Täiskasvanute astma käsitlus esmatasandil
Tõendusmaterjali kokkuvõte

Kliinilineküsimusnr 8

1. *Kliinilise küsimusetekst:*
   Kas astma diagnoosiga püsiravi vajavatele patsientidele tuleks ravi tiitrimisel (step-up) määrata kahe ravimi kombinatsioonid
   a) ISC+LABA vs ISC+leukotrieeni retseptorite antagonist (LRA)
   b) ISC+LABA vs ISC+ pikatoimeline teofülliin
   c) ISC+leukotrieeni retseptorite antagonist (LRA) vs ISC+ pikatoimeline teofülliin

Kokkuvõte, sh kriitiliste tulemusnäitajate kaupa:

Kokkuvõte põhineb Cochrane'i andmebaasi süstemaatilistel ülevaadetel: Ducharme 2011, mis käsitleb küsimust ISC+LABA *vs* ISC+LRA, ja Tee 2007, mis käsitleb ISC+LABA *vs* ISC+ pikatoimeline teofülliin. Lisaks avaldati 2014. a ajakohastatud ISC+LABA *vs* ISC+LRA küsimust käsitlev Cochrane'i andmebaasi süstematiline ülevaade, mis hõlmab uuringuid kuni 2012 detsembrini (Chauchan 2014), järeldused jäid üldjoontes samaks. Nende ülevaadete uuringuperioodist hiljem publitseeritud vastavaid küsimusi käsitlevaid RCT ei leidnud (s.t. kahe ravimi, mitte kolme ravimi kombinatsioonteraapiana).

Kokkuvõte:
a) ISC+LABA vs ISC+LRA – soovitus kasutada ISC+LABA kombinatsiooni
b) ISC+LABA vs ISC+ pikatoimeline teofülliin – soovitus kasutada ISC+LABA kombinatsiooni
c) ISC+LRA vs ISC+ pikatoimeline teofülliin– ravijuhendite soovituste põhjal kergemate astma vormide puhul eelistada pigem ISC+LRA kombinatsiooni, kuna teofülliin põhjustab sagedamini kõrvaltoimeid. Süstemaatilisi ülevaateid selle kohta ei leidnud, publitseeritud RCT ei näidanud astma kontrolli paranemist kummaski kombinatsioonravi rühmas võrreldes ISC+ platseeboga (siiski, rühmas, kus patsiendid ei saanud ICS, parandas teofülliin astma kontrolli)

Kokkuvõte süstemaatilistes ülevaadetes toodud tulemusnäitajatest:

Elukvaliteet –

a) ei ole uuritud

b) ei ole uuritud

Astma ägenemine –

a) patsientide arv, kes vajasid astma ägenemise tõttu süsteemseid kortikosteroide, 0.83 [0.71, 0.97] – **NNT 38**

b) ei ole uuritud

Suremus (astmast tingitud või olenemata põhjusest e *all-causemortality)* –

a) üks surmajuht ICS + LABA grupis, RR 3.02 [0.12, 73.92]

b) ei ole uuritud

Päevaste sümptomite esinemine –

a)võrreldi sümptomskoori muutuseid, RR-0.18 [-0.25, -0.12]

b) võrreldi sümptomite vabade päevade arvu, 4.87 [-12.10, 21.83]

Öösümptomid/unehäired –

a) öiste sümptomite skoori muutused, -0.18 [-0.29, -0.07], öised ärkamised, -0.12 [-0.19, -0.06]

b) võrreldi sümptomite vabade ööde arvu, 5.86 [-9.73, 21.46]

Hooravi vajadus –

a)hooravi vajaduse kordade muutus ööpäevas, -0.49 [-0.75, -0.24]

b) hooravi kasutamise muutus, -0.43 [-0.83, -0.03]

Hospitaliseerimine (olenemata põhjusest) –

a) patsientide arv, kes vajasid hospitaliseerimist ägenemise tõttu, 1.31 [0.58, 2.98]

b) ei ole uuritud

Ravi katkestamine kõrvaltoime tõttu –

a) 1.01 [0.79, 1.29]

b) ei ole uuritud, kuid on olemas uuringud erinevate kõrvaltoimete esinemise kohta mõlemas grupis

Füüsilise aktiivsuse piiratus –

a) ei ole uuritud

b) ei ole uuritud

Ravikulu –

a) ei ole uuritud

b) ei ole uuritud

Ravijuhendid

Kokkuvõte ravijuhendites leiduvatest soovitustest:

a) ICS+LABA vs ICS+LRA

Kõikides ravijuhendites, kus küsimus käsitlust leiab, soovitatakse kasutada ICS + LABA kombinatsiooni.

b) ICS+LABA vsICS+retardteofülliin

Kõikides ravijuhendites, kus küsimus käsitlust leiab, soovitatakse kasutada ICS + LABA kombinatsiooni.

c) ICS+retardteofülliinvs ICS+LRA

Kõikidesravijuhendites, kus küsimus käsitlust leiab, soovitatakse kasutada ICS + LABA kombinatsiooni

SIGN juhendis leitakse, et mõlemad kombinatsioonid võivad vähendada astma sümptomeid, samas kõrvaltoimeid annab rohkem ICS+retardteofülliin: NNTH (*number needed to harm)*9-14 sõltuvalt kõrvaltoimest.

GEMA-2012 juhendis soovitatakse kergemate astmavormide puhul pigem ICS + LRA kombinatsiooni, raskemate puhul sobivad mõlemad alternatiivid.

Süstemaatilisedülevaated

Kokkuvõte süstemaatilistest ülevaadetest:

Süstemaatiline ülevaade, mis käsitles ICS+LABA vs ICS+LRA alapunkti, hõlmas 17 randomiseeritud-kontrolluuringut. Leiti, et ICS + LABA kombinatsioon on tõhusam, kunavähenebvajadussüsteemsetekortikosteroidhormoonidekasutamisejärele, paranebkopsufunktsioonjaelukvaliteet. Samas, kõrvaltoimeid selle kombinatsiooni puhul esines rohkem kui ICS + LRA puhul.

Süstemaatiline ülevaade, miskäsitles b) ICS+LABA vs ICS+ teofülliini alapunkti, hõlmas 13 RCT uuringut. Leiti, et ICS+LABA kombinatsiooni kasutamisega väheneb vajadus kasutada hooravi öiste ja päevaste sümptomite kupeerimiseks. Esineb vähem kõrvaltoimeid võrreldes teofülliini kasutamisega.

a)*http://www.ncbi.nlm.nih.gov/pubmed/21563136*
Cochrane Database Syst Rev. 2011 May 11;(5):CD003137.
Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma.
Ducharme FM, Lasserson TJ, Cates CJ.
Asthma patients who continue to experience symptoms despite being on regular inhaled corticosteroids (ICS) represent a management challenge. Long-acting beta(2)-agonists (LABA) or anti-leukotrienes (LTRA) are two treatment options that could be considered as add-on therapy to ICS.

OBJECTIVES: We compared the efficacy and safety profile of adding either daily LABA or LTRA in adults and children with asthma who remain symptomatic on ICS.
SEARCH STRATEGY: up to and including March 2010

SELECTION CRITERIA: We included randomised controlled trials (RCTs) conducted in adults or children with recurrent asthma that was treated with ICS and where a fixed dose of a long-acting beta(2)-agonist or leukotriene agent was added for a minimum of 28 days.

MAIN RESULTS: We included 17 RCTs (7032 participants), of which 16 recruited adults and adolescents (6850) and one recruited children aged 6 to 17 years (182). Participants demonstrated substantial reversibility to short-acting beta-agonist at baseline. The studies were at a low risk of bias. The risk of exacerbations requiring systemic corticosteroids was lower with the combination of LABA and ICS compared with LTRA and ICS, from 11% to 9% (RR 0.83, 95% CI 0.71 to 0.97; six studies, 5571 adults). The number needed to treat (NNT) with LABA compared to LTRA to prevent one exacerbation over 48 weeks was 38 (95% CI 22 to 244). The choice of LTRA did not significantly affect the results. The effect appeared stronger in the trials using a single device to administer ICS and LABA compared to those using two devices. In the absence of data from the paediatric trial and the clinical homogeneity of studies, we could not perform subgroup analyses. The addition to ICS of LABA compared to LTRA was associated with a statistically greater improvement from baseline in several of the secondary outcomes, including lung function, functional status measures and quality of life. Serious adverse events were more common with LABA than LTRA, although the estimate was imprecise (RR 1.35, 95% CI 1.00 to 1.82), and the NNT to harm for one additional patient to suffer a serious adverse event on LABA over 48 weeks was 78 (95% CI 33 to infinity). The risk of withdrawal for any reason in adults was significantly lower with LABA and ICS compared to LTRA and ICS (RR 0.84, 95% CI 0.74 to 0.96).

*AUTHORS' CONCLUSIONS: In adults with asthma that is inadequately controlled on low doses of inhaled steroids and showing significant reversibility with beta(2)-agonists**, LABA is superior to LTRA in reducing oral steroid treated exacerbations**. Differences favouring LABA in lung function, functional status and quality of life scores are generally modest. There is some evidence of increased risk of SAEs with LABA. The findings support the use of a single inhaler for the delivery of LABA and inhaled corticosteroids. We are unable to draw conclusions about which treatment is better as add-on therapy for children.*

b) http://www.ncbi.nlm.nih.gov/pubmed/17636663
CochraneDatabaseSystRev. 2007 Jul 18;(3):CD001281.
Long-acting beta2-agonists versus theophylline for maintenance treatment of asthma.
Tee AK, Koh MS, Gibson PG, Lasserson TJ, Wilson AJ, Irving LB.

Abstract
BACKGROUND: Theophylline and longacting beta-2 agonists are bronchodilators used for the management of persistent asthma symptoms, especiallynocturnalasthma. They represent different classes of drug with differing side-effect profiles.

OBJECTIVES: Toassessthecomparativeefficacy, safety and side-effects of long-acting beta-2 agonists and theophyllineinthemaintenancetreatment of adults and adolescentswithasthma.

SEARCH STRATEGY: Most recent search: November 2006.

MAIN RESULTS: Thirteenstudieswith a total of 1344 participantsmettheinclusioncriteria of thereview. Theywere of varyingquality. Therewas no significantdifferencebetweensalmeterol and theophyllinein FEV(1) predicted (6.5%; 95% CI -0.84 to 13.83). However, salmeteroltreatmentledtosignificantlybettermorning PEF (meandifference 16.71 L/min, 95% CI 8.91 to 24.51) and evening PEF (meandifference 15.58 L/min, 95% CI 8.33 to 22.83). Salmeterolalsoreducedtheuse of rescuemedication. Formoterol, usedintwostudieswasreportedtobeaseffectiveastheophylline. Bitolterol, usedinonlyonestudy, wasreportedtobelesseffectivethantheophylline. Participantstakingsalmeterolexperiencedfeweradverseeventsthanthoseusingtheophylline (Parallelstudies: Relative Risk 0.44; 95% CI 0.30 to 0.63, Risk Difference -0.11; 95% CI -0.16 to -0.07, NumbersNeededtoTreat (NNT) 9; 95% CI 6 to 14). Significantreductionswerereportedforcentralnervoussystemadverseevents (Relative Risk 0.50; 95% CI 0.29 to 0.86, Risk Difference -0.07; 95% CI -0.12 to -0.02, NNT 14; 95% CI 8 to 50) and gastrointestinaladverseevents (Relative Risk 0.30; 95% CI 0.17 to 0.55, Risk Difference -0.11; 95% CI -0.16 to -0.06, NNT 9; 95% CI 6 to 16).

AUTHORS' CONCLUSIONS: Long-acting beta-2 agonists, particularlysalmeterol, are moreeffectivethantheophyllineinimprovingmorning and evening PEF, but are notsignificantlydifferentintheireffect on FEV1. Thereisevidence of decreaseddaytime and nighttimeshort-acting beta-2 agonistrequirementwithsalmeterol. Feweradverseeventsoccurredinparticipantsusinglong-acting beta-2 agonists (salmeterol and formoterol) ascomparedtotheophylline.

Viited

Kokkuvõte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
BACKGROUND: Asthma patients who continue to experience symptoms despite being on regular inhaled corticosteroids (ICS) represent a management challenge. Long-acting beta(2)-agonists (LABA) or anti-leukotrienes (LTRA) are two treatment options that could be considered as add-on therapy to ICS. **OBJECTIVES:** We compared the efficacy and safety profile of adding either daily LABA or LTRA in adults and children with asthma who remain symptomatic on ICS. **SEARCH STRATEGY:** We searched the Cochrane Airways Group Specialised Register (up to and including March 2010). **SELECTION CRITERIA:** We included randomised controlled trials (RCTs) conducted in adults or children with recurrent asthma that was treated with ICS and where a fixed dose of a long-acting beta(2)-agonist or leukotriene agent was added for a minimum of 28 days.	Cochrane Database Syst Rev. 2011 May 11;(5):CD003137. doi: 10.1002/14651858.CD003137.pub4. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. Ducharme FM[1], Lasserson TJ, Cates CJ.

MAIN RESULTS: We included 17 RCTs (7032 participants), of which 16 recruited adults and adolescents (6850) and one recruited children aged 6 to 17 years (182). Participants demonstrated substantial reversibility to short-acting beta-agonist at baseline. The studies were at a low risk of bias. The risk of exacerbations requiring systemic corticosteroids was lower with the combination of LABA and ICS compared with LTRA and ICS, from 11% to 9% (RR 0.83, 95% CI 0.71 to 0.97; six studies, 5571 adults). The number needed to treat (NNT) with LABA compared to LTRA to prevent one exacerbation over 48 weeks was 38 (95% CI 22 to 244). The choice of LTRA did not significantly affect the results. The effect appeared stronger in the trials using a single device to administer ICS and LABA compared to those using two devices. In the absence of data from the paediatric trial and the clinical homogeneity of studies, we could not perform subgroup analyses. The addition to ICS of LABA compared to LTRA was associated with a statistically greater improvement from baseline in several of the secondary outcomes, including lung function, functional status measures and quality of life. Serious adverse events were more common with LABA than LTRA, although the estimate was imprecise (RR 1.35, 95% CI 1.00 to 1.82), and the NNT to harm for one additional patient to suffer a serious adverse event on LABA over 48 weeks was 78 (95% CI 33 to infinity). The risk of withdrawal for any reason in adults was significantly lower with LABA and ICS compared to LTRA and ICS (RR 0.84, 95% CI 0.74 to 0.96). **AUTHORS' CONCLUSIONS:** In adults with asthma that is inadequately controlled on low doses of inhaled steroids and showing significant reversibility with beta(2)-agonists, LABA is superior to LTRA in reducing oral steroid treated exacerbations. Differences favouring LABA in lung function, functional status and quality of life scores are generally modest. There is some evidence of increased risk of SAEs with LABA. The findings support the use of a single inhaler for the delivery of LABA and inhaled corticosteroids. We are unable to draw conclusions about which treatment is better as add-on therapy for children.	
BACKGROUND: Theophylline and long acting beta-2 agonists are bronchodilators used for the management of persistent asthma symptoms, especially nocturnal asthma. They represent different classes of drug with differing side-effect profiles. **OBJECTIVES:** To assess the comparative efficacy, safety and side-effects of long-acting beta-2 agonists and theophylline in the maintenance treatment of adults and adolescents with asthma. **SEARCH STRATEGY:** Most recent search: November 2006. **SELECTION CRITERIA:**	Cochrane Database Syst Rev. 2007 Jul 18;(3):CD001281. Long-acting beta2-agonists versus theophylline for maintenance treatment of asthma. Tee AK[1], Koh MS, Gibson PG, Lasserson TJ, Wilson AJ, Irving LB.

All included studies were RCTs involving adults and children with clinical evidence of asthma. These studies must have compared oral sustained release and/or dose adjusted theophylline with an inhaled long-acting beta-2 agonist. **MAIN RESULTS:** Thirteen studies with a total of 1344 participants met the inclusion criteria of the review. They were of varying quality. There was no significant difference between salmeterol and theophylline in FEV(1) predicted (6.5%; 95% CI -0.84 to 13.83). However, salmeterol treatment led to significantly better morning PEF (mean difference 16.71 L/min, 95% CI 8.91 to 24.51) and evening PEF (mean difference 15.58 L/min, 95% CI 8.33 to 22.83). Salmeterol also reduced the use of rescue medication. Formoterol, used in two studies was reported to be as effective as theophylline. Bitolterol, used in only one study, was reported to be less effective than theophylline. Participants taking salmeterol experienced fewer adverse events than those using theophylline (Parallel studies: Relative Risk 0.44; 95% CI 0.30 to 0.63, Risk Difference -0.11; 95% CI -0.16 to -0.07, Numbers Needed to Treat (NNT) 9; 95% CI 6 to 14). Significant reductions were reported for central nervous system adverse events (Relative Risk 0.50; 95% CI 0.29 to 0.86, Risk Difference -0.07; 95% CI -0.12 to -0.02, NNT 14; 95% CI 8 to 50) and gastrointestinal adverse events (Relative Risk 0.30; 95% CI 0.17 to 0.55, Risk Difference -0.11; 95% CI -0.16 to -0.06, NNT 9; 95% CI 6 to 16). **AUTHORS' CONCLUSIONS:** Long-acting beta-2 agonists, particularly salmeterol, are more effective than theophylline in improving morning and evening PEF, but are not significantly different in their effect on FEV1. There is evidence of decreased daytime and nighttime short-acting beta-2 agonist requirement with salmeterol. Fewer adverse events occurred in participants using long-acting beta-2 agonists (salmeterol and formoterol) as compared to theophylline.	
BACKGROUND: Asthma treatment guidelines recommend addition of controller medications for patients with poorly controlled asthma. We compared the effectiveness of once-daily oral controller therapy with either an antileukotriene receptor antagonist (montelukast) or low-dose theophylline added to existing medications in patients with poorly controlled asthma. **METHODS:** We conducted a randomized, double-masked, placebo-controlled trial in 489 participants with poorly controlled asthma randomly assigned to placebo, theophylline (300 mg/d), or montelukast (10 mg/d). Participants were monitored for 24 wk to measure the rate of episodes of poor asthma control (EPACs) defined by decreased peak flow, increased beta-agonist use, increased oral corticosteroid use, or unscheduled health care visits. **OBSERVATIONS:** There was no significant difference in EPAC rates (events/person/yr) compared with placebo: low-dose theophylline, 4.9 (95% confidence	Am J Respir Crit Care Med. 2007 Feb 1;175(3):235-42. Epub 2006 Sep 22. Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. American Lung Association Asthma Clinical Research Centers. http://www.ncbi.nlm.nih.gov/pubmed/16998094

interval [CI], 3.6-6.7; not significant); montelukast, 4.0 (95% CI, 3.0-5.4; not significant); and placebo, 4.9 (95% CI, 3.8-6.4). Both montelukast and theophylline caused small improvements in prebronchodilator FEV(1) of borderline significance. Nausea was more common with theophylline only during the first 4 wk of treatment. Neither treatment improved asthma symptoms or quality of life. However, in patients not receiving inhaled corticosteroids, addition of low-dose theophylline significantly ($p < 0.002$) improved asthma control and symptoms as well as lung function. **CONCLUSIONS:** Neither montelukast nor low-dose theophylline lowered the EPAC rate of poor asthma control in patients with poorly controlled asthma despite improved lung function. For patients not using inhaled corticosteroids, low-dose theophylline improved asthma symptom control more than montelukast or placebo, and provides a safe and low-cost alternative asthma treatment.	