or HVS. Sometimes a standardised questionnaire (Nijmegen Questionnaire) is used [Van Dixhoorn, 1984]. Additional tests can be performed such as hyperventilation provocation with or without capnography. Lung function and Bronchial hyperreactivity (histamine or metacholine) can be tested to experience 'real asthmatic' breathlessness and help in differential diagnosis.

Clinical question 1 (PICO 5a)

What is the incidence of dysfunctional breathing in children presenting with asthma symptoms?

Literature Search

We searched Medline (Pubmed) in order to find cohort studies to answer this question. If no studies in children were found, the search was extended without limits for age.

Results

No cohort studies were found in children on prevalence or incidence of DB in children presenting with asthma symptoms.

In adults, one cohort study was found [Thomas, 2001]. This study was performed in a general practice in the United Kingdom in 4381 patients aged 17-65 years. 7% met the criteria of asthma. Postal questionnaires including the Nijmegen questionnaire on HVS were used. The diagnosis of asthma was made on clinical assessment and medication use, as is usual in a general practice (no lung function tests were done). 8% of the non-asthmatic patients had symptoms suggestive of dysfunctional breathing. 29% of patients that were treated for asthma had symptoms suggestive for dysfunctional breathing. Patients with dysfunctional breathing were more likely to be female and younger age.

GRADE

Because of the lack of solid evidence, systematic critical appraisal using GRADE, is considered of no additional value.

Conclusion

There are no reliable data about the incidence of dysfunctional breathing in children presenting with asthma symptoms.

Clinical question 2 (PICO 5b)

What is the best strategy to diagnose (or rule out) dysfunctional breathing in a child presenting with asthma symptoms?

Literature search

We first searched Medline (Pubmed) in order to find RCT's to answer this question, since a gold standard is lacking. Studies on diagnostic accuracy were therefore not taken into account. Search terms, inclusion criteria and results are reported at the end of this document. If no studies in children were found, the search was extended without limits for age.

Results

No RCTs that compare different treatment strategies in children with dysfunctional breathing/hyperventilation syndrome were found.

Several reviews promote the use of a standardized questionnaire [De Groot, 2011; De Groot, 2010; Grüber, 2012; Niggemann, 2010]. This questionnaire (the 'Nijmegen questionnaire') has not been validated for children [Van Dixhoorn, 1984]. A pediatric version or alternative is not (yet) available, although a French group proposed a simplified questionnaire – the so called SHAPE questionnaire – which is to be validated yet [Sznajder, 2009].

Some authors accentuate careful anamnesis, completed by consultation of a medical psychologist as appropriate [Niggeman, 2010]. No comparative studies were found on different tests.

When compared in a double-blind placebo-controlled design, the diagnostic accuracy of hyperventilation provocation with capnography *in adults* is low to moderate and cannot count for a gold standard [Hornsveld, 1996].

GRADE

Because of the lack of solid evidence, systematic critical appraisal using GRADE, is considered of no additional value.

Conclusion

The specificity of additional diagnostic testing, such as hyperventilation provocation with capnography, is too low to use in a routine diagnostic strategy.

Standardized questionnaires (like the 'Nijmegen questionnaire') are probably most discriminating, although not validated for use in children.

Flexible laryngoscopy is useful in diagnosing vocal cord dysfunction, a major differential diagnosis.

Considerations

Given the high prevalence of dysfunctional breathing in the general and asthmatic population in adults, with a trend towards younger patients, dysfunctional breathing is probably also manifest in a younger population.
In adolescents one can speculate that dysfunctional breathing is manifest on a rather frequent basis, most likely in the presence of asthma. DB might be underdiagnosed. However, no studies were identified that confirm this hypothesis. In children and adolescents, no data are available on the prevalence of DB.

Given the high prevalence and the absence of a gold standard, a standardized anamnesis will fit best to gather symptoms of DB. A structured approach on classification of somatoform breathing disorders can be helpful. Gruber et al propose a clear and well designed schematic classification which might be helpful in the diagnostic considerations in the child with breathing problems.

Recommendation (in Dutch)

Overweeg in de differentiële diagnose van astma de diagnose dysfunctionele ademhaling bij kinderen en adolescenten met aanvallen van benauwdheid die vergezeld gaan van specifieke symptomen (kortademigheid, druk op de borst, duizeligheid, tremoren en paresthesieën) en die niet goed reageren op luchtwegverwijding (consensus; expert opinion).

Stel de diagnose dysfunctionele ademhaling op anamnese en de afwezigheid van positieve tests die een andere

diagnose suggereren.

Hyperventilatie provocatietest met capnogram wordt niet aanbevolen.

Het gebruik van een (voor volwassenen gevalideerde) vragenlijst kan behulpzaam zijn.

Clinical question 3 (PICO 5c)

What is the most effective treatment of children with dysfunctional breathing?

Literature search

We first searched the Cochrane library and Medline (Pubmed) for Systematic Reviews or RCTs to answer this question. When studies where found for children and adults, they were only analysed when children were children were reported separately. If no RCT's were available for children, we extended the search to adults, but did not intent to fully analyse adult studies. Systematic search terms, as well as results are reported in Appendix 1 Literature searches DB.

Results

No RCTs were found that compare different treatment strategies in children with DB. Physiotherapy or breathing exercises or breathing retraining are mentioned in 2 narrative reviews on children with DB, both by the same first author [De Groot, 2010; De Groot, 2011]. One Cochrane protocol for adults was found, meaning a review is underway. Different breathing therapies in adults with DB will be evaluated.

In adults some RCTs were found (i.e. selected trials that were included in the mentioned Cochrane protocol) concerning adults with asthma. In one single-blinded (partly) placebo controlled study in 69 adults *with asthma* two different breathing techniques (named Buteyko and pranayama) were compared [Cooper, 2003]. The group that practiced Buteyko breathing exercises showed diminished use of reliever medication (2 puffs less per week) and better asthma symptom scores after 6 months, but no change in PD20.

GRADE

Because of the lack of solid evidence, systematic critical appraisal using GRADE, is considered of no additional value.

Conclusion

The most effective treatment for children and adolescents with DB can not be established yet, because so far no literature exists to answer the question directly. RCT's regarding treatment in children lack completely.

In adults there seems to be an indication that one specific technique (Buteyko) works in patients with asthma, showing a better symptom score with less use of rescue medication (while indeed not changing their inflammatory process).

Considerations

In the experience of the working group:

- referral to an experienced chest physiotherapist can be helpful
- dysfunctional breathing can also be accompanied by bronchoconstriction, and can be treated with bronchodilators
- breathing exercises by speech therapists, or relaxation exercises (e.g. yoga) can relieve symptoms.

Recommendation (in Dutch)

Bij (vermoeden van) dysfunctionele ademhaling kan behandeling door een ervaren oefentherapeut overwogen worden. Afhankelijk van de lokale situatie kunnen ook een (proef)behandeling door een logopedist of ontspanningsoefeningen d.m.v. yoga in individuele gevallen worden uitgeprobeerd.
Bij (een vermoeden van) gelijktijdige of voorafgaande bronchusobstructie is luchtwegverwijding aangewezen.

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Background dysfunctional breathings

Clinical questions

1. What is the incidence of dysfunctional breathing in children presenting with asthma symptoms?
2. What is the best strategy to diagnose (or rule out) dysfunctional breathing in a child presenting with asthma symptoms?
3. What is the most effective treatment of children with dysfunctional breathing?
4. Vocal cord dysfunction

References

Appendix 1 literature search

Appendix 1 literature searches dysfunctional breathing

Search Cochrane review

Jones M, Harvey A, Marston L, O'Connell NE. Breathing exercises for dysfunctional breathing/hyperventilation syndrome in adults. Cochrane Database of Systematic Reviews 2011, Issue 3. Art. No.: CD009041. DOI: 10.1002/14651858.CD009041 *(PROTOCOL Adults)*

Result searches in Medline en Central

Pubmed [dysfunctional breathing] 151 hits AND children 26 hits Of which 5 relevant → 1 t/m 5   [pseudo-asthma] 16 hits AND children 6 hits Of which 2 relevant → 6, 7   [hyperventilation syndrome] limit all child 393 hits, also several metabolic syndroms AND [breathing] 115 hits Of which 5 relevant sinds 1990 → 8 t/m 12

Selection criteria

- Sub question a: cohort study
- Sub question b: RCT
- Sub question c: Systematic review or RCT
- Language: Dutch, English, German
- Exclusion: animal study, conference abstract

Result

file	Number after search	Number after 1st selection	Number after 2nd selection
Search vraag 5 EJG	281	12	7 +3
Extension to adults			

Evidence review SCIT/SLIT

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Erik-Jonas van de Griendt, kinderlongarts, Flevoziekenhuis & De Kinderkliniek Almere / Emma Kinderziekenhuis – AMC Amsterdam

namens de werkgroep NVK-richtlijn astma

Clinical question

- Does immune therapy (A: Subcutaneous; B: Sublingual) for children (6-12yrs.) and adolescents (>12 yrs.) with stable asthma and inhalation allergy to pollen and/or grass and/or house dust mite improve asthma outcome?

Rationale

Recent studies have documented the efficacy and safety of immunotherapy in patients with allergic rhinitis, but the value of this treatment in children with asthma is still debated. We evaluated the efficacy of SCIT and SLIT in the treatment of allergic asthma in children.

Literature search

In January 2012 we searched for evidence to answer the clinical question with a simple search in the Database of Abstracts of Reviews of Effectiveness (DARE), which is outlined in Appendix 1. Since we were not confident with the results, we undertook a more extensive search in March 2012. We searched in the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness, and Cochrane Central Trial Register (to update reviews found in the first and second database). We conducted a relatively simple search strategy that resulted in 83 abstracts. The search strategy is listed in Appendix 1.

Literature selection

Before starting the literature selection, eligibility criteria were established. All abstracts were screened using the following in- and exclusion criteria:

- Methodology: only systematic reviews and randomized controlled trials were included.
- Patient: studies on children with asthma were included. Studies that were carried out only in adults, or only in children with other diseases than asthma, were excluded.
- We only included studies that used subcutaneous or sublingual immunotherapy as intervention.
- We excluded studies that were published in other languages than Dutch, English and German.
- We excluded animal studies.
- We excluded conference abstracts.

The literature selection process resulted in a large decrease of the amount of studies. In the first selection round (carried out by one reviewer, MT), we selected 10 abstracts for further review. A second selection procedure (carried out by another reviewer, EJvdG), focused on clinical relevance and lead to a further reduction. Finally, we selected 8 abstracts for full text review. The literature selection process is described in Appendix 2.

Critical appraisal and results

In the development of this guideline we decided to use the GRADE approach for critically appraising and summarizing the body of evidence. Three predefined outcomes were classified as critical: asthma symptoms, (severe) exacerbations, and asthma control. The other predefined outcomes ((disease-specific) quality of life, change in lung function, and airway inflammation) were classified as important. Characteristics of the included studies are displayed in the evidence table in Appendix 3.

SCIT

Abramson et al. conducted a Cochrane systematic review, in which they studied the effectiveness of SCIT in patients with asthma [Abramson, 2010]. In this review 90 RCT's were included; a total of 3.792 patients (of which 3.459 with asthma) were included. Fourteen of the included RCT's were carried out in children only, and another 24 included children and adults. In a few studies the age inclusion criteria were not clear. It was obvious that, of the studies that had included children, the majority was published in the 20th century, with studies that have been conducted in the seventies or even the fifties. Patients and interventions that have been reported in older studies may vary from patients and interventions nowadays, so results have to be interpreted with care. Unfortunately, results have not been presented separately for children in the review, so we had to calculate these results ourselves.

In order to update the results of the Cochrane review, we added one study. Tsai et al. reported the results of a randomized clinical trial (non-blinded, no intervention in control arm), in which they researched the clinical efficacy of

house dust mite-specific immunotherapy in asthmatic children [Tsai, 2010]. Forty children were included in this study and followed for six months. Twenty children were randomly assigned to the intervention group and received immunotherapy with subcutaneous injections with immunotherapy. However, since this study was not blinded and there was no intervention in the control arm (no real placebogroup), thus we decided to exclude this study. Zielen et al. reported the results of a randomized controlled trial in which they investigated steroid-sparing effects with allergen-specific immunotherapy in children with asthma [Zielen, 2010]. Outcomes, specified in this RCT were not corresponding with outcomes appointed in our evidence review, so we excluded this study.

Concerning the critical outcome asthma symptoms, we took the comparison allergen immunotherapy versus placebo, and looked at asthma symptom scores. A total of four quite small studies that were carried out in children only, reported this outcome in the Cochrane review (and included mite, pollen, and other immune therapy). Little is known about the underlying studies; e.g. follow-up is not stated. There are also other concerns about the quality of the literature, e.g. not all studies are double-blind and placebo-controlled, and randomization procedures are poor. We undertook a meta-analysis of the four studies (including 116 patients with immune therapy and 86 placebo controls), which resulted in a standardized mean difference of --0,01 (95%CI: -0,48-0,50). Studies were not subdivided in age groups.

Second, we looked at asthma exacerbations, and took the outcome symptomatic deterioration in the Cochrane review. Five studies, carried out in children only, reported this outcome (and included mite, pollen, animal dander, and other immune therapy). The quality of these studies was again moderate, because of lack of concealment of allocation, and few information about follow-up. We put the five studies in a meta-analysis; 253 patients were on immune therapy and 153 got a placebo. The pooled risk ratio was 0,47 (95%CI: 0,31-0,72), which favored the use of immune therapy in children with asthma and inhalation allergy in preventing exacerbations. However, this last pooled risk ratio was mainly based on old studies (before 1980), so results have to be interpreted with care. The 2 studies after 1984 did not confirm this result.

Considering the lung function, only two studies in the Cochrane review were carried out in children only and reported peak expiratory flow. FEV_1 was not reported in any study on children only at all. One of the underlying studies was quite well designed, we have methodological concerns about the other, small, study. We pooled the results of both studies and retrieved a non-significant standardized mean difference between immune therapy and placebo of -0,19 (95%CI -0,55-0,17), in favor of immune therapy.

In the Cochrane review, there was no direct outcome for airway inflammation; we therefore took 'increased allergen specific bronchial hyperreactivity' as an indicator. We found three relatively small studies, with quite large methodological shortcomings (in terms of risk of bias, indirectness, and publication bias), so the quality of the evidence was again low. The pooled results showed a risk ratio of 0,67 (95%CI 0,48-0,95), which indicates that subcutaneous immune therapy may prevent children with asthma and inhalation allergy from having increased bronchial hyperreactivity.

SLIT

We found three systematic reviews about sublingual immune therapy(SLIT) in patients with asthma. Calamita et al. reviewed the literature using the Cochrane Collaboration method [Calamita, 2006]. They carried out a methodological well systematic review with meta-analyses. But, they included children as well as adults. We could therefore only use the studies that were included children only. Penagos et al. conducted a meta-analysis of the efficacy of sublingual immune therapy in children with allergic asthma [Penagos, 2008]. Hoeks et al. also investigated the effectiveness of sublingual immune therapy in children [Hoeks, 2008]. Their target population was children with asthma or rhinoconjunctivitis. This study was published in Dutch, but they hardly reported any quantitative results, so we could not use this last study in our evidence review.

For investigating the effectiveness of sublingual immune therapy in children with asthma and inhalation allergy on asthma symptoms, we reanalyzed data from 14 trials in the reviews from Calamita and Penagos. We reanalyzed the full-text articles that were included in the review from Calamtica, whit respect to double-blind placebo-controlled studies that reported children with asthma separately. A description of the single studies was reported in the evidence table in appendix 3. We found a large heterogeneity between the included studies, although single studies were carried out rather well. We tried to discover an aggregated result, but encountered large differences in the interventions, used in the single studies (e.g. on allergens, dose, patient groups, and length of treatment). It is therefore

not possible to pool these data. Results of the single studies are not worthwile mentioning, because of the small number of included patients.

Calamita et al. pooled data for describing the outcome 'worsening of asthma'. We took that results for our outcome exacerbations. In total 497 children in that meta-analysis were treated with immune therapy; 116 of them experienced worsening of asthma. In contrast, 195 out of 379 children on placebo reported worsening of asthma. The pooled risk ratio was 0,48 (95% CI: 0,40-0,57), indicating that sublingual immune therapy may prevent children with asthma and inhalation allergy from getting an exacerbation. Calamita et al. also reported the outcome 'reduction of medication use to asthma'. We took that outcome as an indicator for asthma control, our predefined outcome. In that pooled meta-analysis, 132 children were treated with immune therapy, and 122 with placebo. The standardized mean difference was -0,91 (95% CI: -1,94-0,12). Because of the large confidence interval we downgraded the level of evidence (for imprecision). Again, the subgroups on different allergens were too small, heterogeneous and imprecise to drawany substantial conclusion.

At last, we selected two studies that compared sublingual with subcutaneous immune therapy. When studying the full text of these studies, we decided to exclude them both, because children with asthma were not analyzed as a separate group [Antunez, 2008; Keles, 2011].

The summary of findings table and GRADE evidence profile (both conducted with GRADEPro) are listed in Appendix 4 and Appendix 5. We had to calculate meta-analyses (using RevMan), and present them in Appendix 6.

Conclusions

SCIT

⊕⊕⊖⊖ LOW	There is probably no difference in asthma symptoms between subcutaneous immune therapy and placebo in children with allergic asthma (evidence from pre-ICS era). *custommade metaanalysis, see appendix 6*
⊕⊕⊖⊖ LOW	Subcutaneous immune therapy might be effective in preventing asthma exacerbations in children with allergic asthma (evidence from pre-ICS era). *custommade metaanalysis, see appendix 6*
⊕⊕⊖⊖ LOW	It cannot be concluded that there is any difference in lung function (measured with peak expiratory flow) between subcutaneous immune therapy and placebo in children with asthma and inhalation allergy (evidence from pre-ICS era). *custommade metaanalysis, see appendix 6*
⊕⊕⊖⊖ LOW	Subcutaneous immune therapy may prevent children with allergic asthma from having allergen specific bronchial hyperreactivity (evidence from pre-ICS era). *custommade metaanalysis, see appendix 6*
	There is no evidence about the effectiveness of subcutaneous immune therapy on asthma control and quality of life in children with allergic asthma.
The overall quality of the evidence on the clinical question concerning subcutaneous immune therapy is LOW (⊕⊕⊖⊖).	

SLIT

⊕⊕⊕⊖ MODERATE	There is no clear over-all evidence for the effectiveness of sublingual immune therapy in reducing asthma symptoms in children with allergic asthma. *Calamita 2006*, *Penagos 2008*

⊕⊕⊕⊖ MODERATE	There is no clear over-all evidence for the effectiveness of sublingual immune therapy in preventing children with allergic asthma from getting exacerbations. Calamita 2006

⊕⊕⊖⊖ LOW	There is no effect of sublingual immune therapy on asthma control, measured by reduction of asthma medication use, in children with allergic asthma, when compared to placebo. Calamita 2006

	There is no evidence about the effectiveness of sublingual immune therapy on quality of life, lung function, and airway inflammation in children with allergic asthma.

The overall quality of the evidence on the clinical question concerning sublingual immune therapy is LOW (⊕⊕⊖⊖).

Considerations

Children with asthma often suffer from the comorbidity of inhalation allergies. There is no clear evidence for the improvement of any asthma outcome by using subcutaneous or sublingual immune therapy. This lack of evidence is partly due to large heterogeneity in the interventions studied. More systematic research may get the evidence more clear in the future. Since the effect of immune therapy is not clear, much attention must be given to the other side of the medal: when treating patients with immune therapy above usual care a big effort is necessary. Negative aspects of SCIT are costs, (monthly) injections under adequate medical supervision due to potential (however rare) dangerous side effects. In SLIT the risk of serious side-effects is considered less severe, however therapy lasts 1 to 3 year, producing substantial effort and costs. In order to improve asthma control, to increase symptom free days or to lower the risk of an asthma exacerbation the effect reached should thus be clear and obvious in order to produce a positive balance between desirable and undesirable effects.
Moreover, the body of evidence on SCIT included only studies from the pre-ICS era published decades ago thus the working group considers bias or data not applicable to the actual situation very likely.

Recommendations (in Dutch)

WEAK RECOMMENDATION	Subcutane en sublinguale immuuntherapie worden niet aanbevolen voor de behandeling van het astma van kinderen en adolescenten, vanwege een gebrek aan bewijs voor de effectiviteit van de interventies op astma-uitkomsten, en vanwege de nadelen die met de behandeling gepaard gaan.

References

Appendix 1 literature search

Appendix 2 literature selection

Appendix 1 literature search SCIT/SLIT

Search Cochrane Databases of Systematic Reviews, Dare, and Central

Literature search d.d. 29032012

1. "asthmazoekacties jan 2012".ti. (0)
2. asthma.tw. (14671)
3. Bronchial Spasm.tw. (15)
4. asthma*.tw. (17541)
5. wheez*.tw. (869)
6. bronchospas*.tw. (777)
7. (bronch* adj8 spas*).tw. (52)
8. bronchoconstrict*.tw. (1663)
9. (bronch* adj8 constrict*).tw. (71)
10. airway* inflammation*.tw. (704)
11. or/2-10 (18894)
12. immunotherap*.kw,tw. (2803)
13. 11 and 12 (473)
14. subcutaneou*.kw,tw. (8020)
15. 12 and 14 (259)
16. 15 (259)
17. limit 16 to yr="2008 -Current" (57)

Results

File name	Number of abstracts after literature search
cl systrev 20120329 full systrev vr2 immunotherapy	19
cl dare 20120329 vr2 immunotherapy	7
cl cctr 20120329 vr2 vanaf 2008 immunotherapy	57

Appendix 2 literature selection SCIT/SLIT

Selection criteria

- Methodology: only systematic reviews and randomized controlled trials were included.
- Patient: studies on children with asthma were included. Studies that were carried out only in adults, or only in children with other diseases than asthma, were excluded.
- We only included studies that used subcutaneous or sublingual immunotherapy as intervention.
- We excluded studies that were published in other languages than Dutch, English and German.
- We excluded animal studies.
- We excluded conference abstracts.

Results

File name	Number of abstracts after literature search	Number of abstracts after first literature	Number of abstracts after second literature

		selection	selection
cl systrev 20120329 full systrev vr2 immunotherapy	19	2	8
cl dare 20120329 vr2 immunotherapy	7	1	
cl cctr 20120329 vr2 vanaf 2008 immunotherapy	57	7	

An expert in the working group judged our search and selection process and committed that there were no missing relevant publications.

Appendix 3 evidence table SCIT/SLIT

SCIT

	Abramson, 2010	Calamita, 2006	Penagos, 2008
Study design	Cochrane systematic review, consisting of 90 RCT's. 14 RCT's were carried out in children only; 24 were done in children and adults. The total study population (children and adults) consisted of 3.792 patients (of whom 3.459 had asthma)	Systematic review, consisting of 25 RCT's. Only 9 RCT's were carried out in children only. The total study population consisted of 1.706 patients (adults and children, with asthma and/or rhinitis)	Systematic review, consisting of 9 RCT's, all carried out in children. The total study population comprised 441 patients with asthma (seasonal, mild, moderate, and persistent)
Age (mean)	Not specified, variation between included studies	Not specified, there is a limited description of the characteristics of the included studies	Range specified per study, total range: 4-17.
Setting (in RCT's)	-	-	-
Diagnosis (asthma/rhinitis)	Asthma	Asthma and rhinitis	Asthma
Eligibility criteria	RCT's, patients with asthma, allergen specific subcutaneous immunotherapy (administration of extracts of house dust mites, pollens, animal danders or moulds, chemically modified allergoids or antigen-antibody complexes)	RCT's, double blinded, and open studies, patients with asthma and/or rhinitis, sublingual immunotherapy (with or without swallowing, all types of allergen, all doses, all lengths of treatment)	RCT's, double blinded, placebo control-led, patients ≤ 18 years, with a history of allergic asthma, with identified causal allergen, and proven IgE sensitization. Sublingual immunotherapy (with or without swallowing, all types of allergen, all doses, all durations of treatment)
Type of immunotherapy	Subcutaneous immunotherapy (variation of allergen abstracts in different included studies)	Sublingual immunotherapy, mainly pollen and mite	Sublingual immunotherapy, mainly mites
Intervention	Subcutaneous immunotherapy	Sublingual immunotherapy, mainly pollen and mite	Sublingual immunotherapy (mainly mites, further: O europaea, Holcus, P pretense dermatophagoidespteronyssinus, grass mix), great variation in

			duration, range: 3-32 months
Control	Placebo	Placebo	Placebo
Primary outcomes	Asthmatic symptoms Asthma medication requirements Lung function Nonspecific bronchial hyper-reactivity Allergen specific bronchial hyper-reactivity	Asthmatic symptoms (symptom score) Asthmatic medication requirement Respiratory function tests (PEFR, FEV_1, FEF25-75%) Nonspecific bronchial provocation Adverse effects	Asthma symptoms Medication scores
Secondary outcomes	Local reactions Systemic reactions	-	
Comment	The results have not been presented separately for children in the review. Self-calculated meta-analyses are presented in Appendix 6.	The authors mentioned they used the Cochrane Collaboration method	-

Sublingual immune therapy, from Calamita (double-blind placebo-controlled studies, that study asthma seperately in children)

Author, date	Study design	Setting	Eligibility criteria	Participants (number, gender, age, and descriptive)	Asthma type*, severity (e.g. on ICS?)	Allergy type (mono/ multi, allergens, proven)	Intervention (type, dose, duration)	Control	Follow-up (from start trial)	Outcomes	Results†	Critical appraisal‡	Comments
Bahcecier 2001	DB PC SLIT drops HDM	Monocenter Turkey University hospital	Asthma with need for ICS, HDM allergic, ongoing resp symptoms despite mite avoidance and appropriate ICS treatment, > 7 yr, FEV_1	15, 8 male, 11,7 yr	Moderate asthma, need for ICS, resp symptoms despite mite avoidance, FEV_1> 70%	Monoallergy HDM but neg for all other aeroallergens	Drops SLIT, dose 100 IR/day, 4 weeks run-in, 4 weeks once daily, thereafter 2/week; total 6	Placebo drops	6 months	Symptom scores, compliance, exacerbations**, SPT 6 mo, Lung function, metacholine, serum IgE	Improvement asthma score, fewer asthma exacerbations**, Less use of SABA, trend towards less ICS (n.s.), no change in PD20, no serious side	Randomization and blinding not clear, possible industrial influence, disclosures not stated, small number of patients, no follow-up after	Season not stated; decrease PEF in placebo group – stable in intervention group

							months				effects	stop of interventi on	
Hirsch 1997	DB PC SLIT dro ps HD M	Monoc enter, universi ty hospita l Germa ny	Not strictly specified	30, female N=10, 10,5yr (6-15yr),	'mild to modera te asthma': n=8; allergic rhinitis: n=8; asthma and rhinitis: n=14 Not further specifie d	Allergy SPT pos HDM, part also sensitize d cat, dog, grasses	Drops SLIT HDM, 3 weeks run-in, mainten ance 7 drops 3 days/w eek; TOTAL 12 months	Placebo drops (vehicle only)	12 mon ths	Symptom scores, complianc e, SPT 6 mo, Lung function, metacholi ne, serum IgE , collection of dust monsters (exposure)	Less pulmonar y symptoms No difference use of SABA No change in PD20 No serious side effects	Small number of patients, especiall y when specifid per group. Enrollme nt of patients (possible selection bias) is not clear. Serious differenc es in patients groups, otherwis e than interventi on (type and duration of disease), no follow-up after interventi on. 20% drop-out in interventi on group, no intention-to-treat analysis	Season not stated; Asthma group not well-describe d, exacerb ations not describe d, 8 patients allergic rhinitis only
Pajno 2003	DB PC SLIT dro ps Par	Mono-center, Italy	Inclusion: seaso-nal asthma and rhinoconju nctivitis,	38, 20 female , 11 yr,	DDA, seasona l asthma, poor control	Mono sensibilis ation to Parietar ia, SPT and	Drops SLIT parieta ria, 4 wk run-in,	Placebo drops + flutica-son 2nd	12 mon ths	Symptom scores, VAS score during pollen season,	No diff symptom scores Better VAS in	Patient selection not clear: 30/38 children were	Unclear whether Fluticaso ne was given intranas

	ie-taria (NL glas-kruid)		DDA, poor symp-tom control de-spite antihistami-ne, ICS and ne-docromil use du-ring pollen sea-son, positive skin prick test Parie-taria, Specific IgE to Parietaria. Exclusion: sensiti-zation to other allergens, previ-ous immunothe ra-py, severe asth-ma (FEV_1<70 %), other diseases		despite medicat ion, includin g ICS, patients with PC20< 2.0mg exclude d	RAST positive	mainten ance every other day, total 12 mo, comedi cation with fluticas on	control group: no pro-tocolledm edica-tion		complianc e, SPT 6 mo, serum IgE	SLIT group	randomiz ed; 8 were control (not willing to participa te in trial?), possible selection bias.	ally or orally! No lungfunc tion or PD20
Pajno 2004#	DB PC SLIT dro ps Par ie-taria	Mono-center, Italy	seasonal asthma during spring and allergic rhinitis	30 (8-14 yr)	DDA	Mono sensibilis ation to Parietar ia, SPT and RAST positive	Drops SLIT pa-rietaria, 4 wk run-in, mainte-nance every other day, total 12 mo	Placebo drops	24 mon ths	Lungfuncti on and PD20	No change in lungfuncti on, improvem ent in BHR (PD20) after 2 yr	1 author affiliate d to pharmac eutical industry	
Rolinck-Wernin ghaus 2004	DB PC SLIT dro ps gra ss-	Multi-center, universi ty clinics, Germa	Allergic rhinitis with or without seasonal asthma Exclusion	Total 97 (32 female), 3-14 yr Asthm	DDA, seasona l asthma, no ICS use	Grasspo llen IgE and SPT positive Others not	Drops SLIT 5-grass mixture ##, 4 wk	Placebo drops	32 mo	Primary endpoint: multiple symptom-medicatio n score, lungfuncti	Less use of com-bined medicatio n (asthma medicatio n not	2nd author affiliate d to pharmac eutical	"this is not my patient" (perenni al asthma exclude

	poll en	ny	criteria: perennial asthma, ICS use	a: N=39		mention ed	run-in, 3 doses/ week, TOTAL 32 mo			on, FeNO (part of the participan ts), complicati ons	analysed separatel y). Lung function inconclusiv e; No change in FeNO 1 pt asthma exacerba tion related to SLIT	industry	d); lungfunc tion only analyse d as absolute values (not % predicte d)

* Doctors diagnosed asthma? Stable/seasonal asthma?Mild/severe asthma?

† Asthma symptoms, allergy/rhinitis symptoms, asthma control, (disease specific) quality of life, exacerbations, lung function, airway inflammation, adverse reactions and/or complications

‡ e.g. randomization procedure, blinding, risk of bias

IR index units of reactivity

** defined as an abrupt and/or progressive worsening of symptoms of shortness of breath, chest tightness, or some combination of these symptoms, which did not respond to regular use of beta-2-agonists for a duration of 24 hr

is longterm follow-up of Pajno 2003

The potency was expressed in specific treatment units (STU); 1000 STU were equivalent to 25 biological units (BU) and contained 2.5 lg of major grass pollen allergens. The monthly dose during maintenance treatment was 6 lg (0.5 lg/dose,3 times/week). The median for the total duration of treatment was 32 months (January 1999 to November 2001) with a median cumulated dose of 188 lg allergen

Appendix 4 summary of findings table SCIT/SLIT

Subcutaneous immune therapy

subcutaneous immune therapy for children (6-12 years) and adolescents (>12 years) with stable asthma and inhalation allergy to pollen and/or grass and/or house dust mite

Patient or population: children (6-12 years) and adolescents (>12 years) with stable asthma and inhalation allergy to pollen and/or grass and/or house dust mite
Settings:
Intervention: subcutaneous immune therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Subcutaneous immune therapy				
Asthmasymptoms Asthmasymptom scores		The mean asthma symptoms in the intervention groups was 0.01 standard deviations lower (0.48 lower to 0.50		202 (4 studies[1])	⊕⊕⊖⊖ low[2,3]	

		higher)				
Exacerbations Symptomaticdeterioration	Moderate		RR 0.47 (0.31 to 0.72)	406 (5 studies[1])	⊕⊕⊖⊖ low[2,3]	
Asthma control	Study population		Notestimable	0 (0)	See comment	
	See comment	See comment				
	Moderate					
Quality of life	Study population		Notestimable	0 (0)	See comment	
	See comment	See comment				
	Moderate					
Lung function Peak expiratory flow		The mean lung function in the intervention groups was 0.19 standard deviations lower (0.55 lower to 0.17 higher)		151 (2 studies[1])	⊕⊕⊖⊖ low[2,3,4]	
Airway inflammation Increased allergen specific bronchial hyperreactivity	Study population		RR 0.67 (0.48 to 0.95)	100 (3 studies[1])	⊕⊕⊖⊖ low[2,3,5,6]	
	694 per 1000	465 per 1000 (333 to 659)				
	Moderate					

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI:Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Studies in Cochrane review

[2] The underlying studies had a quite large risk of bias, due to lack of allocation concealment, and lack of information on follow-up (and lost-to-follow-up)
[3] Because the underlying studies are quite old, populations and interventions may have altered during the time.
[4] Wide confidence interval with the point of no effect, and the point of large effect in it.
[5] We took increased allergen specific bronchial hyperreactivity as a measure for airway inflammation, which is an indirect outcome.
[6] The funnel plot of this comparison shows some suspected publication bias

Sublingual immune therapy

sublingual immune therapy for children (6-12 years) and adolescents (>12 years) with stable asthma and inhalation allergy to pollen and/or grass and/or house dust mite

Patient or population: children (6-12 years) and adolescents (>12 years) with stable asthma and inhalation allergy to pollen and/or grass and/or house dust mite
Settings:
Intervention: sublingual immune therapy

Outcomes	**Illustrativecomparativerisks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	Corresponding risk				
	Control	**Sublingual immune therapy**				
Asthma symptoms[1]	See comment	See comment	Not estimable[1]	677 (14 studies[2])	⊕⊕⊕⊖ **moderate**[3]	
Exacerbations worse of asthma	**Study population**		**RR 0.48** (0.4 to 0.57)	876 (7 studies[2])	⊕⊕⊕⊖ **moderate**[3]	
	515 per 1000	**247 per 1000** (206 to 293)				
	Moderate					
Asthma control Reduction of medication use to asthma		The mean asthma control in the intervention groups was **0.91 standard deviations lower** (1.94 lower to 0.12 higher)		254 (6 studies[2])	⊕⊕⊖⊖ **low**[3,4]	
Quality of life	**Study population**		Notestimable	0 (0)	See comment	
	See comment	See comment				
	Moderate					
Lungfunction	**Study population**		Notestimable	0 (0)	See comment	
	See comment	See comment				

	Moderate					
Airwayinflammation	**Study population**		Notestimable	0 (0)	See comment	
	See comment	See comment				
	Moderate					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Because of large heterogeneity, we decided not to pool and report the results
[2] Studies in 2 systematic reviews
[3] Methodological properties of the trials that were included were scarcely reported. Although the Jadad scores were high, we decided to downgrade the risk of bias, because we cannot control the high quality of the data.
[4] The pooled standardized mean difference had a large confidence interval, including the points of no effect, and large effect.

Appendix 5 GRADE evidence profile SCIT/SLIT

Subcutaneous immune therapy

Author(s): Mariska Tuut - PROVA
Date: 2012-06-13
Question: Should subcutaneous immune therapy be used in children (6-12 years) and adolescents (>12 years) with stable asthma and inhalation allergy to pollen and/or grass and/or house dust mite?
Settings:
Bibliography: Abramson MJ, PuyRM,Weiner JM. Injection allergen immunotherapy for asthma. Cochrane Database of Systematic Reviews 2010, Issue 8. Art. No.: CD001186. DOI: 10.1002/14651858.CD001186.pub2.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Subcutaneous immune therapy**	**Control**	**Relative (95% CI)**	**Absolute**		
Asthma symptoms (measured with: Asthma symptom scores; Better indicated by lower values)												
4[1]	randomised	very serio	no seriousinconsi	serious[3]	no seriousimpre	none	116	186	-	RR 0.47 (0.31	⊕⊕⊖⊖ LOW	CRITICAL

	trials	us[2]	stency		cision					to 0.72)		
Exacerbations (assessed with: Symptomatic deterioration)												
5[1]	randomised trials	very serious[2]	no seriousinconsistency	serious[3]	no seriousimprecision	none	64/253 (25.3%)	0%	RR 0.47 (0.31 to 0.72)	-	⨁⨁⨀⨀ LOW	CRITICAL
Asthma control												
0	No evidence available					none	-	-	-	-		CRITICAL
								0%		-		
Quality of life												
0	No evidence available					none	-	-	-	-		IMPORTANT
								0%		-		
Lung function (measured with: Peak expiratory flow; Better indicated by lower values)												
2[1]	randomised trials	serious[2]	no seriousinconsistency	serious[3]	serious[4]	none	77	74	-	SMD 0.19 lower (0.55 lower to 0.17 higher)	⨁⨁⨀⨀ LOW	IMPORTANT
Airway inflammation (assessed with: Increased allergen specific bronchial hyperreactivity)												
3[1]	randomised trials	very serious[2]	no seriousinconsistency	serious[3, 5]	no seriousimprecision	reporting bias[6]	24/51 (47.1%)	34/49 (69.4%)	RR 0.67 (0.48 to 0.95)	229 fewer per 1000 (from 35 fewer to 361 fewer)	⨁⨁⨀⨀ LOW	IMPORTANT
								0%		-		

[1] Studies in Cochrane review
[2] The underlying studies had a quite large risk of bias, due to lack of allocation concealment, and lack of information on follow-up (and lost-to-follow-up)
[3] Because the underlying studies are quite old, populations and interventions may have altered during the time.
[4] Wide confidence interval with the point of no effect, and the point of large effect in it.
[5] We took increased allergen specific bronchial hyperreactivity as a measure for airway inflammation, which is an indirect outcome.
[6] The funnel plot of this comparison shows some suspected publication bias

Sublingual immune therapy

Author(s): Mariska Tuut - PROVA
Date: 2012-04-07
Question: Should sublingual immune therapy be used in children (6-12 years) and adolescents (>12 years) with stable asthma and inhalation allergy to pollen and/or grass and/or house dust mite?
Settings:
Bibliography: Calamita Z, Saconato H, Pela AB, Atallah AN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. Allergy 2006; 61: 1162-72. Penagos M, Passalacqua G, Compalati E, Baena-Cagnani CE, Orozco S, Pedroza A, et al. Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. Chest 2008; 133: 599-609.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sublingual immune therapy	Control	Relative (95% CI)	Absolute		
Asthma symptoms[1] (Better indicated by lower values)												
14[2]	randomised trials	serious[3]	no seriousinconsistency	no seriousindirectness	no seriousimprecision	none	343	334	-[1]	not pooled[1]	⨁⨁⨁⊖ MODERATE	CRITICAL
Exacerbations (assessed with: worse of asthma)												
7[2]	randomised trials	serious[3]	no seriousinconsistency	no seriousindirectness	no seriousimprecision	none	116/497 (23.3%)	195/379 (51.5%)	RR 0.48 (0.4 to 0.57)	268 fewer per 1000 (from 221 fewer to 309 fewer)	⨁⨁⨁⊖ MODERATE	CRITICAL
								0%		-		
Asthma control (measured with: Reduction of medication use to asthma; Better indicated by lower values)												

6[2]	randomised trials	serious[3]	no seriousinconsistency	no seriousindirectness	no seriousimprecision	none	132	122	-	SMD 0.91 lower (1.94 lower to 0.12 higher)	⊕⊕⊖⊖ LOW	CRITICAL
Quality of life												
0	no evidence available					none	-	-	-	-		IMPORTANT
								0%		-		
Lungfunction												
0	no evidence available					none	-	-	-	-		IMPORTANT
								0%		-		
Lungfunction												
0	no evidence available					none	-	-	-	-		IMPORTANT
								0%		-		

[1] Because of large heterogeneity, we decided not to pool and report the results

[2] Studies in 2 systematic reviews

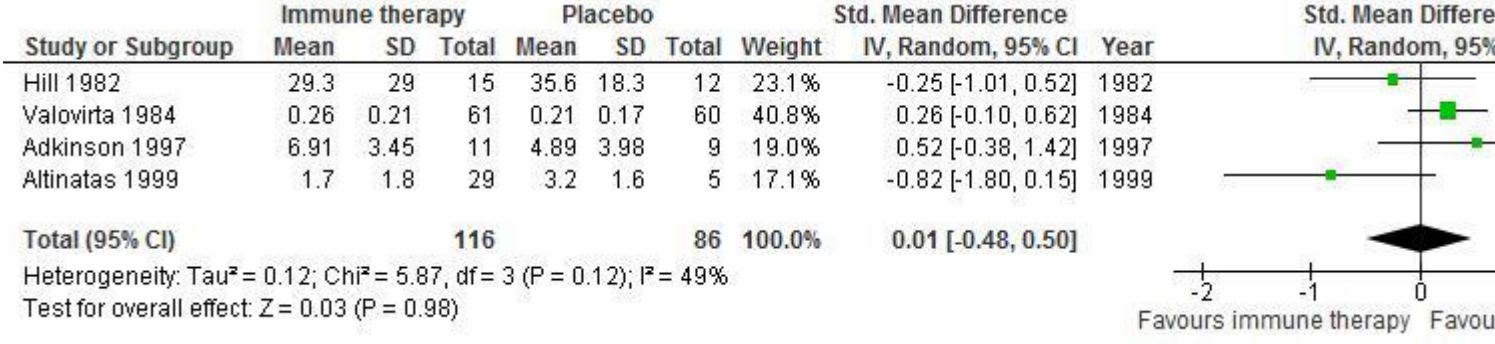
[3] Methodological properties of the trials that were included were scarcely reported. Although the Jadad scores were high, we decided to downgrade the risk of bias, because we cannot control the high quality of the data.

[4] The pooled standardized mean difference had a large confidence interval, including the points of no effect, and large effect.

Appendix 6 meta-analyses SCIT

Subcutaneous immune therapy

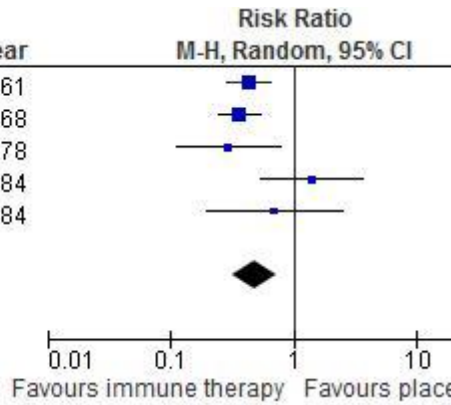
Outcome: Asthma symptom score



Outcome: exacerbations (symptom deterioration)

Study or Subgroup	Immune therapy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Johnstone 1961	31	131	23	42	32.4%	0.43 [0.29, 0.65]	1961
Johnstone 1968	19	67	49	63	32.9%	0.36 [0.24, 0.55]	1968
Warner 1978	4	27	12	24	12.8%	0.30 [0.11, 0.80]	1978
Valovirta 1984	7	15	4	12	13.3%	1.40 [0.53, 3.68]	1984
Price 1984	3	13	4	12	8.6%	0.69 [0.19, 2.48]	1984
Total (95% CI)		**253**		**153**	**100.0%**	**0.47 [0.31, 0.72]**	
Total events	64		92				

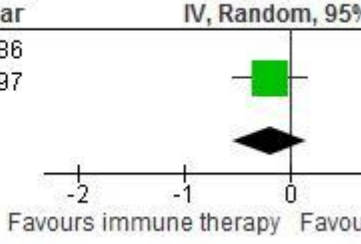
Heterogeneity: Tau² = 0.09; Chi² = 7.45, df = 4 (P = 0.11); I² = 46%
Test for overall effect: Z = 3.54 (P = 0.0004)



Outcome: lung function (peak expiratory flow)

Study or Subgroup	Immune therapy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Dreborg 1986	-346	0	16	-289	0	14		Not estimable	1986
Adkinson 1997	-84.4	2.56	61	-83.4	7.02	60	100.0%	-0.19 [-0.55, 0.17]	1997
Total (95% CI)			**77**			**74**	**100.0%**	**-0.19 [-0.55, 0.17]**	

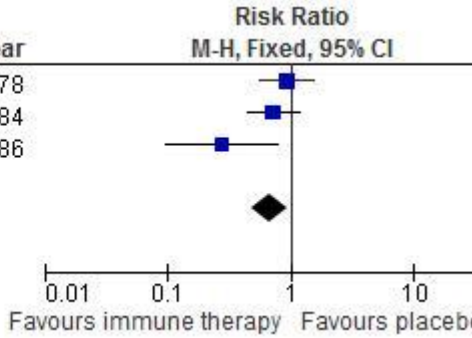
Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)



Outcome: airway inflammation (increased allergen specific bronchial hyperreactivity)

Study or Subgroup	Immune therapy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Warner 1978	12	22	14	24	38.4%	0.94 [0.56, 1.56]	1978
Valovirta 1984	9	15	10	12	31.9%	0.72 [0.44, 1.17]	1984
Dreborg 1986	3	14	10	13	29.7%	0.28 [0.10, 0.79]	1986
Total (95% CI)		**51**		**49**	**100.0%**	**0.67 [0.48, 0.95]**	
Total events	24		34				

Heterogeneity: Chi² = 4.42, df = 2 (P = 0.11); I² = 55%
Test for overall effect: Z = 2.26 (P = 0.02)



Evidence review self-management

Mariska Tuut, epidemioloog, PROVA Varsseveld

Erik-Jonas van de Griendt, kinderlongarts, Flevoziekenhuis & De Kinderkliniek Almere / Emma Kinderziekenhuis – AMC Amsterdam

namens de werkgroep NVK-richtlijn astma

Clinical questions

- What is the efficacy of self-management or written action plans in children (0-5 years, 6-12 AND 12 >) with asthma despite a normal ICS dose?
- Which elements in self-management and written action plans contribute most to improved asthma outcome?

Rationale and definitions

The target of asthma treatment has importantly shifted from severity of the disease (and or level of medication) towards disease control. Self-management plays an important role in controlling the disease. Self-management of asthma incorporates a range of strategies including (1) education, (2) self-monitoring of the condition, (3) regular review by a healthcare provider and (4) the use of a written action plan [Gibson, 2004]. Asthma education programmes are aimed at improving patients' knowledge, understanding and self-management of asthma by providing information about asthma and its management [Tapp, 2010; Wolf, 2008]. Self-monitoring of asthma involves the regular measurement of peak expiratory flow, FEV_1, asthma control or symptoms. Regular review consists of regular consultation with a healthcare provider during the intervention period for the purpose of reviewing the patients' asthma status and medications. A written action plan is an individualised written plan produced for the purpose of patient self-management of asthma exacerbations, which informs participants about when and how to modify medications in response to worsening asthma and how to access the medical system in response to worsening asthma [Gibson, 2004; Rank, 2008; Toelle, 2009;].

We aimed to disentangle specific aspects (education, self-monitoring, regular review, written action plan) of self-management and its contribution to asthma control. Given the clinical question above, we particularly focused on aspect 1 and 4 (education and written action plan).

Literature search and selection

In February 2012, we searched for evidence to answer this clinical question. We started from three Cochrane systematic reviews, that we knew, and decided to update them, where necessary [Bhogal, 2006; McLean, 2010; Toelle, 2004]. We did a combined search to update the Cochrane reviews, where we must pose that Toelle's review has been withdrawn. We undertook a literature search in the Database of Abstracts of Reviews of Effectiveness, in Medline, and in Cochrane Central Trial Register. We combined the search strategies that had been done in the Cochrane reviews, and added two filters (RCT filter, child filter). The full search strategy is listed in Appendix 1. In total, we retrieved 747 abstracts.

Before starting the literature selection, we established eligibility criteria. All abstracts were screened using the following in- and exclusion criteria:

- Methodology: only systematic reviews and randomized controlled trials were included.
- Patient: studies on children with asthma were included. Studies that were carried out only in adults, or only in children with other diseases than asthma, were excluded.
- We only included studies that focused on self-management (e.g. education, written action plan).
- We excluded studies that were published in other languages than Dutch, English and German.
- We excluded animal studies.
- We excluded conference abstracts.

Since we retrieved a very large amount of abstracts in the literature search, we quite specifically selected the abstracts, which led to a great reduction of the possible body of evidence. The literature selection process is described in Appendix 2. However, the amount of studies that had to be studied was still far too large, so we decided to select three extra Cochrane systematic reviews on different aspects of educational interventions, [Wolf, 2002], [Boyd, 2009], [Welsh, 2011]. We then wrote the critical appraisal and results, for reasons of feasibility. Since we were not willing to focus on a specific small aspect of self-management (e.g. a very specific question about certain techniques in a particular population), we think this approach is justified in order to include the broader aspect of self-management.

Critical appraisal and results

1. education. Wolf et al. wrote a Cochrane systematic review about educational interventions for asthma in children [Wolf, 2002]. They reanalysed randomised controlled trials and controlled clinical trials, in which children and adolescents with asthma from two to 18 years were included. They looked at any educational intervention to teach self-management skills or instructional strategies, either individual or in group sessions. In this review different parameters

were used for physiological function (e.g. FEV_1), morbidity and functional status (e.g. exacerbations), self-perception measures (e.g. asthma severity and self-efficacy), and health care utilization (e.g. hospitalization). A total of 32 trials involving 3706 children and adolescents with asthma were selected for inclusion.
[1. Lungfunction]. In four included studies the lung function was reported, in total 258 children participated in those studies. The standardized mean difference was reported as 0,50 (95% CI 0,25-0,75). FEV_1 was reported in just one RCT carried out in 110 patients. The mean FEV_1 in the education group was 2,13 (sd 0,51), compared to 1,90 (sd 0,47) in the control group (this difference was statistically significant). Herewith, we can conclude that self-management may lead to better results on lung function than usual care. However, we have to handle these conclusions with care, because there is some risk of bias, as there is uncertainty about the allocation of concealment in all included studies in this meta-analysis.
[2. Exacerbations]. The effect of self-management on the presence of exacerbations was studied in two studies in the review (total: 363 patients). This led to a pooled odds ratio of 1,43 (95% CI 0,94-2,18) (with the same quality limitations as the former equation).
[3. Asthma severity]. The last outcome, interesting for this review was the asthma severity score that was reported in this Cochrane review. A total of four studies with 212 participants resulted in a pooled standardized mean difference of -0,15 (95% CI -0,43-0,12), again with risk of bias because of randomisation weaknesses.

Welsh et al. published a Cochrane systematic review about home-based educational interventions for children with asthma [Welsh, 2011]. They included 12 randomised controlled trials, reporting about 2342 participants. They reported quite large possibilities of bias, because of randomisation issues, lack of blinding, selective reporting en incomplete outcome data. We therefore decided to exclude this study for further analysis.

Boyd et al. conducted a Cochrane systematic review to identify whether asthma education leads to improved health outcomes in children who have attended the emergency department for asthma [Boyd, 2009]. They included 38 studies comprising 7843 children. Outcomes of interest were subsequent emergency department visits, hospital admissions, unscheduled doctor visits, lung function, quality of life and days home sick. Any type of education was compared to control in a total of 3010 children. These data were pooled in the Cochrane review, which resulted in a conclusion of low evidence level (because of a rather great risk of bias, and indirectness of the outcome measure). The risk ratio for visiting the emergency department was 0,73 (95% CI 0,65-0,91) for having had any type of education compared to control. Subgroups, divided by age groups had similar results for children 1-5 years old, and 6-14 years old, while the age group > 15 years resulted in a non-significant effect (the result tended towards the same direction, only a few participants, thus large confidence interval). A combination of information, self-monitoring and action plan (compared to control) resulted in a risk ratio of 0,60 (95% CI 0,47-0,77) for having an exacerbation that lead to emergency department visit, whereas information only (compared to control) got no significant results. Educational and environmental remediation intervention resulted in a risk ratio (when compared to control) of 0,74 (95% CI 0,63-0,86). We realize that direct comparisons have not been made in this meta-analysis, but we may assume (from indirect evidence) that more extensive approaches give better results.

2 and 3. selfmonitoring and regular clinical review. McLean et al. wrote a Cochrane review about telehealthcare for asthma [McLean, 2010]. Unfortunately, children and adults were not separately analysed, so we had to exclude this data.

4. written action plans. Bhogal et al. wrote a Cochrane systematic review about written action plans for asthma in children [Bhogal, 2006]. They studied the independent effect of providing action plans versus not providing action plans. Outcomes assessed in this review were asthma exacerbations (requiring an unscheduled medical or emergency department visit, indicating a failure of the written action plan), severity of exacerbations, asthma control (including lung function, symptom scores, and quality of life), satisfaction, inflammation, and adverse effects. The review consisted of four trials representing 355 patients. All trials included a symptom-based versus a peak-flow-based action plan (thus, no comparison to no action plan provided). Therefore, we cannot answer the question in the strict sense. Blinding is not possible in this trial design, so a reasonable risk of bias is introduced. Besides, three of the four included studies reported some bias, and unclear allocation.
[1. Exacerbations] All included studies described the number of patients with at least one acute care visit for asthma. We took that outcome for our critical outcome exacerbations. Three studies used daily peak flow, two studies used peak flow when symptomatic (one study took both). There was a slight advantage for the symptom-based written action plans (RR 0,73; 95% CI 0,55-0,99), but the confidence interval is wide and nearly touches 1.

[2. Lung function] Two studies, in total comprising 257 patients, analysed the average percentage predicted FEV_1 during 3 months of intervention. We took that measure for our critical outcome lung function. The mean difference between peak-flow based written action plans and symptom-based written action plans was -0,73 (% predicted FEV_1) (95% CI: -4,75-3,28).
[3. Symptoms]. One study (168 patients) took 'change in symptom score at 3 months' in the analyses. This study did not differentiate between peak-flow-based and symptom-based written action plans (mean difference 0,04; 95% CI: -0,22-0,29).
[4. Quality of life] Two studies, including 257 children, described the outcome change in child quality of life at 3 months. It was not described how quality of life was measured in the studies. The mean difference between both groups was -0,25 (95% CI -0,55-0,05).

The summary of findings table and GRADE evidence profile (both conducted with GRADEPro) are listed in Appendix 3 and Appendix 4.

Conclusions

⊕⊕⊕⊖ MODERATE	Educational interventions (targeted at improved self-management) in children and adolescents with asthma, may lead to better lung functions, than usual care. *Wolf, 2009*
⊕⊕⊖⊖ LOW	Education may prevent children with asthma from having an exacerbation, reflected by less emergency department visits than controls. *Boyd, 2009*
⊕⊕⊖⊖ LOW	There is some evidence that combined interventions, aimed at self-management (e.g. information, self-monitoring and action plan, or educational and environmental measures may reduce asthma exacerbations. *Boyd, 2009*
⊕⊕⊖⊖ LOW	There is some evidence of equal effectivity of written-action-plans, based on peak-flow in comparison with written-action-plan, based on symptoms, when looking at lung functions, symptoms and quality of life. There may be a slight difference in risk of exacerbations, in favour of symptom-based written-action-plans. *Bhogal, 2006*

Considerations

Self-managements incorporates a range of strategies that might be beneficial regarding important health care issues for children with asthma. Undesirable effects (like side-effects of the strategy) are not likely, although not fully covered in the available literature (for example written action plans are meant to prevent unplanned medical visits thus reducing stress and fear for an exacerbation, but verification of stress reduction was not covered in the literature we analysed). Education can be quite easily organised for children and their parents, and at relatively low costs, but implies a certain amount of time and effort of health care workers, patients and their family. A written action can be made up easily, whereas no undesirable effects are to be expected. Moreover, only little extra effort (time) is necessary to provide a patient with a written action plan. Even if this helps in preventing only a small percentage of unscheduled (emergency care) visits, cost-effectiveness will be positive. The evidence review concluded that educational interventions may lead to better lung functions than usual care. This improvement however may not be clinically relevant.

Some studies on educational interventions have been carried out in populations that are less comparable to the Dutch situation (e.g Innercity studies in socioeconomic less developed populations in the United States). We have to interpret the results of those studies with care.

The available literature does not very specifically describe which aspects of education lead to better patient relevant outcomes. Therefore, only general recommendations can be formulated.

Recommendation

WEAK RECOMMENDATION	In children with unstable asthma, educational measures should be taken to improve lung function and disease control. In children with frequent exacerbations educational measures are recommended A written action plan is recommended, especially for children with unstable asthma.

References self-management

- Bhogal SK, Zemek RL, Ducharme F. Written action plans for asthma in children. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD005306. DOI: 10.1002/14651858.CD005306.pub2.
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- Gibson PG, Powell H. Written action plans for asthma: an evidence-based review of the key components. Thorax 2004; 59: 94-9.
- Rank MA, Volcheck GW, Li JT, Patel AM, Lim KG. Formulating an effective and efficient written asthma action plan. Mayo Clin Proc 2008; 83: 1263-70.
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- Tapp H, Dulin M. The science of primary health-care improvement: potential and use of community-based participatory research by practice-based research networks for translation of research into practice. Exp Biol Med 2010; 235: 290-9.
- Toelle B, Ram FSF. Written individualised management plans for asthma in children and adults. Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD002171. DOI: 10.1002/14651858.CD002171.pub2.
- Welsh EJ, Hasan M, Li P. Home-based educational interventions for children with asthma. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD008469. DOI: 10.1002/14651858.CD008469.pub2
- Wolf F, Guevara JP, Grum CM, Clark NM, Cates CJ. Educational interventions for asthma in children. Cochrane Database of Systematic Reviews 2002, Issue 4. Art. No.: CD000326. DOI: 10.1002/14651858.CD000326.

Appendix 1 literature search self-management

Cochrane reviews

We started from three Cochrane reviews:

- Bhogal SK, Zemek RL, Ducharme F. Written action plans for asthma in children. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD005306. DOI: 10.1002/14651858.CD005306.pub2.

- McLean S, Chandler D, Nurmatov U, Liu J, Pagliari C, Car J, Sheikh A. Telehealthcare for asthma. Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD007717. DOI: 10.1002/14651858.CD007717.pub2.
- Toelle B, Ram FSF. Written individualised management plans for asthma in children and adults. Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD002171. DOI: 10.1002/14651858.CD002171.pub2.

Search Medline

We did a combined update of the three reviews, where we must say that Toelle's review has been withdrawn.

Literatuursearch d.d. 11022012:

Update literaturesearch McLean:

1. Telemedicine/ (8613)
2. self care/ or self administration/ or self medication/ (30927)
3. (telehealth* or tele-health* or telemedicine* or tele-medicine*).tw. (6000)
4. (telephone or phone or SMS or tele-monitor* or telemonitor*).tw. (42153)
5. (email or e?mail or wireless or bluetooth).tw. (5088)
6. (remote adj consult*).tw. (127)
7. ((mobile adj healthcare) or (computer adj mediated adj therapy)).tw. (38)
8. (ehealth or e?health or mhealth or m?health).tw. (492)
9. or/3-8 (52422)
10. 1 or 9 (55984)
11. "onderdeel telemedicine".ti. (0)
12. "asthma zoekacties jan 2012".ti. (0)
13. exp asthma/ (95872)
14. exp Bronchial Spasm/ (3971)
15. asthma$.mp. (123257)
16. wheez$.mp. (8559)
17. bronchospas$.mp. (4409)
18. (bronch$ adj3 spas$).mp. (4260)
19. bronchoconstrict$.mp. (9796)
20. (bronch$ adj3 constrict$).mp. (559)
21. airway$ inflammation$.mp. (8313)
22. or/13-21 (136300)
23. "P voor asthma".ti. (0)
24. 10 and 22 (863)
25. "med101005 Cochrane gemaximaliseerde strategie voor Randomized Trials in Medline START".ti. (0)
26. randomized controlled trial.pt. (317020)
27. controlled clinical trial.pt. (83282)
28. (randomized or randomised).ab. (278207)
29. placebo.ab. (131759)
30. clinical trials as topic/ (156964)
31. randomly.ab. (171532)
32. trial.ti. (99688)
33. or/26-32 (775659)
34. 33 not (exp animals/ not humans/) (718057)
35. "med101005 Cochrane gemaximaliseerde strategie voor Randomized Trials in Medline EINDE".ti. (0)
36. 24 and 34 (202)
37. 36 (202)
38. limit 37 to yr="2009 -Current" (45)

Ad 10: This is I, as formulated in the Cochrane review.

Ad 22: This is P, as formulated in the Cochrane review about FeNO.

Ad 24: Combination of P and I.

Ad 26-34: RCT-filter.

Ad 38: Search result.

Update literaturesearch Bhogal/Toelle:

1. "written action plans zoekactie jan 2012".ti. (0)
2. (educat* or self?manag* or (self adj manag*) or (action adj plan*)).tw. (317377)
3. (self-care or (self adj care) or self-medicat*).tw. (10466)
4. action-plan*.tw. (2825)
5. (management-plan or (management adj plan) or (management adj program) or (self adj medicat*)).tw. (7765)
6. or/2-5 (329521)
7. "asthma zoekacties jan 2012".ti. (0)
8. exp asthma/ (95872)
9. exp Bronchial Spasm/ (3971)
10. asthma$.mp. (123257)
11. wheez$.mp. (8559)
12. bronchospas$.mp. (4409)
13. (bronch$ adj3 spas$).mp. (4260)
14. bronchoconstrict$.mp. (9796)
15. (bronch$ adj3 constrict$).mp. (559)
16. airway$ inflammation$.mp. (8313)
17. or/8-16 (136300)
18. "P voor asthma".ti. (0)
19. 6 and 17 (5104)
20. "med101005 Cochrane Highly Sensitive Search Strategy for Randomized Trials in Medline START".ti. (0)
21. randomized controlled trial.pt. (317020)
22. controlled clinical trial.pt. (83282)
23. (randomized or randomised).ab. (278207)
24. placebo.ab. (131759)
25. drug therapy.fs. (1488787)
26. randomly.ab. (171532)
27. trial.ab. (240448)
28. groups.ab. (1126293)
29. or/21-28 (2850147)
30. 29 not (exp animals/ not humans/) (2432725)
31. "med101005 Cochrane Highly Sensitive Search Strategy for Randomized Trials in Medline EINDE".ti. (0)
32. 19 and 30 (2216)
33. self care/ or self administration/ or self medication/ (30927)
34. 2 or 3 or 33 (346214)
35. 4 or 5 (10533)
36. 34 and 35 (6307)
37. 17 and 30 and 36 (368)
38. 37 (368)
39. limit 38 to yr="2004 -Current" (204)
40. (child??? or childhood or infant* or p?ediatr* or perinat* or neonat* or newborn* or infan* or boy? or girl? or kid? or schoolage* or juvenil* or adolescen* or toddler?).tw. (1469580)
41. exp Child/ (1400869)
42. exp infant/ (854319)
43. "Adolescent"/ (1434825)
44. 40 or 41 or 42 or 43 (2944836)
45. "filter child cbo medline".tw. (0)
46. 39 and 44 (131)

Ad 6: Original I.

Ad 17: This is P.

Ad 19: Combination of P and I.

Ad 21-29: RCT filter.

Ad 32: Search result (without restriction on publication year).

Ad 33-38: Focus on self-management.

Ad 39: Update from 2004

Ad 40-44: Child filter.

Ad 46: Search result.

Search DARE

Literatuursearch d.d. 16012012

Telemedicine

1. "asthma zoekacties jan 2012".ti. (0)
2. asthma.tw. (319)
3. Bronchial Spasm.tw. (1)
4. asthma*.tw. (330)
5. wheez*.tw. (30)
6. bronchospas*.tw. (12)
7. (bronch* adj8 spas*).tw. (1)
8. bronchoconstrict*.tw. (13)
9. (bronch* adj8 constrict*).tw. (1)
10. airway* inflammation*.tw. (2)
11. or/2-10 (347)
12. Telemedicine.kw. (55)
13. (self care or self administration or self medication).kw. (145)
14. (telehealth* or tele-health* or telemedicine* or tele-medicine*).tw. (64)
15. (telephone or phone or SMS or tele-monitor* or telemonitor*).tw. (303)
16. (email or e?mail or wireless or bluetooth).tw. (25)
17. (remote adj consult*).tw. (13)
18. ((mobile adj healthcare) or (computer adj mediated adj therapy)).tw. (0)
19. (ehealth or e?health or mhealth or m?health).tw. (3)
20. or/12-19 (462)
21. 11 and 20 (29)

Health plans

1. "asthma zoekacties jan 2012".ti. (0)
2. asthma.tw. (319)
3. Bronchial Spasm.tw. (1)
4. asthma*.tw. (330)
5. wheez*.tw. (30)
6. bronchospas*.tw. (12)
7. (bronch* adj8 spas*).tw. (1)
8. bronchoconstrict*.tw. (13)
9. (bronch* adj8 constrict*).tw. (1)
10. airway* inflammation*.tw. (2)
11. or/2-10 (347)
12. (educat* or self?manag* or (self adj manag*) or (action adj plan*)).tw. (1574)
13. (self-care or (self adj care) or self-medicat*).tw. (186)
14. action-plan*.tw. (8)
15. (management-plan or (management adj plan) or (management adj program) or (self adj medicat*)).tw. (16)
16. or/12-15 (1635)
17. 11 and 16 (61)
18. 17 (61)

Search control

Literatuursearch 16012012, update Cochrane reviews

Telemedicine

1. "asthma zoekacties jan 2012".ti. (0)
2. asthma.tw. (14625)
3. Bronchial Spasm.tw. (15)
4. asthma*.tw. (17493)
5. wheez*.tw. (864)
6. bronchospas*.tw. (777)
7. (bronch* adj8 spas*).tw. (52)
8. bronchoconstrict*.tw. (1663)
9. (bronch* adj8 constrict*).tw. (71)
10. airway* inflammation*.tw. (701)
11. or/2-10 (18846)
12. Telemedicine.kw. (19)
13. (self care or self administration or self medication).kw. (175)
14. (telehealth* or tele-health* or telemedicine* or tele-medicine*).tw. (325)
15. (telephone or phone or SMS or tele-monitor* or telemonitor*).tw. (4855)
16. (email or e?mail or wireless or bluetooth).tw. (180)
17. (remote adj consult*).tw. (4)
18. ((mobile adj healthcare) or (computer adj mediated adj therapy)).tw. (0)
19. (ehealth or e?health or mhealth or m?health).tw. (19)
20. or/12-19 (5416)
21. 11 and 20 (186)
22. 21 (186)
23. limit 22 to yr="2009 -Current" (38)

Health plans

1. "asthma zoekacties jan 2012".ti. (0)
2. asthma.tw. (14625)
3. Bronchial Spasm.tw. (15)
4. asthma*.tw. (17493)
5. wheez*.tw. (864)
6. bronchospas*.tw. (777)
7. (bronch* adj8 spas*).tw. (52)
8. bronchoconstrict*.tw. (1663)
9. (bronch* adj8 constrict*).tw. (71)
10. airway* inflammation*.tw. (701)
11. or/2-10 (18846)
12. (educat* or self?manag* or (self adj manag*) or (action adj plan*)).tw. (14484)
13. (self-care or (self adj care) or self-medicat*).tw. (863)
14. action-plan*.tw. (164)
15. (management-plan or (management adj plan) or (management adj program) or (self adj medicat*)).tw. (889)
16. or/12-15 (15470)
17. 11 and 16 (903)
18. 17 (903)
19. limit 18 to yr="2004 -Current" (443)
20. 19 (443)
21. limit 20 to medline records (246)
22. 20 not 21 (197)

Results

File name	Number of abstracts after literature search
med 20120111 vr 6 telemedicine P rct vanaf 2009	45
med 20120111 vr 6 health plans P rct child vanaf 2004	131

cl dare 20120116 vr 6 telemedicine	29
cl dare 20120116 vr 6 health plans	61
cl cctr 20120116 vr 6 telemedicine	38
cl cctr 20120116 vr 6 health plans medline	246
cl cctr 20120116 vr 6 health plans not medline	197

Appendix 2 litarature selection self-management

Selection criteria

- Methodology: only systematic reviews and randomized controlled trials were included.
- Patient: studies on children with asthma were included. Studies that were carried out only in adults, or only in children with other diseases than asthma, were excluded.
- We only included studies that focused on self-management (e.g. education, written action plan).
- We excluded studies that were published in other languages than Dutch, English and German.
- We excluded animal studies.
- We excluded conference abstracts.

Results

File name	Number of abstracts after literature search	Number of abstracts after literature selection*
med 20120111 vr 6 telemedicine P rct vanaf 2009	45	51
med 20120111 vr 6 health plans P rct child vanaf 2004	131	
cl dare 20120116 vr 6 telemedicine	29	
cl dare 20120116 vr 6 health plans	61	
cl cctr 20120116 vr 6 telemedicine	38	
cl cctr 20120116 vr 6 health plans medline	246	Not selected
cl cctr 20120116 vr 6 health plans not medline	197	Not selected

*After the literature selection, we decided to move on with some additional found Cochrane systematic reviews, and update these if necessary.

Appendix 3 summary of findings table self-management

Educational interventions compared to usual care for children and adolescents with asthma					
Patient or population: children and adolescents with asthma **Settings:** **Intervention:** educational interventions **Comparison:** usual care					
Outcomes	**Illustrative comparative risks* (95% CI)**	**Relative**	**No of**	**Quality of**	**Comments**

	Assumed risk	Corresponding risk	effect (95% CI)	Participants (studies)	the evidence (GRADE)	
	Usual care	**Educational interventions**				
Lung function FEV1, PEFR Follow-up: 10-26 weeks		The mean lung function in the intervention groups was **0.50 standard deviations higher** (0.25 to 0.75 higher)		258 (4 studies)	⊕⊕⊕⊖ **moderate**[1]	
Exacerbations % Patients reporting exacerbations Follow-up: 6-18 months	**Study population**		**OR 1.43** (0.94 to 2.18)	363 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	
	482 per 1000	**571 per 1000** (467 to 670)				
	Moderate					
Asthma severity Asthma severity score Follow-up: 3-24 months		The mean asthma severity in the intervention groups was **0.15 standard deviations lower** (0.43 lower to 0.12 higher)		212 (4 studies)	⊕⊕⊕⊖ **moderate**[1]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Risk of selection bias in all included studies

Educational interventions for children with asthma at risk of asthma-related department attendance

Patient or population: children with asthma at risk of asthma-related department attendance[1]
Settings:
Intervention: educational interventions

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95%	No of Participants	Quality of the evidence	Comments
	Assumed risk	Corresponding risk				

	Control	Educational interventions	CI)	(studies)	(GRADE)	
Exacerbation Emergency department visit	**Study population**		**RR 0.73** (0.65 to 0.81)	3008 (17 studies[2])	⊕⊕⊖⊖ **low**[3,4]	
	307 per 1000	**224 per 1000** (200 to 249)				
	Moderate					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Originally formulated clinical question used the following description for population: children with uncontrolled asthma despite a normal ICS dose
[2] studies that were included in the Cochrane systematic review
[3] A proper amount of the studies had randomisation problems and lack of concealment of allocation. There were also quite a lot of studies that had incomplete outcome data.
[4] We took emergency department visits as an indicator for the outcome exacerbations.

written action plans for children with asthma

Patient or population: children with asthma
Settings:
Intervention: written action plans

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	**Written action plans**				
Exacerbations nr. of patients with at least one acute care visit for asthma	**Study population**		**RR 0.73** (0.55 to 0.99)	353 (4 studies[1])	⊕⊕⊖⊖ **low**[2,3,4]	
	395 per 1000	**288 per 1000** (217 to 391)				

Follow-up: 3-24 months	**Moderate**					
Lung function Average % predicted FEV1 Follow-up: 3-12 months		The mean lung function in the intervention groups was **0.73 lower** (4.75 lower to 3.28 higher)		257 (2 studies[1])	⊕⊕⊖⊖ **low**[2,3,5]	
Symptoms change in symptom score at 3 months Follow-up: 1 years		The mean symptoms in the intervention groups was **0.04 higher** (0.22 lower to 0.29 higher)		168 (1 study[1])	⊕⊕⊖⊖ **low**[2,3,5]	
Quality of life change in child quality of life[6]		The mean quality of life in the intervention groups was **0.25 lower** (0.55 lower to 0.05 higher)		257 (2 studies[1])	⊕⊕⊖⊖ **low**[3,5,7]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] RCT's in systematic review Bhogal
[2] Blinding is impossible in this trial design. And, there was a quite large risk of bias in 3/4 studies included.
[3] The question does not fullfill the question that was posed in our evidence review
[4] The point estimate has a rather large confidence interval, that includes the point of large effect, and nearly touches 1.
[5] Very large confidence interval, with the point of relevant effect (both sides) and the point of no effect in it
[6] It was not described in the review how this outcome was assessed. Therefore, we decided to downgrade more on risk of bias
[7] See 2 and 6

Appendix 4 GRADE evidence profile self-management

Author(s): Mariska Tuut - PROVA
Date: 2012-05-30
Question: Should educational interventions vs usual care be used in children and adolescents with asthma?
Settings:
Bibliography: Wolf F, Guevara JP, Grum CM, Clark NM, Cates CJ. Educational interventions for asthma in children. Cochrane Database of Systematic Reviews 2002, Issue 4. Art. No.: CD000326. DOI: 10.1002/14651858.CD000326.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Educational interventions	Usual care	Relative (95% CI)	Absolute		
Lung function (follow-up 10-26 weeks; measured with: FEV1, PEFR; Better indicated by higher values)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	141	117	-	SMD 0.50 higher (0.25 to 0.75 higher)	⊕⊕⊕⊖ MODERATE	CRITICAL
Exacerbations (follow-up 6-18 months; assessed with: % Patients reporting exacerbations)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	112/193 (58%)	82/170 (48.2%)	OR 1.43 (0.94 to 2.18)	89 more per 1000 (from 15 fewer to 188 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
								0%		-		
Asthma severity (follow-up 3-24 months; measured with: Asthma severity score; Better indicated by lower values)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	111	101	-	SMD 0.15 lower (0.43 lower to 0.12 higher)	⊕⊕⊕⊖ MODERATE	CRITICAL

[1] Risk of selection bias in all included studies

Author(s): Mariska Tuut - PROVA
Date: 2012-04-12
Question: Should educational interventions be used in children with asthma at risk of asthma-related department attendance?[1]
Settings:
Bibliography: Boyd M, Lasserson TJ, McKean MC, Gibson PG, Ducharme FM, Haby M. Interventions for educating children who are at risk of asthma-related emergency department attendance. Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD001290. DOI: 10.1002/14651858.CD001290.pub2

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Educational interventions	Control	Relative (95% CI)	Absolute		
Exacerbation (assessed with: Emergency department visit)												
17[2]	randomised trials	serious[3]	no serious inconsistency	serious[4]	no serious imprecision	none	337/1505 (22.4%)	462/1503 (30.7%)	RR 0.73 (0.65 to 0.81)	83 fewer per 1000 (from 58 fewer to 108 fewer)	ÅÅOO LOW	CRITICAL
								0%		-		

[1] Originally formulated clinical question used the following description for population: children with uncontrolled asthma despite a normal ICS dose

[2] studies that were included in the Cochrane systematic review

[3] A proper amount of the studies had randomisation problems and lack of concealment of allocation. There were also quite a lot of studies that had incomplete outcome data.

[4] We took emergency department visits as an indicator for the outcome exacerbations.

Evidence review FeNO

Mariska Tuut, epidemioloog, PROVA Varsseveld

Erik-Jonas van de Griendt, kinderlongarts, Flevoziekenhuis & De Kinderkliniek Almere / Emma Kinderziekenhuis – AMC Amsterdam

namens de werkgroep NVK-richtlijn astma

Clinical questions

1. Does the use of non-invasive measurements of airway inflammation (FeNO) either in addition to, or instead of standard measures of asthma diagnosis in children (preschool: 0-5, schoolaged: 6-12, adolescent >12 years) with asthma improve asthma outcome?
2. Does tapering down the dose of inhaled corticosteroids based on FeNO instead of based on standard asthma measures (symptoms, lung function, etc) in children on high dose ICS prevent relapse (symptoms, exacerbations)?

Rationale

The diagnosis of asthma in children is made on clinical assessment and, if possible, made more likely by supplementary tests. Strictly speaking, the diagnosis lacks a gold standard. The background pathology of asthma is often but not always due to eosinophilic airway inflammation. Exhaled nitric oxide (FeNO) is a biomarker that indicates eosinophilic airway inflammation. Measurement of FeNO is a quantitative, noninvasive, easy to perform, and safe method of measuring this. Airway inflammation and its measurement has been standardised by the ATS. However, no standardised guidance for its use and implication can be stated yet.

Since asthma in children is often due to eosinophilic airway inflammation, FeNO may be a valuable diagnostic tool. However, if the asthma is not due to airway eosinophilia, FeNO may be low. There are certain known confounders of the measurement, such as smoking, diet, and allergy.

A diagnostic tool that differentiates in asthma and other causes of wheeze (episodic or multiple trigger wheeze) especially in the younger years of life would help the diagnostic challenges. FeNO may fulfil this gap.

Methodologic challenges

The ideal method for researching the value of a (new) diagnostic tool is comparing it to the gold standard, with reflect to patient relevant outcomes, such as asthma control and reduction of asthma exacerbations. Since this study design is difficult to perform, it is generally accepted to compare a new method to the gold standard, and calculate diagnostic accuracy, such as sensitivity and specificity. In children with asthma, the diagnosis is a clinical one and based on symptoms, supported by a post bronchodilator change in FEV_1 and made more probable with a positive test for bronchial hyperreactivity. This method is accepted as the gold standard, although it may be imprecise.

Literature search

In January 2012, we searched for evidence to answer the clinical questions. We used a stepped search strategy, in which relevant systematic reviews in the Cochrane Library were searched for first. The result was a Cochrane review about tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults, written by Petsky and colleagues, in 2009 [Petsky, 2009]. We decided to use that review and updated the searches that were carried out in the review. Therefore, we undertook a literature search in the Medline and Central databases and used the same search strategy as was done in the Cochrane review written by Petsky et al. In the Medline search, we added a child filter, to differentiate between child studies and adult studies. However, we also screened the abstracts that were excluded by that child filter. In the Central search, we added a Medline filter, so that we could exclude studies that should have been retrieved by the Medline search (Though, also in this case we screened the abstracts that were excluded by the Medline filter). The full search strategy is listed in Appendix 1. The Medline search resulted in 366 abstracts and the Central search retrieved 97 abstracts. The search was carried out by the Dutch Institute for Healthcare Improvement with input from one literature reviewer (MT).

Initially, we searched with strict criteria, and focused on patient relevant outcomes (RCT's aimed at e.g. asthma control and lung function). Herewith insufficient conclusive evidence was retrieved. Therefore, an additional search was performed, to collect evidence for the use of FeNO in diagnosing asthma on a lower level of evidence. We also compared the results of our literature study with the evidence from the recent ATS practice guideline.

Literature selection

Before starting the literature selection, criteria were established. All abstracts were screened by one reviewer using the following in- and exclusion criteria:

- Methodology: only systematic reviews and randomized controlled trials were included in the first search.
- Patients: studies on children with asthma were included. Studies that were carried out only in adults, or only in children with other diseases than asthma, were excluded.
- We only included studies that used FeNO as an intervention (not as an outcome).
- We excluded studies that were published in languages other than Dutch, English and German.
- We excluded animal studies.
- We excluded conference abstracts.

The literature selection process resulted in a large decrease of the amount of studies. In the first selection round (carried out by one reviewer, MT) we selected 21 abstracts for further review. A second selection procedure (on clinical relevance, carried out by another reviewer, EJvdG), lead to a further reduction. Finally, we selected five abstracts for full text critical review. One selected article was not available in Dutch libraries [Dinakar, 2009], so we took four studies in the critical review. The literature selection procedure is described in Appendix 2. When searching for diagnostic accuracy and FeNO 20 abstracts were found. None of these fulfilled the selection criteria (with exclusion of the first methodology criterion), so this additional search yielded no further evidence.

When considering the ATS practice guideline on the use of FeNO in de diagnosis of asthma, 3 referred articles were found. In studying the fulltext of these, we concluded these were all carried out in adults only.

Critical appraisal and results

Looking at the full text of the included articles, we noticed that the study from Szefler et al. was included in the Cochrane review from Petsky et al. Therefore, this study was not described further [Szefler, 2008]. Kercsmar published a narrative review on the role of exhaled nitric oxide in the diagnosis and management of childhood asthma [Kercsmar, 2010]. As this study had no systematic design, we excluded it for further analysis. Grob et al. described developments since the introduction of FeNO and explained the need for further establishment of normal and normative values [Grob, 2008]. This article did not answer the clinical question for this guideline.

Petsky et al. conducted a Cochrane systematic review to evaluate the efficacy of tailoring asthma interventions based on exhaled nitric oxide in comparison to clinical symptoms (with or without spirometry/peak flow) for asthma related outcomes in children and adults [Petsky, 2009]. This review focuses on treatment of asthma, not new diagnosis. Primary outcome of this review was asthma exacerbations during follow-up, or exacerbation rates. Secondary outcomes included hospitalisation, rescue courses of oral corticosteroids, symptomatic measures assessed by patients and/or carers, spirometry parameters, and use of beta-agonists. The methods of searching, selecting and judging the evidence and results are clearly described. Subgroup analyses for children were carried out. Six studies were included in the review, of which four studies were accomplished in children and adolescents only and one combining adolescents and adults. All included studies compared asthma management based on either clinical strategy/symptoms (control arm) or exhaled nitric oxide, with or without taking the symptoms into account (intervention arm). The intervention arms were all primarily based on FeNO level, but differed in the cut off for FeNO for change in therapy (< 15 ppb - < 35 ppb). In most studies FeNO was determined using clinical measurement; in one study portable at home analysers were used. Follow-up of the studies ranged from six months to two years. Different definitions for the outcome exacerbations were used between the included studies. In four of five studies in which children were included allocation concealment was unclear. One included study was not blinded, and blinding was unclear in one study. There might be incomplete data on outcomes in three of five studies included in the review, and there is uncertainty of the presence of selection bias in three of five studies. In one study selective reporting is confirmed. Other kinds of bias may play a role as well. Moreover, there is massive indirectness, due to the fact that the included patients were not diagnosed using different strategies.

In the development of this guideline we decided to use the GRADE approach for critically appraising and summarizing the body of evidence. The studies that included only children and adolescents recruited 838 participants, of which 813 completed the studies. Three predefined outcomes were classified as critical: asthma symptoms, (severe) exacerbations, and asthma control. The other predefined outcomes ((disease-specific) quality of life, change in lung function, and airway inflammation) were classified as important. The summary of findings table and the GRADE evidence profile are listed in Appendix 3 and Appendix 4.

Considering the critical outcomes, we noticed that there were only data on two out of three outcomes. There was no evidence available on asthma control (score on ACT (Asthma Control Test) or c-ACT (childhood-ACT)). The quality of evidence on the remaining critical outcomes was low. Therefore, the overall quality of evidence across all critical outcomes actually cannot be determined, but will be at most low.

Conclusions

⊕⊕⊖⊖ LOW	The overall quality of the evidence on these clinical questions is low.

	There is no evidence available that compares FeNO versus or in addition to standard measures of **asthma diagnosis** in children with asthma on the outcomes quality of life, asthma control, airway inflammation, asthma symptoms, exacerbations, and FEV_1.

⊕⊕⊖⊖ LOW	**Monitoring** with FeNO has no additional value if compared to standard measures on asthma symptoms, in children with asthma, when followed 46-52 weeks (SMD 0,04; 95% CI: -0,11 – 0,20).

⊕⊕⊖⊖ LOW	Interventions based on **monitoring** with FeNO do not reduce the risk of exacerbations, when compared to interventions based on standard measures, in children with asthma, when followed 30-52 weeks (OR = 0,75; 95% CI: 0,55-1,01).

⊕⊕⊕⊖ MODERATE	**Monitoring** with FeNO has no additional value compared to standard measures when used as tailored intervention in children with asthma, when looking at FEV_1 at a follow-up of 30-52 weeks (MD 1,81; 95%CI: -0,64 – 4,25).

Considerations

FeNO seems a valuable and easy, i.e. non-invasive way of measuring eosinophilic inflammation and might be of great value in the field of research. There are no known additional considerations (e.g. uncertainty about the balance of benefits versus harms and burdens, certainty or difference in patients' or professional values, organizational or resource implications) that should be taken in to account in formulating the recommendation.

Recommendation (in Dutch)

WEAK RECOMMENDATION	FeNO heeft bij kinderen met astma vooralsnog geen toegevoegde waarde in aanvulling op of in de plaats van de standaard diagnostiek (gestructureerde anamnese, lichamelijk onderzoek tijdens klachten, spirometrie en provocatietesten). Titreren (afbouwen van inhalatiecorticosteroïden) van de behandeling op geleide van FeNO-metingen leidt niet tot een betere uitkomst en wordt niet aangeraden.

Appendix 1 literature search FeNO

Search Cochrane review

- Petsky HL, Cates CJ, Li A, Kynaston JA, Turner C, Chang AB. Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD006340. DOI: 10.1002/14651858.CD006340.pub3.

Search Medline

Update literatuursearch Cochrane review Petsky, d.d. 11012012:

1. "asthma zoekacties jan 2012".ti. (0)
2. exp asthma/ (95872)
3. exp Bronchial Spasm/ (3971)
4. asthma$.mp. (123257)
5. wheez$.mp. (8559)
6. bronchospas$.mp. (4409)
7. (bronch$ adj3 spas$).mp. (4260)
8. bronchoconstrict$.mp. (9796)
9. (bronch$ adj3 constrict$).mp. (559)
10. airway$ inflammation$.mp. (8313)
11. or/2-10 (136300)

12. "P voor asthma".ti. (0)
13. Nitric Oxide/ (63122)
14. exhaled nitric oxide.mp. (1824)
15. nitric$.mp. (115470)
16. eno.mp. (693)
17. feno.mp. (518)
18. or/13-17 (115784)
19. 11 and 18 (2785)
20. 19 (2785)
21. limit 20 to yr="2008 -Current" (985)
22. randomized controlled trial.pt. (317020)
23. controlled clinical trial.pt. (83282)
24. (randomized or randomised).ab. (278207)
25. placebo.ab. (131759)
26. drug therapy.fs. (1488787)
27. randomly.ab. (171532)
28. trial.ab. (240448)
29. groups.ab. (1126293)
30. or/22-29 (2850147)
31. 30 not (exp animals/ not humans/) (2432725)
32. 21 and 31 (366)
33. 32 (366)
34. (child??? or childhood or infant* or p?ediatr* or perinat* or neonat* or newborn* or infan* or boy? or girl? or kid? or schoolage* or juvenil* or adolescen* or toddler?).tw. (1469580)
35. exp Child/ (1400869)
36. exp infant/ (854319)
37. "Adolescent"/ (1434825)
38. 34 or 35 or 36 or 37 (2944836)
39. "filter child cbo medline".tw. (0)
40. 33 and 38 (183)
41. 33 not 40 (183)

Ad 11: P as in Cochrane review.

Ad 18: I as in Cochrane review.

Ad 19: Combination of P en I.

Ad 21: The Cochrane review searched literature until February 2009. Because the Medline database is not always up-to-date, we searched literature upward of 2008.

Ad 22-31: RCT filter.

Ad 32: This is the proper result of the search. We added a childfilter and distinguished the sets 40 (child) and 41 (not child). We downloaded the abstracts from both sets.

Search Central

Update literatuursearch Cochrane review Petsky, d.d. 11012012:

1. "asthma zoekacties jan 2012".ti. (0)
2. asthma.tw. (14625)
3. Bronchial Spasm.tw. (15)
4. asthma*.tw. (17493)
5. wheez*.tw. (864)
6. bronchospas*.tw. (777)
7. (bronch* adj8 spas*).tw. (52)
8. bronchoconstrict*.tw. (1663)
9. (bronch* adj8 constrict*).tw. (71)
10. airway* inflammation*.tw. (701)
11. or/2-10 (18846)
12. Nitric Oxide.kw. (129)

13. exhaled nitric oxide.tw. (394)
14. eno.tw. (83)
15. feno.tw. (71)
16. nitric*.ti. (1374)
17. or/12-16 (1617)
18. 11 and 17 (400)
19. 18 (400)
20. limit 19 to yr="2008 -Current" (97)
21. 20 (97)
22. limit 21 to embase records (1)
23. 21 not 22 (96)
24. 23 (96)
25. limit 24 to medline records (68)
26. 23 not 25 (28)
27. 21 not 25 (29)

Ad 11: P as in Cochrane review.

Ad 18: I as in Cochrane review.

Ad 19: Combination of P en I.

Ad 20: This is the proper search result. We added a Medline filter, to distinguish between abstracts that should have been retreived in the Medline search and other abstracts. We downloaded both sets.

Results

File name	Number of abstracts
med 20120111 vr 1 P NO rct child vanaf 2008	183
med 20120111 vr 1 P NO rct rest not child vanaf 2008	183
cl cctr 20120111 vr 1 medline	96
cl cctr 20120111 vr 1 not medline	1

Additional search (to retrieve evidence on a lower level)

PubMed, d.d. 01092012:

Search asthma [Title]

Search NO or FeNo [Title]

Search #1 and #2

Result: 20 abstracts

Appendix 2 literature selection FeNO

Selection criteria

- Methodology: only systematic reviews and randomized controlled trials were included.
- Patients: studies on children with asthma were included. Studies that were carried out only in adults, or only in childs with other diseases than asthma, were excluded.
- We only included studies that used FeNO as an intervention (not as an outcome).
- We excluded studies that were published in languages other than Dutch, English and German.
- We excluded animal studies.
- We excluded conference abstracts.

Results

File name	Number of abstracts after literature search	Number of abstracts after first literature selection (methodological expert)	Number of abstracts after second literature selection (clinical expert)
med2012011 vr P NO rct child vanaf 2008	183	12	5*
med 20120111 vr 1 P NO rct rest not child vanaf 2008	183	5	
cl cctr 20120111 vr 1 medline	96	4	
cl cctr 20120111 vr 1 not medline	1	-	
Additional search	20	0	

* The full text of this abstracts was requested. One study was not available in Dutch libraries, so the final number of studies that was critically appraised was four.

Appendix 3 summary of findings table FeNO

non-invasive measurement of airway inflammation (FeNO) compared to standard measures of asthma diagnosis for children with asthma

Patient or population: children with asthma1
Settings:
Intervention: non-invasive measurement of airway inflammation (FeNO)
Comparison: standard measures of asthma diagnosis2

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Standard measures of asthma diagnosis	Corresponding risk Non-invasive measurement of airway inflammation (FeNO)	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Asthma symptoms asthma symptom score and number of symptom free days and use of rescue medication Follow-up: 46-52 weeks		The mean asthma symptoms in the intervention groups was **0.04 standard deviations higher** (0.11 lower to 0.2 higher)		631 (2 studies[3])	⊕⊕⊖⊖ **low**[4,5]	
(Severe) exacerbations Hospital admission	**360 per 1000**	**297 per 1000** (236 to 362)	**OR 0.75** (0.55 to 1.01)	782 (3 studies[7])	⊕⊕⊖⊖ **low**[4,5,8]	

or visit to emergency room or need for additional course of oral corticosteroids[6] Follow-up: 30-52 weeks						
(Disease specific) Quality of Life Quality of Life	**Study population**		Not estimable	0	See comment	
	See comment	See Comment		(0[9])		
	Moderate					
Asthma control Score on ACT (Asthma Control Test) or c_ACT (childhood ACT)		The mean asthma control in the intervention groups was **0 higher** (0 to 0 higher)		631 (0[9])		
Change in lung function FEV1, MEF50, reversibility Follow-up: 30-52 weeks		The mean change in lung function in the intervention groups was **1.81 higher** (0.64 lower to 4.25 higher)		778 (3 studies[7])	⨁⨁⊖⊖ **low**[4,5]	
Airway inflammation Histamine (or Metacholine or Mannitol) Provocation or Eosinophil count in induced sputum or lavage	**Study population**		Not estimable	0	See comment	
	See comment	See comment		(0[9])		
	Moderate					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] preschool: 0-5; schoolaged: 6-12; adolescent: > 12 years
[2] Comparison of FeNO in addition to standard measures, and, instead of standard measures
[3] 2 RCT's in the systematic review from Petsky et al.
[4] The methodological quality summary of the Cochrane review shows serious limitations in design of the underlying studies. One study was not blinded; in another one there was uncertainty about blinding. There might be selective reporting, lack of allocation concealment, selective follow-up and other kinds of bias as well.
[5] Since we were interested in the value of FeNO in diagnosing, instead of monitoring, asthma, we score serious indirectness on all outcomes, because the review from Petsky et al. focused on monitoring asthma.
[6] In Cochrane review defined as: number of subjects who had one or more exacerbations over the study period
[7] 3 RCT's in the systematic review from Petsky et al.
[8] The pooled odds ratio is 0,75 which favours FeNO. The 95% CI just touches the point of no effect (1,01). The lower limit of the 95% CI is 0,55. This is quite a large CI. If the lower limit was real, it would represent a benefit that would overweigh the downsides
[9] No studies available on this outcome

Appendix 4 GRADE evidence profile FeNO

Author(s): Mariska Tuut - PROVA
Date: 2012-03-26
Question: Should non-invasive measurement of airway inflammation (FeNO) vs standard measures of asthma diagnosis be used in children with asthma?[1,2]
Settings:
Bibliography: Petsky HL, Cates CJ, Li AM, Kynaston JA, Turner C, Chang AB. Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults. Cochrane Database Syst Rev 2009, issue 4. Art. No.: CD006340; DOI: 10.1002/14651858.CD006340.pub3.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-invasive measurement of airway inflammation (FeNO)	Standard measures of asthma diagnosis	Relative (95% CI)	Absolute		
Asthma symptoms (follow-up 46-52 weeks; measured with: asthma symptom score and number of symptom free days and use of rescue medication; Better indicated by lower values)												
2[3]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	no serious imprecision	none	316	315	-	SMD 0.04 higher (0.11 lower to 0.2 higher)	⊕⊕OO LOW	CRITICAL
(Severe) exacerbations (follow-up 30-52 weeks; assessed with: Hospital admission or visit to emergency room or need for additional course of oral corticosteroids[6])												
3[7]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	serious[8]	none	116/393 (29.5%)	140/389 (36%)	OR 0.75 (0.55 to 1.01)	63 fewer per 1000 (from 124 fewer	⊕⊕OO LOW	CRITICAL

										to 2 more)		
(Disease specific) Quality of Life (assessed with: Quality of Life)												
0[9]	no evidence availabl e					none	-	-	-	-		
								0%		-		
Asthma control (measured with: Score on ACT (Asthma Control Test) or c_ACT (childhood ACT); Better indicated by lower values)												
0[9]	no evidence availabl e	[4]		[10]		none	315	316	-	MD 0 higher (0 to 0 higher)		CRITICAL
Change in lung function (follow-up 30-52 weeks; measured with: FEV1, MEF50, reversibility; Better indicated by higher values)												
3[7]	randomi sed trials	serio us[4]	no serious inconsisten cy	very serious[5]	no serious imprecisi on	none	390	388	-	MD 1.81 higher (0.64 lower to 4.25 higher)	⨁⨁ OO LOW	IMPORT ANT
Airway inflammation (assessed with: Histamine (or Metacholine or Mannitol) Provocation or Eosinophil count in induced sputum or lavage)												
0[9]	no evidence availabl e					none	-	-	-	-		IMPORT ANT
								0%		-		

[1] Comparison of FeNO in addition to standard measures, and, instead of standard measures

[2] preschool: 0-5; schoolaged: 6-12; adolescent: > 12 years

[3] 2 RCT's in the systematic review from Petsky et al.

[4] The methodological quality summary of the Cochrane review shows serious limitations in design of the underlying studies. One study was not blinded; in another one there was uncertainty about blinding. There might be selective reporting, lack of allocation concealment, selective follow-up and other kinds of bias as well.

[5] Since we were interested in the value of FeNO in diagnosing, instead of monitoring, asthma, we score serious indirectness on all outcomes, because the review from Petsky et al. focused on monitoring asthma.

[6] In Cochrane review defined as: number of subjects who had one or more exacerbations over the study period

[7] 3 RCT's in the systematic review from Petsky et al.

[8] The pooled odds ratio is 0,75 which favours FeNO. The 95% CI just touches the point of no effect (1,01). The lower limit of the 95% CI is 0,55. This is quite a large CI. If the lower limit was real, it would represent a benefit that would overweigh the downsides

[9] No studies available on this outcome

[10] Because the type of symptom score was not specified in the Cochrane review (in the description of the underlying studies) it is plausible that the outcomes in the review are not exactly the outcomes we're interested in in our guideline.

Evidence review family therapy

Erik-Jonas van de Griendt, kinderlongarts, Flevoziekenhuis & De Kinderkliniek Almere / Emma Kinderziekenhuis – AMC Amsterdam
Mariska Tuut, epidemioloog, PROVA Varsseveld

namens de werkgroep NVK-richtlijn astma

Psychosocial and emotional factors are important in childhood asthma. Nevertheless, drug therapy alone continues to be the main treatment. Treatment programmes that include behavioural or psychological interventions have been developed to improve disturbed family relations in the families of children with severe asthma. These approaches have been extended to examine the efficacy of family therapy to treat childhood asthma in a wider group of patients.

Definition and delimitation

Psychoeducational interventions can facilitate the challenges of a chronic disease. These interventions can take many forms, including simple provision of written information, single-session educational talks, structured series of seminars, and highly elaborative group interventions for patients and their caretakers.

We here defined family therapy as any psycho-educational intervention that aims to improve family relations or cognitions (such as maternal fear) or reduce stress (related to dyspnoeic attacks), involving the child as well as its parents.

Pure education regarding inhalation instruction, use of medication, use of a written action plan and/or instruction for (sub)acute deterioriation was considered a separate entity and excluded from this definition.

Clinical question

- What is the efficacy of family therapy in the treatment of children with (difficult) asthma?

Literature search

In April 2012, we searched for evidence to answer this clinical question. We started from one Cochrane systematic reviews, that we knew, and decided to update this. We did a combined search to update (years 2008 – april 2012) the Cochrane review in the Database of Abstracts of Reviews of Effectiveness, in Medline, and in Cochrane Central Trial Register. We combined the search strategies that had been done in the Cochrane review, and added two filters (RCT filter, child filter). The full search strategy is listed in Appendix 1. In total, we retrieved 25 abstracts.

Literature selection

Before starting the literature selection, we established eligibility criteria. All abstracts were screened using the following in- and exclusion criteria:

- Methodology: only systematic reviews and randomized controlled trials were included.
- Patient: studies on children with asthma were included. Studies that were carried out only in adults, or only in children with other diseases than asthma, were excluded.
- We only included studies that focused on psychoeducational measures or family therapy.
- We excluded studies that were published in other languages than Dutch, English and German.
- We excluded animal studies.
- We excluded conference abstracts.

One Cochrane Review (Yorke 2005; edited (no change to conclusion) 2009) was found. 25 additional publications were found that were screened manually by one author (EJG). After selection 4 publications (RCT's) remained (Ng 2008, Watson 2009, Chiang 2009, Szczepanski 2010).

Criticial appraisal and results

Yorke et al. wrote a review about family therapy for asthma in children, which selected only 2 RCT's including 55 children in total. The individual studies have been published in 1979 and 1986 thus representing mainly the pre-ICS-era, and could not be combined due to different outcome measures [Yorke, 2005]. The authors conclude that there is some indication that family therapy may be a useful adjunct to medication for children with asthma. This conclusion is limited by small study sizes and lack of standardisation in the choice of outcome measures, and might have given a different outcome in more recent therapy regimes.

Ng et al. published a waitlist controlled cross-over design study in 46 children that compares an integrated program of improving self-management AND family therapy (6 sessions of 2 hours systemic/familial emotion management), but has no control with for example selfmanagement alone [Ng, 2008]. Moreover, the study design (cross-over) is not suitable for any behavorial intervention and there are several risks on bias. We decided to exclude this study due to methodological shortcomings.

Watson et al. conducted a smallgroup interactive pure education study without any extra psychological intervention and was thus excluded for this review [Watson, 2009].

Chiang et al. compared the effectiveness of combined self-management and relaxation breathing training for children with moderate-to-severe asthma to self-management-only training in 48 children 6-14 yrs with mild to moderate stable asthma [Chiang, 2009]. Children in the experimental group were also given 30 min of training in a relaxation-breathing technique and a CD for home practice. Since this study does not describe family therapy as described above, we decided to remove it.

Finally, Szczepanski et al. published a large RCT that compares psycho-educational measures in a group of 2-5 years old with doctors diagnosed asthma [Szczepanski, 2010]. In fact, the program is a pure educational program and the 'family part' is incorporated mainly because of the young age of this group. This study was excluded for this review.

Grade

Because of the lack of solid evidence, systematic critical appraisal using GRADE, is considered of no additional value.

Conclusions

There is no evidence that family therapy may be a useful adjunct to medication for children with asthma. Asthma symptoms, lung function and medication levels are not likely to change by family therapy.

Considerations

The concept family therapy is not defined uniformly in literature and comprises several psychosocial/psycho-educational interventions. Various interventions are possible, such as fear reduction (e.g. by cognitive therapy (of child and parents)), comorbidity treatment and bonding disorders. Incorrectly, joint breathing exercises are considered as family therapy.

In the experience of the working group:

- Elements of family therapy may be useful in individual patients
- Psychosocial comorbidity can play an important sustaining role in children with asthma, especially in persistent severe asthma
- Family therapy is probably to lower anxiety levels in children with asthma.

Family therapy is time consuming for both health care workers as well as families. Undesirable effects are not likely to develop.

Recommendation (in Dutch)

Gezinstherapie is geen standaard aanvulling op medicamenteuze behandeling van kinderen met astma. In individuele gevallen (met name bij kinderen met problematisch ernstig astma / moeilijk behandelbaar

astma) kan gezinstherapie bijdragen aan het verminderen van psychosociale gevolgen van astma.

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Appendix 1 literature search

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Appendix 1 literature search family therapy

Pubmed

((asthma AND psychotherap* OR (psych* OR famil* OR complian* OR anxiet* OR comply and AND (therap*)))) AND (asthma[Title] AND (Humans[Mesh] AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Guideline[ptyp] OR Multicenter Study[ptyp] OR Technical Report[ptyp]) AND (English[lang] OR German[lang] OR Dutch[lang]) AND (infant[MeSH] OR child[MeSH] OR adolescent[MeSH]) AND "last 3 years"[PDat])) AND (Humans[Mesh] AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Guideline[ptyp] OR Multicenter Study[ptyp] OR Technical Report[ptyp]) AND (English[lang] OR German[lang] OR Dutch[lang]) AND (infant[MeSH] OR child[MeSH] OR adolescent[MeSH]) AND "last 3 years"[PDat])

Evidence review vocal cord dysfunction

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namens de werkgroep NVK-richtlijn astma

Synonym: Paradoxical vocal cord motion (PVCM). Vocal cord dysfunction is a descriptive term for inappropriate adduction of the vocal folds during respiration. The laryngeal mistiming leads to breathing difficulty and is often misdiagnosed as (refractory) asthma.

Clinical questions

- What is the incidence of vocal cord dysfunction in children presenting with asthma symptoms? And what is the incidence of VCD in children presenting with exercise-induced respiratory symptoms alone?
- What is the best way to diagnose (or rule out) VCD?

Literature Search

We searched Medline (Pubmed) and The Cochrane library in order to find cohort studies (incidence), or RCT's or systematic reviews (treatment). Apart from VCD, the term PVCM was studied separately. The additional search strategy is listed in Appendix 2 Literature search VCD.

Results

1. Incidence

Some observational studies were found, however not in the target population (i.e. children presenting with asthma symptoms). No cross-sectional cohort studies were found in children. Most of the literature is based on case-studies, and collected in some narrative reviews.

A case control study in children analysed a referred population of 84 children with problematic severe asthma and looked primarily at psychological outcomes. Of these, 12 (14.3%) were finally diagnosed as VCD [Gavin, 1998].

From a narrative review in children, exercise as a trigger for VCD is relatively common, but no percentages are known [Tilles, 2010].

2. Diagnosis

In a larger narrative general – i.e. not specificially children – review on VCD [[[Kenn, 2011]]], laryngoscopic demonstration of the paradoxical motion while wheezing or stridorous is considered the diagnostic gold standard. A recent prospective study in 117 adults with proven VCD on laryngoscopy, a flat inspiratory arm of the flow volume loop during spirometry showed a good correlation with the diagnosis of VCD made by laryngoscopy [Forrest, 2012]

GRADE

Because of the lack of solid evidence, systematic critical appraisal using GRADE, is considered of no additional value.

Conclusion

There are no reliable data about the incidence of vocal cord dysfunction in children presenting with asthma symptoms or exercise induced airway symptoms.

Laryngoscopic demonstration of the paradoxical motion while wheezing or stridorous is the diagnostic gold standard in adults with VCD.

A flat inspiratory arm of the flow volume loop in spirometry in adults can be caused by VCD

Considerations

Spirometry is easy to perform and not very expensive, however flexible laryngoscopy causes extra costs and certain stress for the (young) patient. Anatomical proportions are different in children and adults, so extrapolation of adult data to a child population is difficult, however in the experience of the working group also in children / adolescents with VCD, abnormalities in the inspiratory loop of the flow-volume curve can be present.

Recommendations (in Dutch)

Flexibele laryngoscopie kan tijdens een benauwdheidaanval die verdacht lijkt voor VCD worden overwogen.

Spirometrie met aandacht voor de inspiratoire curve wordt aangeraden bij een benauwdheidsaanval verdacht voor VCD.

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Appendix 2. Literature searches vocal cord dysfunction

1. terminology: Up-to-date (www.utdol.com) refers to the term Paradoxical vocal cord motion (PVCM), obviously synonymous to vocal cord dysfunction

2. search

a. Cochrane Library: no hits for PVCM, VCD 1 hit to an observational study (Gavin 1998), no systematic reviews
b. Pubmed

(paradoxical vocal cord motion) OR ((vocal cord dysfunction) IN TI)		74 hits
(paradoxical vocal cord motion) OR ((vocal cord dysfunction) IN TI)	limit 10 yr	41 hits
(paradoxical vocal cord motion) OR ((vocal cord dysfunction) IN TI)	limit 10 yr, limit all child	12 hits
(paradoxical vocal cord motion) OR ((vocal cord dysfunction) IN TI)	limit all child	23 hits
RCT:		0 hits
SR:		1 hit

manually selected: 9 (Gavin 1998, Tilles 2010 (=SR), 5 others)

Evidence review titreren behandeling o.b.v. FeNO (uit NVK richtlijn 2011, zie aldaar, reeds geautoriseerd)

Evidence review leukotrieenreceptorantagonisten uit NVK richtlijn 2011, zie aldaar, reeds geautoriseerd)

Evidence review fijne deeltjes ICS (uit NVK richtlijn 2011, zie aldaar, reeds geautoriseerd)

Evidence review ICS met klachten (uit NVK richtlijn 2011, zie aldaar, reeds geautoriseerd)

Achtergrondinformatie diagnose astma bij kinderen

Kernsymptomen:

- piepen
- hoesten
- kortademigheid
- benauwd op de borst

Expiratoir piepen is een van de vele ademhalingsgeluiden die kunnen voorkomen. Ouders gebruiken de term 'piepen' vaak om (elk) abnormaal hoorbare ademhaling aan te duiden. Er zijn verschillende oorzaken van expiratoir piepen op kinderleeftijd en verschillende klinische patronen ('fenotypes'). In het algemeen worden deze retrospectief vastgesteld. Er kan geen betrouwbaar onderscheid worden gemaakt in fenotype als het kind zich voor het eerst presenteert met piepen.

Episodisch piepen

Het meest voorkomende klinische patroon, vooral bij zuigelingen, peuters en kleuters, is periodes van piepen, hoesten en kortademigheid geassocieerd met virale bovenste luchtweginfecties (blwi), zonder blijvende symptomen, dus tussendoor symptoomvrij [episodisch (viraal) piepen, *episodic viral wheeze*]. Het grootste deel van deze kinderen zal geen symptomen meer hebben op de schoolgaande leeftijd.

Piepen op meerdere prikkels

Een minderheid van de kinderen met episodisch piepen ten tijde van virale infecties ontwikkelt piepen dat ook optreedt bij andere prikkels zodat ze tussen acute episodes ook symptomen hebben, net zoals oudere kinderen met astma [piepen op meerdere prikkels, *multiple trigger wheeze*].

Kinderen met persisterende symptomen of symptomen tussen acute episodes door hebben de meeste kans om baat te hebben van therapeutische interventies.

Leeftijd

in het algemeen geldt, hoe vroeger de start van het piepen, hoe gunstiger de prognose. Cohortstudies tonen een 'breekpunt' rond de leeftijd van 2 jaar. Kinderen die zich voor deze leeftijd presenteren met eerste symptomen worden het vaakst asymptomatisch.

Gelijktijdig vóórkomen van atopie is een risicofactor voor persisterend piepen onafhankelijk van de leeftijd van presentatie.

Geslacht

Astma komt voor de puberteit meer voor bij jongens. Jongens met astma groeien er vaker 'overheen' gedurende de adolescentie dan meisjes. Vrouwelijk geslacht is een risicofactor voor het blijven bestaan van astma tot in de volwassenheid.

Ernst en frequentie van voorgaande periodes met piepen

Frequente of zwaardere periodes met piepen zijn geassocieerd met terugkerend piepen dat blijft bestaan in de adolescentie.

Atopie

Het gelijktijdig vóórkomen van andere atopische aandoeningen zoals eczeem en allergische rhinitis vergroot de kans op de diagnose astma. Een positieve test voor atopie bij een kind met piepen vergroot ook de kans op astma. Een verhoogd specifiek IgE voor tarwe, kippenei-eiwit of inhalatieallergenen zoals huisstofmijt of kattenroos, voorspelt later astma.

Het opsporen en zo nodig behandelen van allergische rhinitis kan een bijdrage leveren aan de stabiliteit van de onderste luchtweg (*common airway concept*). Zie voor een overicht van diagnostiek en behandeling van allergische rhinitis: http://www.whiar.org/docs/ARIAReport_2010.pdf.

Familieanamnese

Een positieve familieanamnese voor atopie is de duidelijkste risicofactor voor atopie en astma bij kinderen. Maternale atopie is het sterkst geassocieerd met *childhood onset of asthma*.

Alternatieve diagnoses

Klinische aanwijzingen voor een alternatieve diagnose voor kinderen met piepen (verschijnselen die doorgaans *niet* gevonden worden bij astma)

Anamnese	Mogelijke diagnose
Symptomen aanwezig direct vanaf de geboorte of perinataal longprobleem	Cystische fibrosis (CF); chronische longziekte van de neonaat (CLD); primaire ciliaire diskinesie (PCD); aanlegstoornis*
Familieanamnese van bijzondere longziekte	CF; neuromusculaire aandoening

Ernstige bovenste luchtweginfecties	Afweerstoornis; PCD
Klachten en symptomen	
Persisterende productieve hoest	CF; bronchiectasie; bronchitis; recidiverende aspiratie; afweerstoornis; PCD; aanlegstoornis
Excessief spugen	Gastroesofageale reflux ziekte (GERD) (al dan niet met aspiratie)
Dysfagie	Slikstoornis (al dan niet met aspiratie)
Benauwd en licht in het hoofd en perifere tintelingen	Hyperventilatie/disfunctionele ademhaling
Inspiratoire stridor	Trachea- of larynxprobleem
Abnormaal stemgeluid (evt bij huilen)	Larynxprobleem
Focale afwijkingen (auscultatie)	Aanlegstoornis; post-infectieus; bronchiectasie; tuberculose
Clubbing / horlogeglasnagels	CF; bronchiectasie
'Failure to thrive'	CF; afweerstoornis; GERD
Onderzoeksbevindingen	
Focale of persisterende radiologische afwijkingen	Aanlegstoornis; CF; post-infectieus; recidiverende aspiratie; corpus alienum; bronchiectasie; tuberculose

*aanlegstoornis: ook vaatring, tracheamalacie, bronchomalacie

Inhalatie-instructie

Inhalatietechniek dosisaerosol met voorzetkamer

- Schud de dosisaerosol voor gebruik en verwijder de beschermdop.
- Bij gebruik van een nieuwe dosisaerosol of als de aangebroken dosisaerosol twee weken niet gebruikt is, spuit dan eerst twee puffjes in de lucht.
- Plaats de dosisaerosol met de opening naar beneden in de voorzetkamer.
- Laat de patiënt rechtop zitten of staan met het hoofd iets achterover (de mond moet leeg zijn).
- Plaats bij de (coöperatieve) patiënt vanaf ongeveer de leeftijd van 4 jaar het mondstuk van de voorzetkamer tussen de tanden en sluit de lippen om het mondstuk.
- Of plaats bij de jonge en/of niet coöperatieve patiënt het kapje over neus en mond. Zorg dat het masker goed aansluit op het gezicht!
- Breng het voorgeschreven medicijn in de voorzetkamer, niet meer dan één puff tegelijk. Let op: de medicatie blijft na de puff 20 seconden in de voorzetkamer en slaat dan neer.
- Laat de patiënt rustig in- en uitademen door de voorzetkamer. Bij kinderen > 12 jaar is vijf keer voldoende. Kinderen die ernstig benauwd zijn moeten vijf tot tien keer rustig in- en uitademen. Het klepje van de voorzetkamer moet zichtbaar heen en weer bewegen.
- Herhaal de handelingen als er meerdere doses geïnhaleerd moeten worden.

Verkorte instructie dosisaerosol:

- Rechte houding, kin iets omhoog
- Dosisaerosol goed schudden en kapje eraf

- Plaats dosisaerosol op de voorzetkamer
- Masker voor mond en neus, goed aansluiten of mondstuk tussen de tanden plaatsen, lippen omheen
- Dosisaerosol 1x indrukken
- 5-10 keer rustig in- en uitademen
- Mond spoelen na gebruik van onderhoudsmedicijn

Inhalatietechniek poederinhalator

- Rechte houding, kin iets omhoog
- Inhalator gebruiksklaar maken
- Inhalator horizontaal (Diskus) of rechtop (Turbuhaler) houden
- Uitademen
- Mondstuk tussen de tanden plaatsen, lippen omheen
- Krachtig en diep inademen
- Inhalator uit de mond nemen en 5-10 tellen adem vasthouden
- Mond spoelen na gebruik van onderhoudsmedicijn

Schoonmaken voorzetkamer

Maak de voorzetkamer schoon bij de eerste ingebruikname en daarna 1 keer per week:

- Verwijder eerst de dosisaerosol.
- Haal de voorzetkamer uit elkaar en maak schoon in lauwwarm water met afwasmiddel, niet afspoelen met water.
- Laat de voorzetkamer drogen aan de lucht op een schone theedoek, dus niet droogwrijven!
- Statische elektriciteit: Bij het gebruik van een plastic voorzetkamer kan de wand hiervan statisch geladen worden. Hierdoor slaat het medicijn op de wand van de voorzetkamer neer. Dan is het rendement van inhaleren verlaagd. Om de statische lading te vermijden is het belangrijk plastic voorzetkamers minstens 1 keer per week schoon te maken zoals beschreven. Niet föhnen of op de verwarming drogen en zeker niet in de vaatwasser doen.

Soorten voorzetkamers

De keuze van een voorzetkamer voor een kind hangt af van de leeftijd:

- 0-4 jaar: dosisaerosol met voorzetkamer en een passend baby- of kindermasker.
- Vanaf ongeveer 4 jaar: voorzetkamer met mondstuk (als kind bewust door de mond kan ademen).

Er is onvoldoende evidence om onderbouwd advies te kunnen geven over 1 dosis-aerosol in combinatie met 1 voorzetkamer, wanneer de klinische effectiviteit als maat aangehouden wordt. Wel is er bewijs bij kinderen dat inhalatie met een combinatie van dosis-aerosol en voorzetkamer voordeel biedt boven de inhalatie van een dosis-aerosol zonder voorzetkamer.

Overwegingen bij het voorschrijven van een dosisaerosol en voorzetkamer

- Is het kind in staat om de juiste techniek van inhalatie toe te passen?
- Is de handzaamheid en de afmeting van voorzetkamer zodanig dat deze gemakkelijk meegenomen en gebruikt gaat worden?
- Welke voorkeur hebben kind en ouders zelf ten aanzien van de verschillende voorzetkamers?
- Indien uit technisch oogpunt en gebruiksvriendelijkheid meerdere opties in aanmerking komen, dient het middel met de laagste kostprijs voorgeschreven te worden.

Voorbeeld actieplan

Met dank aan mw. J. Willekes, Almere

Astma behandelplan van:

Naam: .....

Geboortedatum: .....

Telefoonnummers:

Polikliniek: .....

's Avonds / 's nachts: .....

GROENE ZONE: HET GAAT GOED

- Geen piepen, hoesten, benauwdheid of kortademigheid gedurende dag of nacht
- Kan deelnemen aan alle normale activiteiten
- Geen klachten bij inspanning

Medicijnen die elke dag moeten worden ingenomen, ook als het goed gaat!	Dosering
.....	.....
.....	.....
.....	.....

Evt. 15 minuten vóór het sporten innemen:

.....

ORANJE ZONE: ASTMAKLACHTEN NEMEN TOE

- Hoesten, piepen, benauwdheid of kortademigheid
- Wordt 's nachts wakker door de astmaklachten
- Kan aan sommige, maar niet alle activiteiten deelnemen

Wat moet u doen?

- **Stap 1: Let op uw kind.** Let bijv. op piepen, hoesten, plotseling wallen onder de ogen, temperatuursverhoging

Als een andere soort benauwdheid mee kan spelen (disfunctionele ademhaling), doe dan hier *ademhalingsoefeningen*

- **Stap 2: Inhaleren** met luchtwegverwijdende medicijnen*: ……

- **Stap 3: Rust** (minimaal 5 minuten) Let op de houding!
- **Stap 4: Let op uw kind,** zoals bij stap 1 en let op verbetering. Wat is het resultaat? Heeft het gewerkt?

*Het inhaleren met deze medicijnen mag maximaal 6x per dag, elke 3 à 4 uur.

LET OP:

Niet langer dan 24 – 48 uur zonder overleg extra medicatie gebruiken. Dan contact opnemen met de kinderlongverpleegkundige of dienstdoende kinderarts.

Bij allergische klachten zoals jeuk, niezen, rode ogen e.d.

Gebruik de volgende medicijnen:

……

RODE ZONE: ERNSTIGE KLACHTEN

Alarmsignalen:

- Zeer kortademig, benauwd
- Piepende en/of snelle ademhaling
- De luchtwegverwijdende medicijnen helpen niet
- Kan in het geheel geen normale activiteiten verrichten
- Moeite met praten of lopen door de benauwdheid
- Blauwe lippen of nagels
- Gebruik van hulpademhalingsspieren, zoals neusvleugelen, intrekken van de borstkas tussen de ribben en/of kuiltje in de keel, hoge schouders

NB: niet al deze alarmsignalen komen bij benauwdheid voor

Wat moet u achtereenvolgens doen?

- **Stap 1: Let op uw kind.** Let op bovenstaande alarmsignalen
- **Stap 2: Inhaleren** met luchtwegverwijdende medicijnen: ……
- **Stap 3: Rust (5-10 minuten);** let hierbij op de lichaamshouding en op verbetering. Wat is het resultaat? Heeft het gewerkt?
- **Stap 4: Bij onvoldoende verbetering stap 2 en 3 herhalen**
- **Stap 5: Nog onvoldoende effect?** Neem contact op met de kinderlongverpleegkundige of dienstdoende kinderarts

Tips:

- Blijf bij uw kind en kijk en luister goed naar uw kind
- Noteer de tijd en hoeveelheid van de medicijnen
- Blijf rustig en zoek afleiding
- Vermijd prikkels, zoals inspanning, tabaksrook

Hoe werken de medicijnen?

- **Kortwerkende luchtwegverwijders** ontspannen de spiertjes rondom de luchtwegen en werken 3 tot 6 uur. Binnen 5 tot 10 minuten moet je merken dat het werkt. (bijv. Ventolin, Airomir, Salbutamol, Atrovent)
- **Ontstekingsremmende medicijnen** beschermen de luchtwegen en moeten elke dag gebruikt worden (bijv. Qvar, Flixotide, Pulmicort). *Na gebruik altijd de mond spoelen.*

- **Combinatiepreparaten** zijn een combinatie van een langwerkende luchtwegverwijder en een ontstekingsremmer (bijv. Seretide, Foster, Symbicort). *Na gebruik altijd de mond spoelen.*

Kennislacunes

- Prospectieve follow-up van de klinische fenotypes episodisch viraal piepen en piepen door meerdere prikkels
- Klinisch toegevoegde waarde van FeNO in de diagnostiek van astma (zie ook evidence review FeNO)
- Vermijding van inhalatie-allergenen ter voorkoming van het ontstaan van astma
- Langetermijn follow-up van het effect van hypoallergene voeding op het ontstaan van astma
- Effect van voedingssupplementen tijdens de zwangerschap ter voorkoming van het ontstaan van astma bij het kind
- Effect van immuuntherapie (SCIT / SLIT) ter voorkoming van het ontstaan van astma
- Effect van probiotica ter voorkoming van het ontstaan van astma
- Eenduidig bewijs van het effect van luchtverontreiniging in de behandeling van astma
- Eenduidig bewijs van het effect van vermijden van dierlijk allergeen en/of huisstofmijt in de behandeling van astma
- Effect van ademhalingstherapie op de behandeling van astma bij kinderen
- Effect van hypnose / ontspanningstherapie op de behandeling van astma
- Specifiek effect van lichaamsbeweging op de behandeling van astma
- Effect van influenza vaccinatie op de behandeling van astma
- Plaats van Magnesiumsulfaat bij de behandeling van acuut astma (richtlijn acuut astma)
- Incidentie van disfunctionele ademhaling bij kinderen met astma (zie ook evidence review dysfunctional breathing)
- Incidentie van stembanddisfunctie bij kinderen met astma (zie ook evidence review vocal cord dysfunction)
- Effect van gebruik van c-ACT, ACT of PAQLQ op de behandeling van astma
- Effect van monitoring met longfunctie of testen van bronchiale hyperreactiviteit op de behandeling van astma
- Effect van immuuntherapie (SCIT / SLIT) op de behandeling van astma (zie ook evidence review SCIT/SLIT)

Indicatoren

Indicatoren als onderdeel van het kwaliteitsbeleid

Voor een oordeel over de kwaliteit van zorg is informatie nodig. Door te meten kunnen gegevens verzameld worden die informatie over de kwaliteit van zorg verschaffen. Dit kan onder meer door de toepassing van indicatoren. Professionals kunnen indicatoren gebruiken om gegevens te verzamelen over de uitkomsten van de zorgprocessen waar zij (direct) bij betrokken zijn (spiegelinformatie). Deze informatie kan vervolgens weer gebruikt worden om vergelijkingen te maken met de prestaties van zorgverleners in andere instellingen (benchmark informatie). Indicatoren leveren ook informatie op die gebruikt kan worden om richting te geven aan wetenschappelijk onderzoek, doordat zicht ontstaat op de gebieden waarvoor meer bewijs moet komen voor gepast medisch handelen.
Indicatoren kunnen ook een ander doel dienen. De overheid, Inspectie voor de Gezondheidszorg (IGZ) en patiënten / consumenten willen beoordelen of zorgaanbieders voldoende kwaliteit leveren en streven daarvoor naar geschikte indicatoren. Indicatoren met dit doel worden ook wel **externe** indicatoren genoemd. De externe indicatoren kunnen ook bij DBC-onderhandelingen worden ingezet.

Wat zijn indicatoren?

Indicatoren zijn meetbare elementen van de zorgverlening die een aanwijzing geven over de mate van kwaliteit van de geleverde zorg. Een indicator heeft een signaalfunctie: het is geen directe maat voor kwaliteit maar wijst op een bepaald aspect van presteren en kan aanleiding zijn tot nader onderzoek.
Een bruikbare indeling van indicatoren is die in structuur-, proces- en uitkomstindicatoren. Een **structuurindicator** geeft informatie over de (organisatorische) randvoorwaarden waarbinnen zorg wordt geleverd. Een **procesindicator** geeft informatie over de handelingen die binnen een zorgproces worden uitgevoerd om kwaliteit te leveren. Het kenmerk van procesindicatoren is dat ze direct beïnvloedbaar zijn: ze meten hoe (vaak) iets is gedaan. Deze indicatoren geven informatie of de juiste groep patiënten de juiste behandeling krijgt. Een **uitkomstindicator** geeft informatie over de uitkomsten van zorgprocessen gemeten op patiëntniveau. Uitkomstindicatoren zijn van vele factoren afhankelijk en daardoor vaak moeilijk te herleiden tot directe patiëntenzorg.

Richtlijnen en indicatoren

Een gefundeerde uitspraak over kwaliteit van een bepaald zorgproces is pas mogelijk als op een valide wijze (aan de hand van indicatoren) kan worden gemeten of wordt voldaan aan de kwaliteitscriteria zoals beschreven in een (multidisciplinaire) evidence-based richtlijn die door de wetenschappelijke verenigingen is geautoriseerd. Per definitie worden indicatoren dan gebaseerd op een richtlijn.

Kwaliteitsindicatoren bij de richtlijn astma bij kinderen

De kwaliteitsindicatoren behorend bij deze richtlijn kwamen tot stand in overleg met de multidisciplinaire werkgroep waarvan de samenstelling is genoemd in het richtlijndocument (link naar de richtlijn). Er vond afstemming plaats met de Zorgstandaard Astma bij kinderen van de Long Alliantie Nederland (LAN).

De hieronder beschreven indicatoren zijn indicatoren **voor intern gebruik**, dat wil zeggen voor toetsing van implementatie van de richtlijn en voor gebruik bij interne kwaliteitsvisitaties van de vakgroep kindergeneeskunde of kinderlongziekten.

- percentage astmapatiënten bij wie de inhalatietechniek is gecontroleerd in de afgelopen 12 maanden in de groep patiënten die chronisch inhalatiemedicatie gebruikt
- percentage kinderen onder 6 jaar met astma(klachten) dat een LABA of combinatiepreparaat ICS+LABA voorgeschreven krijgt*
- percentage patiënten met astma dat een schriftelijk astma actieplan verstrekt kreeg na een exacerbatie
- percentage astmapatiënten van wie a. het rookgedrag en b. het rookgedrag van ouders is vastgelegd in het patiëntendossier
- percentage astma patiënten dat heropgenomen wordt na een doorgemaakte exacerbatie (in de 2e lijn)

Beschrijving van definities en kengetallen

Definities

1. Astma: de diagnose astma wordt gesteld bij patiënten die periodiek klachten hebben van dyspnoe, piepen op de borst en/of (productief) hoesten. Reversibiliteit na bronchusverwijding ondersteunt de diagnose en is obligaat voor de diagnose bij patiënten met periodiek hoesten zonder dyspnoe of piepen op de borst.
2. Exacerbatie: opvlamming van bekend astma waarbij een door de kinder(long)arts voorgeschreven stootkuur prednisolon noodzakelijk was, al dan niet tijdens een ziekenhuisopname
3. Geschreven astma actieplan (*written action plan*): systematisch schriftelijk stappenplan voor onderhoudsmedicatie en noodmedicatie bij lichte, matige en ernstige exacerbatie van astma, gepersonaliseerd voor de patiënt

Kengetallen

1. aantal patiënten bekend met astma van 4-18 jaar in de praktijkpopulatie aan het einde van de rapportageperiode
   subgroep 1a: met chronisch gebruik van inhalatiemedicatie (dagelijks ICS) of LTRA
2. aantal exacerbaties per patiënt bij patiënten met bekend astma

Kwaliteitsindicatoren bij de richtlijn astma bij kinderen

Kwaliteits Indicator	Omschrijving	Type indicator
1	Omschrijving: percentage astma patiënten waarbij de inhalatietechniek is gecontroleerd in de afgelopen 12 maanden in de groep patiënten die chronisch inhalatiemedicatie gebruikt Definities: astma patiënten: zie definitie 1; chronisch inhalatiemedicatie gebruik: voorschrift van dagelijks te inhaleren medicatie Teller: patiënten bij wie de inhalatietechniek is gecontroleerd de afgelopen 12 maanden door kinderarts of kinderlongverpleegkundige Noemer: patiënten die chronisch inhalatiemedicatie gebruiken in de afgelopen 12 maanden (kengetal 1, subgroep 1a) Benodigde data: classificatie: diagnose DBC 3202, controle inhalatietechniek (geaggregeerd uit patiëntendossier kinder(long)arts of kinderlongverpleegkundige)	Proces
2	Omschrijving: percentage patiënten < 6 jaar oud met (verdenking op) astma dat eenonderhoudsbehandeling met langwerkende luchtwegverwijders kreeg voorgeschreven Definitie: astma patiënten: zie definitie 1; verdenking op astma: klachten en klinische verdenking passend bij astma maar nog geen definitieve klinische diagnose gesteld (bv bij afwezigheid van longfunctie) Teller: aantal patiënten dat langwerkende luchtwegverwijders kreeg voorgeschreven onder 6 jaar oud Noemer: totaal aantal patiënten met astma of verdenking op astma onder 6 jaar oud Benodigde data: classificatie: diagnose DBC 3202; medicatievoorschrijfsysteem; leeftijd op peildatum	Proces
3	Omschrijving: percentage patiënten met astma dat eengeschreven astma actieplan verstrekt kreeg na een exacerbatie Definitie: astma patiënten: zie definitie 1; exacerbatie: zie definitie 3; geschreven astma actieplan (*written action plan*): zie defnitie 4 verstrekken: overhandigen én toelichten door ervaren	Proces

	astmabehandelaar Teller: aantal patiënten dat een geschreven astma actieplan verstrekt kreeg Noemer: aantal patiënten van 4 -18 jaar die een exacerbatie astma doormaakten waarvoor prednisolon nodig was (kengetal 3) Benodigde data: classificatie: diagnose DBC 3202, registratie exacerbaties (geaggregeerd uit patiëntendossier kinder(long)arts of kinderlongverpleegkundige), registratie verstrekking; opmerking: het evalueren van een reeds verstrekt actieplan naar aanleiding van een exacerbatie scoort eveneens positief op deze indicator	
4	Omschrijving: percentage astma patiënten waarvan a. het rookgedrag en b. het rookgedrag van ouders is vastgelegd in het patiëntendossier Definitie: astma patiënten: zie definitie 1; rookgedrag: of wordt gerookt en zo ja hoeveel en waar Teller: aantal patiënten bij wie het eigen rookgedrag (a) en dat van de ouders (b) bekend is Noemer: patiënten bekend met astma van 4 -18 jaar Benodigde data: classificatie: diagnose DBC 3202, registratie rookgedrag (geaggregeerd uit patiëntendossier kinder(long)arts of kinderlongverpleegkundige)	Proces
5	Omschrijving: percentage astma patiënten dat heropname behoeft na een doorgemaakte exacerbatie Definitie: astma patiënten: zie definitie 1; exacerbatie: zie definitie 3; heropname: a. opname binnen 4 dagen nadat patient opgenomen is geweest in het ziekenhuis en meer dan 12 uur ontslagen is of b. opname bij poliklinische patient die meer dan 48 uur prednisolon gebruikt én kon verminderen met inhalatiemedicatie Teller: aantal patiënten bij wie heropname nodig is Noemer: aantal patiënten met een exacerbatie Benodigde data: classificatie: diagnose DBC 3202, registratie opnames Opmerking: deze indicator is casemix gevoelig; mogelijk leidt een populatie met ernstiger astma of meer post IC opnames (ivm status astmaticus) tot een groter percentage heropname	uitkomst

Informatie voor patiënten

Voor goede informatie over de zorg voor kinderen met astma verwijst de werkgroep naar de patiëntenversie van de zorgstandaard astma voor kinderen en jongeren, die door het Longfonds is opgesteld.