Antibiotika til tette og surklete småbarn

Er *det* så lurt?

Agenda

- Akutt syke barn
- Protrahert Bakteriell Bronkitt (PBB)

Research

Original Investigation

Early Administration of Azithromycin and Prevention of Severe Lower Respiratory Tract Illnesses in Preschool Children With a History of Such Illnesses

A Randomized Clinical Trial

Leonard B. Bacharier, MD; Theresa W. Guilbert, MD; David T. Mauger, PhD; Susan Boehmer, MA; Avraham Beigelman, MD; Anne M. Fitzpatrick, PhD; Daniel J. Jackson, MD; Sachin N. Baxi, MD; Mindy Benson, MSN, PN; Carey-Ann D. Burnham, PhD; Michael Cabana, MD; Mario Castro, MD, MPH; James F. Chmiel, MD, MPH; Ronina Covar, MD; Michael Daines, MD; Jonathan M. Gaffin, MD, MMSc; Deborah Ann Gentile, MD; Fernando Holguin, MD; Elliot Israel, MD; H. William Kelly, PharmD; Stephen C. Lazarus, MD; Robert F. Lemanske Jr, MD; Ngoc Ly, MD; Kelley Meade, MD; Wayne Morgan, MD; James Moy, MD; Tod Olin, MD; Stephen P. Peters, MD; Wanda Phipatanakul, MD, MS; Jacqueline A. Pongracic, MD; Hengameh H. Raissy, PharmD; Kristie Ross, MD; William J. Sheehan, MD; Christine Sorkness, PharmD; Stanley J. Szefler, MD; W. Gerald Teague, MD; Shannon Thyne, MD; Fernando D. Martinez, MD; for the National Heart, Lung, and Blood Institute's AsthmaNet

IMPORTANCE Many preschool children develop recurrent, severe episodes of lower respiratory tract illness (LRTI). Although viral infections are often present, bacteria may also contribute to illness pathogenesis. Strategies that effectively attenuate such episodes are needed.

OBJECTIVE To evaluate if early administration of azithromycin, started prior to the onset of severe LRTI symptoms, in preschool children with recurrent severe LRTIs can prevent the progression of these episodes.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, placebo-controlled, parallel-group trial conducted across 9 academic US medical centers in the National Heart, Lung, and Blood Institute's AsthmaNet network, with enrollment starting in April 2011 and follow-up complete by December 2014. Participants were 607 children aged 12 through 71 months with histories of recurrent, severe LRTIs and minimal day-to-day impairment.

INTERVENTION Participants were randomly assigned to receive azithromycin (12 mg/kg/d for

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CONCLUSIONS AND RELEVANCE Among young children with histories of recurrent severe LRTIs, the use of azithromycin early during an apparent RTI compared with placebo reduced the likelihood of severe LRTI. More information is needed on the development of antibiotic-resistant pathogens with this strategy.

Azithromycin for episodes with asthma-like symptoms in young children aged 1–3 years: a randomised, double-blind, placebo-controlled trial

Jakob Stokholm, Bo L Chawes, Nadja H Vissing, Elin Bjarnadóttir, Tine M Pedersen, Rebecca K Vinding, Ann-Marie M Schoos, Helene M Wolsk, Sunna Thorsteinsdóttir, Henrik W Hallas, Lambang Arianto, Susanne Schjørring, Karen A Krogfelt, Thea K Fischer, Christian B Pipper, Klaus Bønnelykke, Hans Bisgaard

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Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital (J Stokholm PhD, B L Chawes PhD, N H Vissing PhD, E Bjarnadóttir MD, T M Pedersen MD, R K Vinding MD, A-M M Schoos PhD, H M Wolsk MD, S Thorsteinsdóttir MD, H W Hallas MD, L Arianto MD, K Bønnelykke PhD, Prof H Bisgaard DMSc), **and**

Summary

Background Bacteria and viruses are equally associated with the risk of acute episodes of asthma-like symptoms in young children, suggesting antibiotics as a potential treatment for such episodes. We aimed to assess the effect of azithromycin on the duration of respiratory episodes in young children with recurrent asthma-like symptoms, hypothesising that it reduces the duration of the symptomatic period.

Methods In this randomised, double-blind, placebo-controlled trial, we recruited children aged 1–3 years, who were diagnosed with recurrent asthma-like symptoms from the Copenhagen Prospective Studies on Asthma in Childhood 2010 cohort; a birth cohort consisting of the general Danish population of Zealand, including Copenhagen. Exclusion criteria were macrolide allergy, heart, liver, neurological, and kidney disease, and, before each treatment, one or more clinical signs of pneumonia (respiratory frequency of ≥50 breaths per min; fever of ≥39°C; C-reactive protein concentration of ≥476·20 nmol/L [≥50 mg/L]). Each episode of asthma-like symptoms lasting at least 3 days was randomly allocated to a 3-day course of azithromycin oral solution of 10 mg/kg per day or placebo after thorough examination by a study physician at the Copenhagen Prospective Studies on Asthma research unit. Each episode was randomly allocated independently of previous treatment from a computer-generated list of random numbers in blocks of ten (generated at the Pharmacy of Glostrup). Investigators and children were masked until the youngest child turned 3 years of age and throughout the data validation and analysis phases. The primary outcome was duration of the respiratory episode after treatment, verified by prospective daily diaries and analysed with Poisson regression. Analyses were per protocol (excluding those without a primary outcome measure or who did not receive treatment). This trial is registered with ClinicalTrials.gov, number NCT01233297.

Interpretation Azithromycin reduced the duration of episodes of asthma-like symptoms in young children, suggesting that this drug could have a role in acute management of exacerbations. Further research is needed to disentangle the inflammatory versus antimicrobial aspects of this relation.

1. Bacharier LB et al. JAMA **2015**; 314:2034-44.
2. Stokholm J et al. Lancet Respir Med **2016**; 4:19-26.

Bacharier et al

Inklusjonskriterier – ≥ 1 siste år
>3 episoder wheezing, hvorav ≥1 *signifikant LTRI*
>2 *signifikant LRTI* wheezing
≥4 mnd vedlikeholdsbehandling og >1 *signifikant LRTI* episode

Eksklusjonskriterier
>4 systemiske steroider siste år, eller siste 2 uker
>1 innleggelse siste år
>8 mnd vedlikeholdsbehandling siste år
Daglige symptomer eller ≥2 nattlige oppvåkninger med salbutamol-behov siste 2 uker

"Klinisk signifikant LTRI"
Systemiske steroider
Akutt legekonsultasjon
Legevaktsbesøk
Innleggelse

Bacharier - studiepopulasjon

Table 1. Demographic Characteristics of Study Participants

	All Randomized Participants (N = 607)
Demographics, No. (%)	
Age at enrollment, mean (SD), mo	41.5 (16.5)
12-42	327 (53.9)
43-71	280 (46.1)
Boys	365 (60.1)
Entered study on controller medication	48 (7.9)
Race	
American Indian or Alaskan Native	8 (1.3)
Asian	10 (1.6)
Black or African American	157 (25.9)
White	362 (59.6)
More than 1 race specified	70 (11.5)
Ethnicity	
Hispanic or Latino	183 (30.1)
Not Hispanic or Latino	424 (69.9)
Height, mean (SD), cm	98.5 (11.7)
Weight, mean (SD), kg	16.8 (4.6)

Abbreviation: RTI, respiratory tract illness.

Table 2. Characteristics of Study Participants

	All Randomized Participants (N = 607)
Exposures, No. (%)	
Day-care attendance	307 (50.6)
Tobacco smoke exposure, No./total (%)	240/601 (39.9)
Pet in home	280 (46.1)
Feature of Previous Wheezing	
No. of wheezing episodes in the past year, mean (SD)	4.45 (3.15)
No. of urgent and/or ED visits in the past year, mean (SD)	2.48 (1.64)
Hospitalized in the past year, No. (%)	87 (14.3)
No. of hospitalizations in the past year, median (IQR)	0 (0-1)
At least 1 course of OCS in past year, No. (%)	361 (59.5)
No. of OCS courses in the past year, median (range)	1 (0-4)
ICS use in past year, No./total (%)	150/605 (24.8)
Montelukast use in the past year, No. (%)	54 (8.9)

Intervensjon

- Azithromycin eller placebo i fem dager
- Skulle startes ved symptomer eller tegn som foresatte definerte som barnets vanlige start ved utvikling av "alvorlig LRTI"
  - Forkjølelse? Hoste?
- Opptil 4 episoder i hvert individ
- Vedlikeholdsbehandling (inhalasjonssteroider eller montelukast) seponert ved inklusjon (!)

Utfall

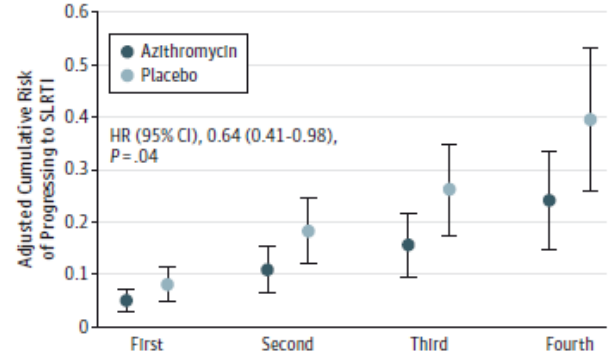
- Antall RTI som ikke utviklet seg til “severe LRTI” innen 14 dager etter behandlingsstart

Severe LRTI (SLRTI)
Mer enn milde symptomer etter 3 salbutamol <1 time
Salbutamol-inhalasjoner >hver 4. time
>6 salbutamol-inhalasjoner siste 24t
≥5 dager alvorlig hoste eller wheeze etter medisinstart

Resultater

- NNT for å forhindre utvikling av 1ste SLRTI: 33!
- Innleggelser:
  - 13 versus 15 (placebo)
  - 5 versus 6 innen 14dg beh.
- Lik tid til neste episode
- Virus fra nese/pensel:
  - 81% RTI
  - 89% SLRTI

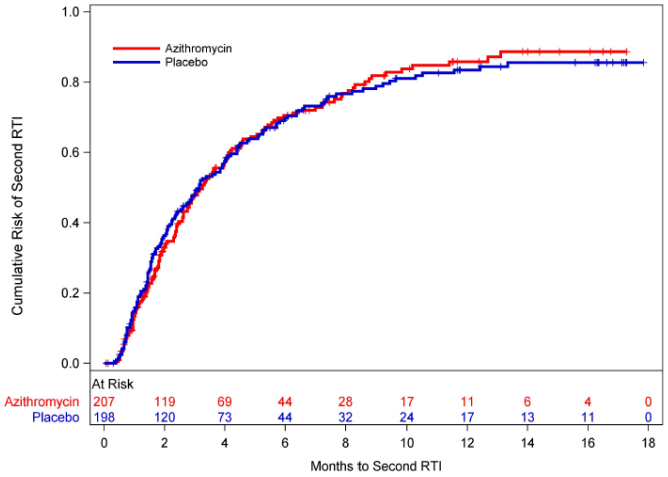
Figure 2. Cumulative Risk of Experiencing an Episode of Severe LRTI Across Treated RTIs for Preschool Children With a History of Severe LRTI



No. of treated RTIs	223	220	146	147	78	74	26	23
No. of SLRTIs	16	22	13	19	5	9	1	7

RTI indicates respiratory tract illness; SLRTI, severe lower RTI. Shown are risks and 95% CIs based on the discrete-time proportional hazards model of treatment effect adjusted for clinical site, age, modified Asthma Predictive Index status, season during which the treated RTI occurred, and whether the child enrolled before or after the study was extended to 78 weeks.

eFigure 3



Stokholm et al

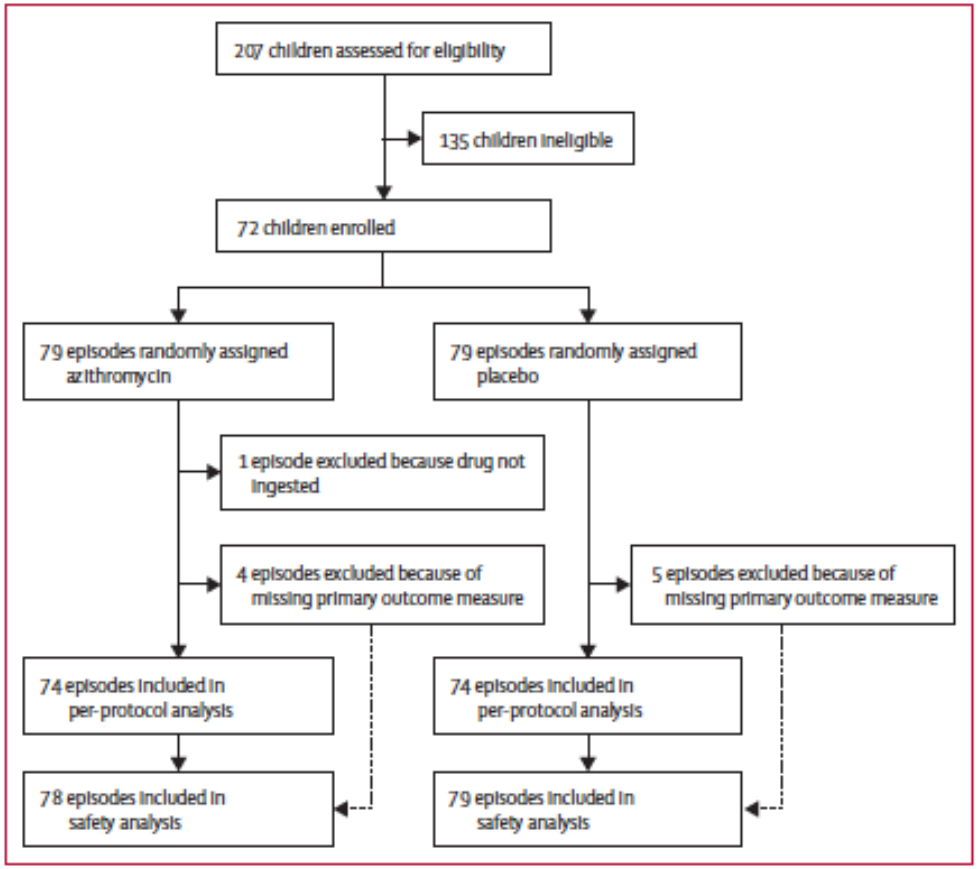
deep clinical phenotyping.[11] Children aged 1–3 years diagnosed with recurrent asthma-like symptoms (troublesome lung symptoms) as defined in the Procedures section were eligible each time they had an episode of troublesome lung symptoms lasting at least 3 days. Exclusion criteria were macrolide allergy, heart, liver, neurological, and kidney disease, and, before each treatment, one or more clinical signs of pneumonia (respiratory frequency of 50 breaths per min or higher, fever of 39°C or higher, or C-reactive protein [CRP]

Procedures

Troublesome lung symptoms, consisting of cough, wheeze, or dyspnoea, severely affecting the wellbeing of the child, were monitored using daily diary cards filled out by the parents from birth.[11] We defined an episode as

Randomisation and masking

Each episode of troublesome lung symptoms that occurred up to the age of 3 years or up to a maximum of seven treatments per child was randomised individually to either azithromycin or placebo. Treatments were randomly



Resultater

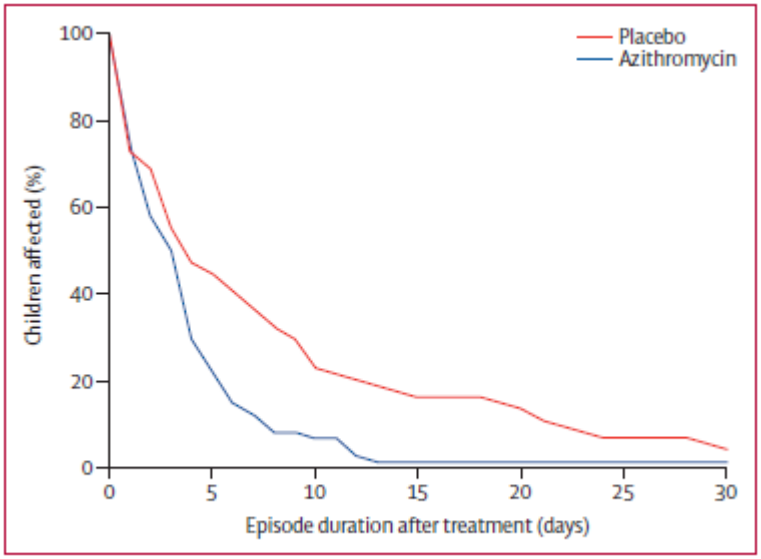


Figure 2: **Duration of episodes of troublesome lung symptoms after treatment**

- Mean 3.4 vs 7.7 dager, 63% (95% CI 56.0-69.3) reduksjon, p<0.0001
- P.o. steroider/innlagt: totalt 5 episoder
- Tid til neste episode lik (hazard ratio 0.95)

	n (%)	Mean azithromycin episode duration (days)	Mean placebo episode duration (days)	% reduction (95% CI)	p value
All	148	3·4	7·7	63·3% (56·0 to 69·3)	<0·0001
Clinical measures					
C-reactive protein concentration (nmol/L)	133 (100%)				
≥76·19 nmol/L (≥8 mg/L)	23 (17%)	3·6	6·3	45·6% (–53·9 to 80·8)	0·2510
<76·19 nmol/L (<8 mg/L; lowest detection)	110 (83%)	3·5	8·4	59·4% (15·6 to 80·5)	0·0158
Fever (°C)	136 (100%)				
≥38	23 (17%)	3·8	4·9	21·4% (–61·6 to 61·8)	0·5122
<38	113 (83%)	3·6	7·2	47·3% (2·9 to 71·4)	0·0401
Objective wheeze	144 (100%)				
Yes	26 (18%)	3·4	8·8	55·0% (6·3 to 78·4)	0·0330
No	118 (82%)	3·6	13·0	60·1% (18·3 to 80·5)	0·0120
Bacterial infection					
Any pathogenic bacteria	135 (100%)				
Present	90 (67%)	4·2	7·9	41·6% (–8·3 to 68·5)	0·0881
Not present	45 (33%)	2·0	5·5	64·7% (35·6 to 80·7)	0·0007

Diskusjon

benefit from early initiation of azithromycin. Until a higher-risk population can be prospectively identified (rather than all children with intermittent wheezing associated with viral RTI) for progression to severe LRTI, the consequences of widespread use of azithromycin, both known and hypothesized, outweigh the benefit for most children.

nesses in preschool children with a history of wheezing, but we agree with Drs Cohen and Pelton[5] that at this time, the risks of azithromycin outweigh the benefit of preventing these children from needing additional rescue albuterol treatments without preventing urgent care or emergency visits, hospitalizations, or future episodes.

Overall, the study by Stokholm and colleagues[11] cannot, without further evidence from trials using markers of clinically severe wheeze as the primary outcome, be used to justify the widespread or even selective use of azithromycin for troublesome lower respiratory tract symptoms with wheeze in this age group. By signposting new mechanisms underlying

1. Cohen RT, Pelton SI. Individual Benefit vs Societal Effect of Antibiotic Prescribing for Preschool Children With Recurrent Wheeze. JAMA **2015**; 314:2027-9.
2. Fleming-Dutra KE, Friedman CR, Hicks LA. Early Azithromycin Treatment to Prevent Severe Lower Respiratory Tract Illnesses in Children. JAMA **2016**; 315:2121-2.
3. Grigg J. Antibiotics for preschool wheeze. Lancet Respir Med **2016**; 4:2-3.

Protrahert Bakteriell Bronkitt (PBB)

- Vanligste årsak til kronisk, våt hoste hos barn
- Opprinnelig 3 kriterier
  1. Kronisk våt eller produktiv hoste
  2. Holdepunkter for bakteriell infeksjon (ikke pertussis, mycoplasma) i bronchoalveolær lavage (BAL)
  3. Opphør av hoste etter 2 uker med antibiotika
- Pkt 2 modifisert på grunn av manglende bronkoskopikapasitet
  - Fravær av andre årsaker
- PBB-extended: behandlingsrespons først innen 4 uker
- Recurrent PBB: >3/år

1. Chang et al. 2016. Pediatric Pulmonology. 51:225-242

Symptombilde

- Høy sykelighet[1]
  - >75% >5 legebesøk
  - Livskvalitet↓ pga hoste
- "Wheeze" selvrapporteres ofte (40-81%)[2]
  - men sjelden lege-bekreftet obstruktivitet
- Eosinofile, IgE, prikktest[2]
  - Ikke signifikant høyere
- ØNH
  - Ikke økt forekomst kronisk sinusitt eller øresykdom[2]

1. Chang et al, Chest 2015; 147:745-53
2. Wurzel et al, Chest 2014; 145: 1271-78

Tilleggsundersøkelser

- Rtg thorax
  - Perihilære forandringer
- Spirometri
  - Normal
  - Negativ provokasjonstester
- Bronkoskopi
  - Opptil ¾ også trachebronchomalaci (men høyt også i kontrollgruppe…)
  - BAL: oppvekst bakterier hos stort flertall[1]

1. Wurzel et al, Chest 2014; 145: 1271-78

BAL-analyser

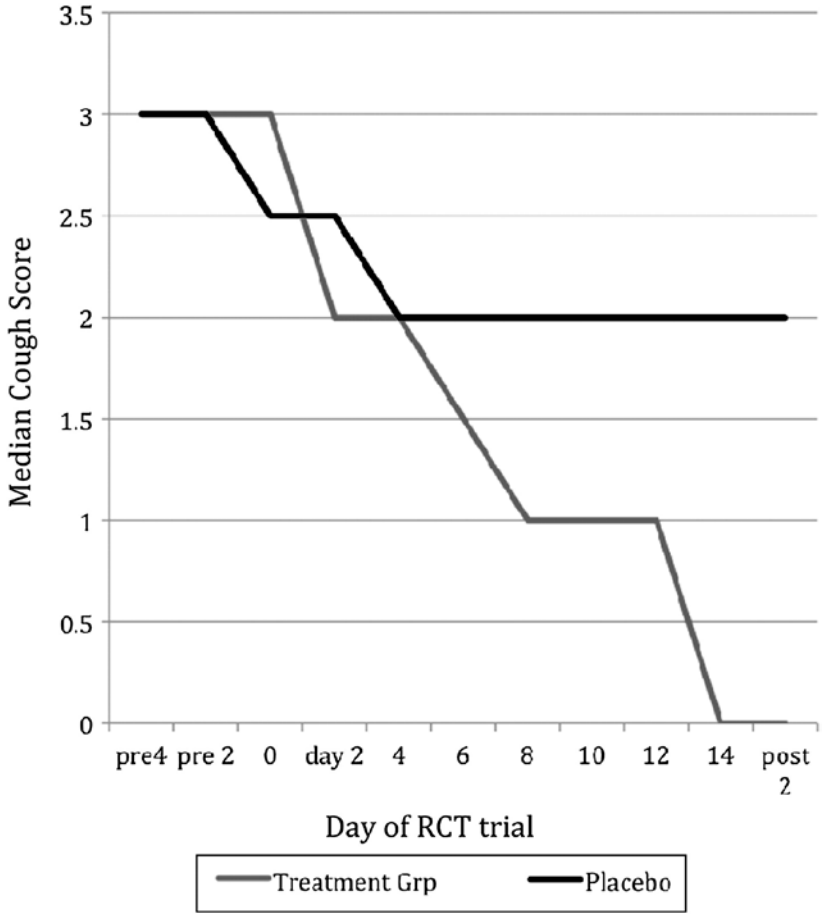
- Bakteriell dyrkning:
  - oppvekst av bakterier[1] hos opptil 100%
- Virus PCR
  - Adenovirus 23% (4% ktr-gruppe)
- Microbiotia
  - 16S rRNA pyrosekvensering og fylogenetiske analyser viste like kjernemikrobiota som hos barn med bronkiektasier
- Immunologisk respons mer uttalt
  - Mot ktr, og gruppe over/under 3 episoder siste 12 mnd

Behandling

- 2 uker amoxicillin-klavulansyre
- Kun hos de med klar mistanke
- Ubehandlet sykdom kan øke risikoen for bronkiektasier

Amoxycillin-klavulansyre

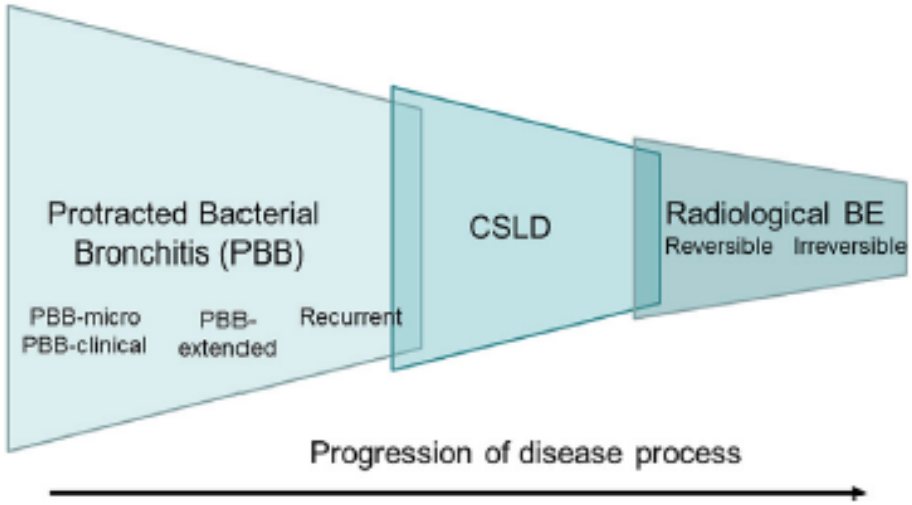
- >3 uker våt hoste
- 2.2 år, n=50
- BAL (n=37):
  - H.influenzae 38%
  - S.pneumoniae 24%
  - M.catarrhalis 19%
- NNT (75% bedring e. 2 uker): 4



1. Marchant et al, Thorax 2012; 689

Prognose

- Mulig forløper til andre kroniske, suppurative lungesykdommer, som bronkiektasier
- Ingen prospektive langtidsstudier



Differensial-/tilleggsdiagnoser

- Astma
- Aspirasjon – refluks eller svelgfeil
- Trakebronkomalaci
- Virale infeksjoner
- Bronkiektasier
- Immunsvikt

Diskusjon

- Få robuste RCTer, gjort på selektert gruppe
  - Lang sykdomsvarighet
  - Høy bronkoskopiandel
- Differensialdiagnoser
- Bronkoskopi med dyrkning?

- **Skal vi gi antibiotika til ellers frisk barn som hoster?**