Con: Severe asthma 환자에서 low dose macrolide 사용이 천식조절과 급성악화예방에 도움이 되는가?

울산의대 울산대학교병원
호흡기내과 나승원

Definition of Severe Asthma

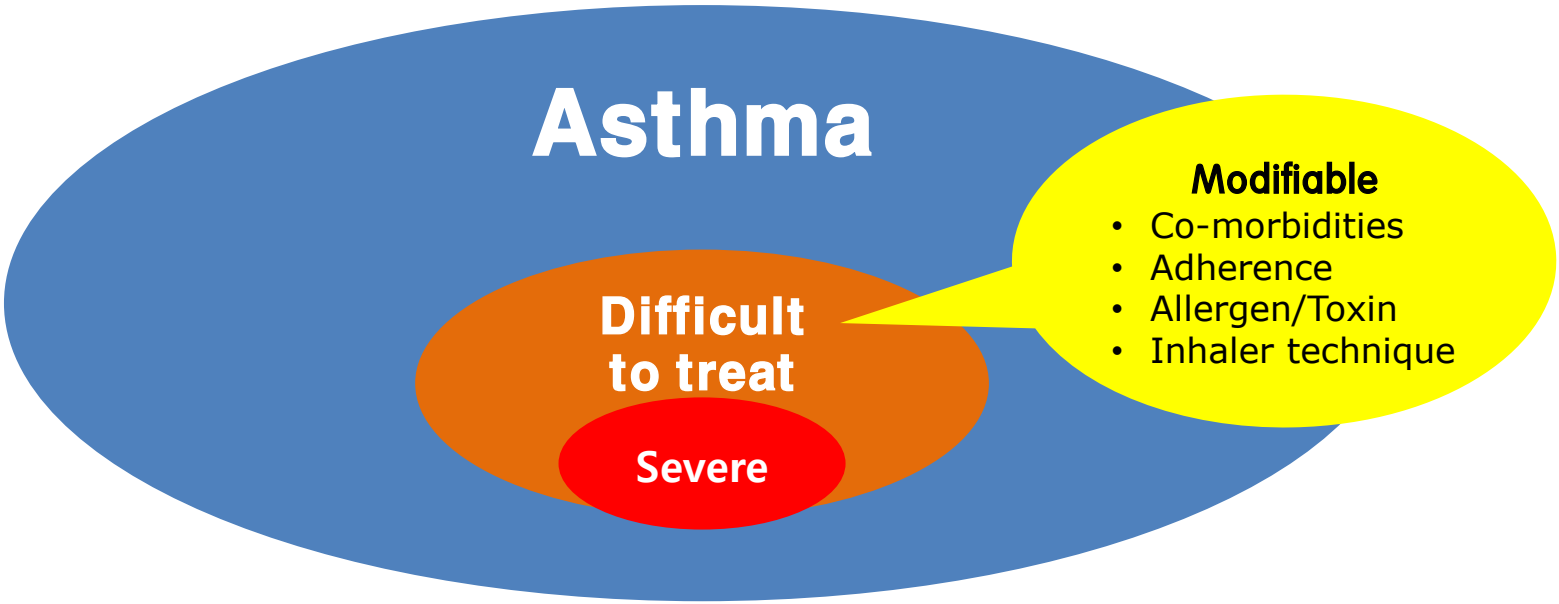
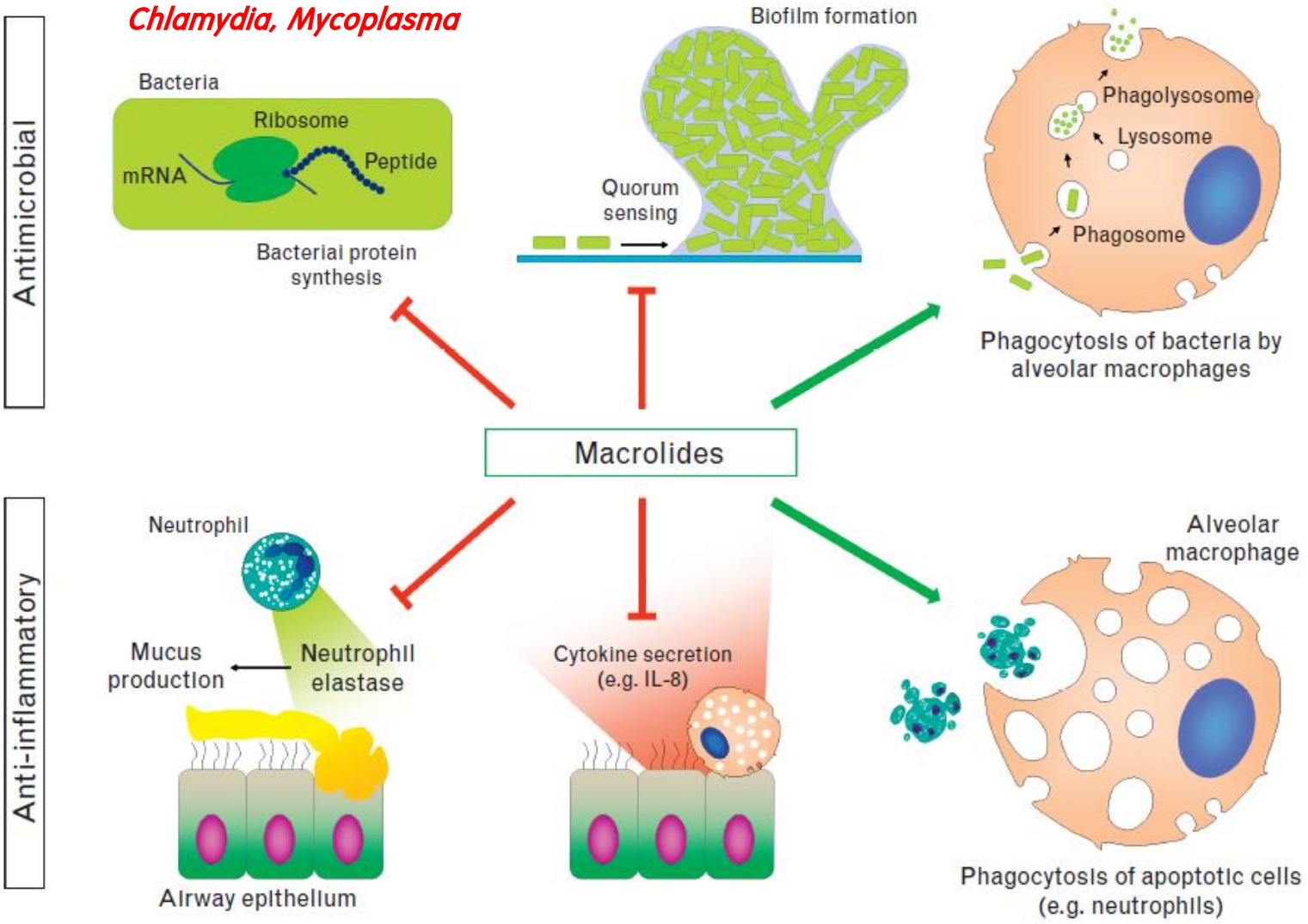


표 6-1. 지침에 따른 중증 천식의 정의 (천식진료지침 2014)

지침	사용 용어	정의
ERS/ATS 2013[1]	Severe asthma	고용량의 흡입스테로이드와 2차 조절제 혹은 전신스테로이드를 써야 조절되거나 사용함에도 불구하고 조절 되지 않는 천식
GINA 2014	Difficult-to-treat asthma	동반질환, 낮은 순응도, 알레르기항원에 의한 노출 등의 여러 인자로 인해 조절이 어려운 천식환자
	Treatment-resistant/ refractory asthma	1) 천식이 진단이 명확하고, 2) 고용량의 흡입스테로이드 및 지속성베타작용제와 같은 2차 조절제 (전신스테로이드)의 사용에도 불구하고 증상 및 악화가 있고, 3) 치료 단계 내림을 할 경우 동반 증상이나 천식의 조절이 악화되는 경우
	Severe asthma	Refractory asthma를 포함하며, 동반질환에 대한 반응이 불완전한 경우

Macrolides for Tx of severe asthma: Scientific plausibility



Brusselle GG *et al.* Curr Opin Pulm Med 2014

RCTs: Macrolides for severe asthma

- Richeldi L *et al.* cochrane review 2005, Reiter *et al.* Allergy 2013
  - **5 RCTs of Macrolides for severe asthma**
    - Kamada JACI 1993, Nelson Am Rev Resp Dis 1993, Strunk JACI 2008, Simpson AJRCCM 2009, Brusselle Thorax 2013
    - Children: 2 studies, Adult: 3 studies
    - Systemic steroids: 2 studies
  - **ATS/ERS, GINA definition of severe asthma: n=4 studies (8주 ~ 96주)**
- Macrolides: what was used?
  - **Troleandomycin**
    - 2 studies: Kamada 1993, Nelson 1993
    - ¼ dose
  - **Clarithromycin**
    - Standard dose: Simpson 2008
  - **Azithromycin**
    - Standard dose: Strunk 2008, Low dose: Brusselle 2013

MARS: Strunk R, JACI 2008

- 292 children
- 237 screen failures
  - Nonadherence = **80**
  - Improved control under close medical supervision = **49**
- 55 randomized, no obvious effect and trial ceased.
- 중증천식 진단 전에 Adherence와 Inhaler technique 평가하는 것이 매우 중요!

Results: Macrolides for Severe Asthma

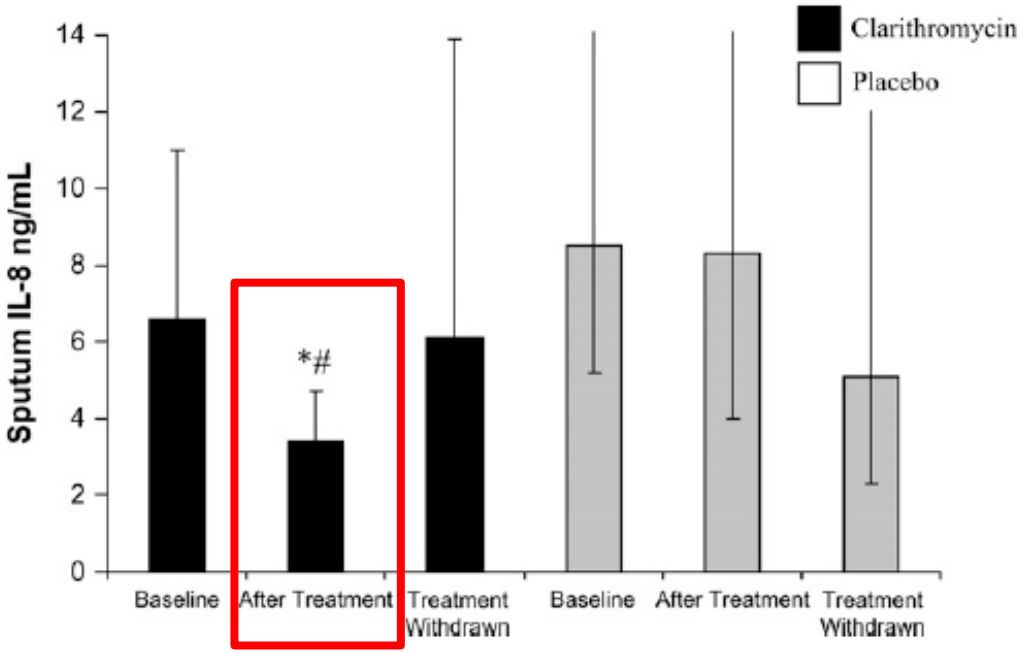
OCS dose	Kamada 1993 Nelson 1993	N=67		SMD=−0.32 [−0.81, 0.18] 5mg lower in macrolide arm
SYMPTOMS	Kamada 1993 Simpson 2008 Brusselle 2013	N=56 N=109	 Change from baseline	SMD=−0.1 [−0.62 to 0.43] MD=−0.12 [−0.43 to 0.19]
CONTROL	Simpson 2008 Brusselle 2013	N=45 N=109	 Change from baseline	MD=0.1 [−0.34 to 0.54] MD=−0.12 [−0.44 to 0.21]
QOL	Simpson 2008 Brusselle 2013	N=45 N=109	Median (IQR)	MD=0.21 [−0.10 to 0.52] MD=0.12 [−0.19 to 0.43]
Exacerbation	Brusselle 2013	N=109		RR=0.98 [0.68 to 1.43]

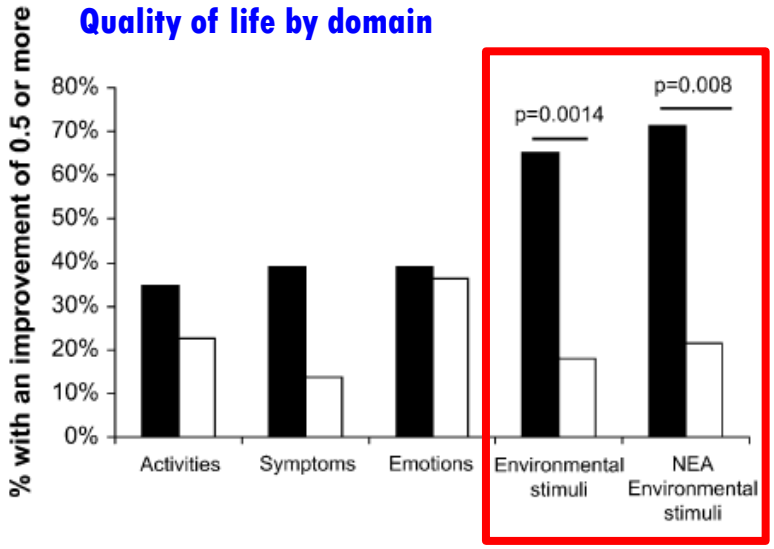
SMD: Standardized Mean Difference [95%CI]

RR: Relative Risk [95%CI]

Clarithromycin Targets Neutrophilic Airway Inflammation in Refractory Asthma

- RCT (Clarithromycin 500mg bid vs placebo)
- Severe persistent asthma (N=45), 8주
- Predefined subgroup analysis by phenotype
  - **Eosinophilic (sputum eos ≥ 3%) vs NEA (sputum neut > 61% or paucigranulocytic)**

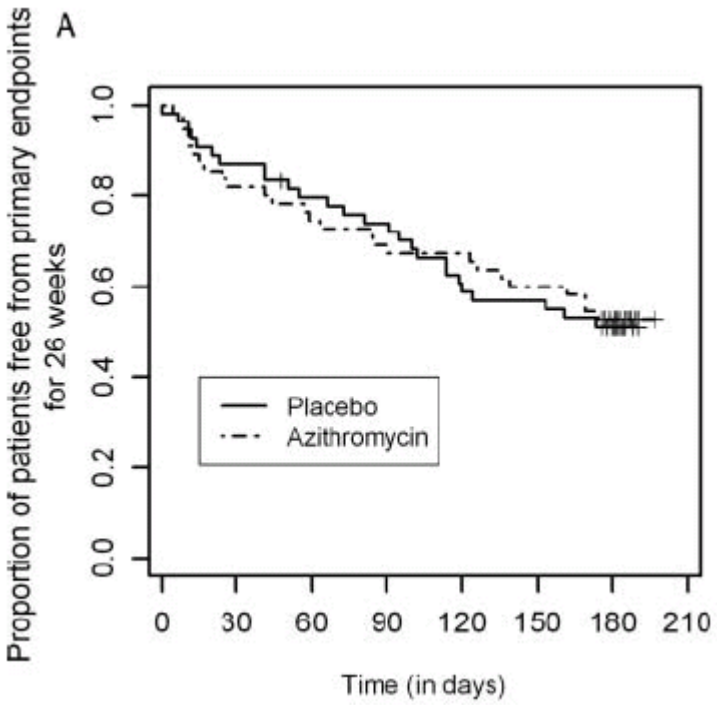


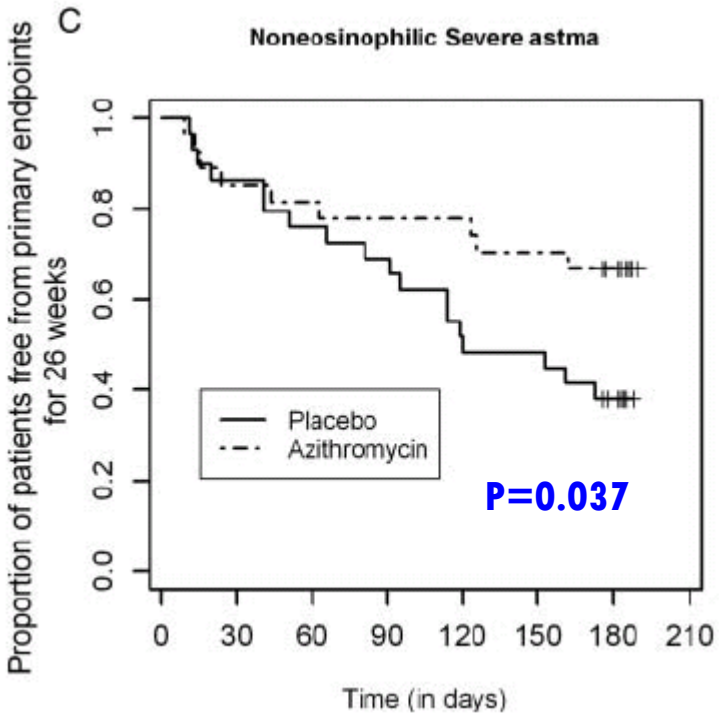


Simpson JL *et al.* AJRCCM 2008

AZIthromycin for prevention of exacerbations in Severe ASThma (AZISAST)

- RCT, azithromycin low dose vs placebo, 6months
- Severe asthma, Low FENo (N=109)
- Predefined subgroup analysis, NEA (Blood eosinophil ≤ 200/µL)





Brusselle GG *et al.* Thorax 2013

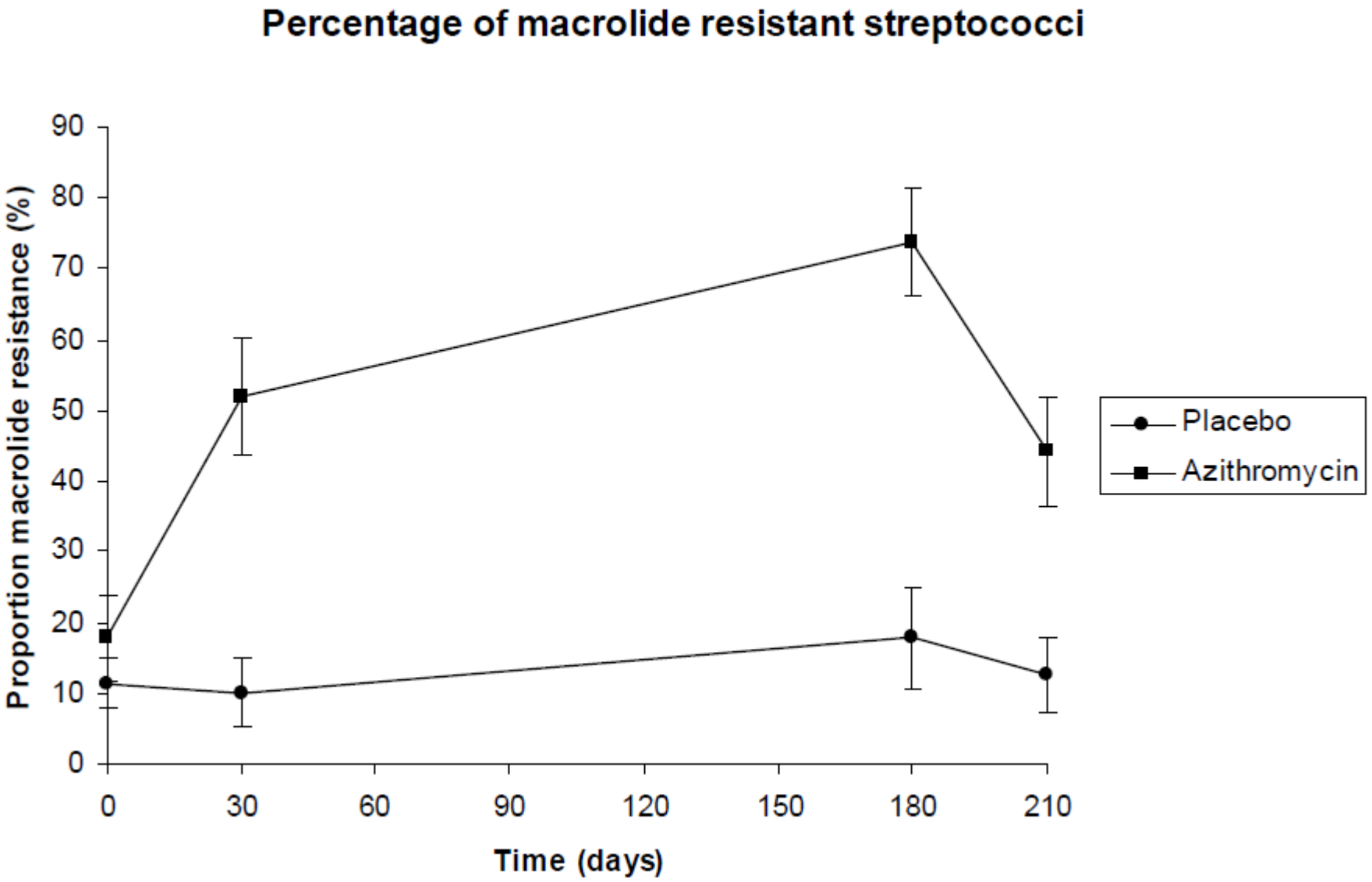
Randomized controlled trial of azithromycin in smokers with asthma

- Mild to moderate non-eosinophilic asthma
- Already receiving treatment with inhaled corticosteroids
- 3달간 Azithromycin 250mg qd
- 폐기능, 기도과민성 그리고 삶의 질 등 모든 측면에서 효과를 증명하지 못함.

Cameron EJ *et al.* Eur Respir J. 2013

Inconsistent data even in patients with the non-eosinophilic asthma

Resistance to macrolide in AZISAST trial



Brusselle GG *et al.* Thorax 2013

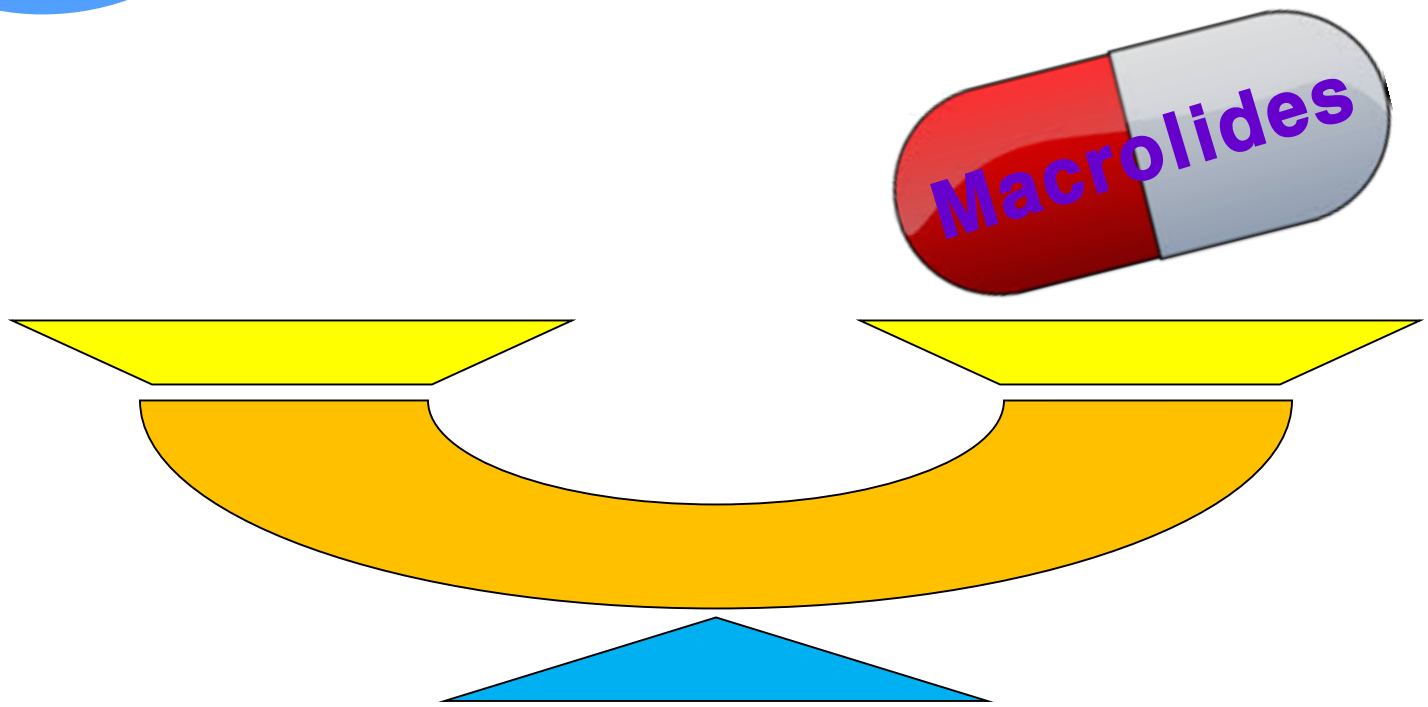
Downside of **Long-term** Macrolide Tx

- Bacterial Macrolide Resistance
- NTM Macrolide Resistance
- QT prolongation & Cardiovascular risk
- Hearing loss, hepatic injury & GI trouble
- Drug-Drug interaction

Long–term Macrolides for Severe Asthma

Very Low Evidence

Risk



Conclusion

- **Severe asthma 환자에서 low dose macrolide 사용이 천식조절과 급성악화예방에 도움이 되는가?**
  - **아니다**. (중증천식에서 macrolide 유지요법을 **권고하지 않는다**.)
  - 근거수준: 높음　　권고강도: 약함
  - Conditional recommendation
    - Macrolides may have clinical benefits in non-eosinophilic severe asthma → 추가 연구가 필요함.
- **Significant concern about Downside of Long-term macrolide Tx**
- **중증천식 진단 전에 Adherence와 Inhaler technique 평가!**

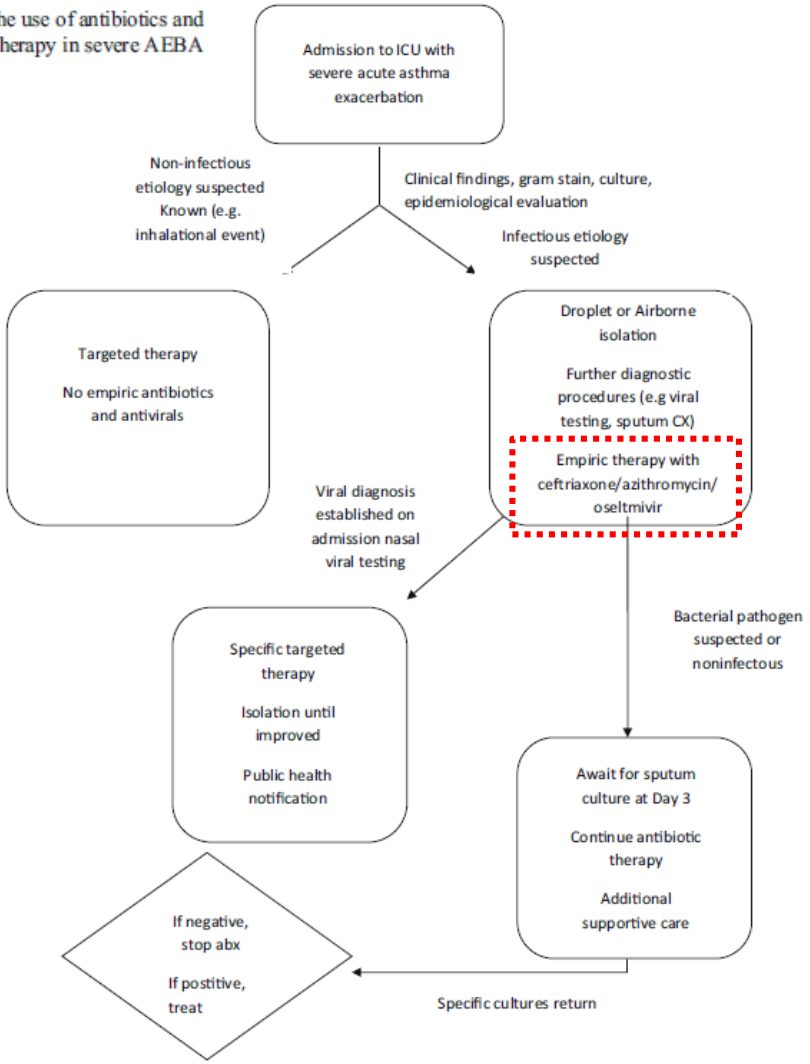
Infection in Severe Asthma Exacerbations and Critical Asthma Syndrome

Christian E. Sandrock • Andrew Norris

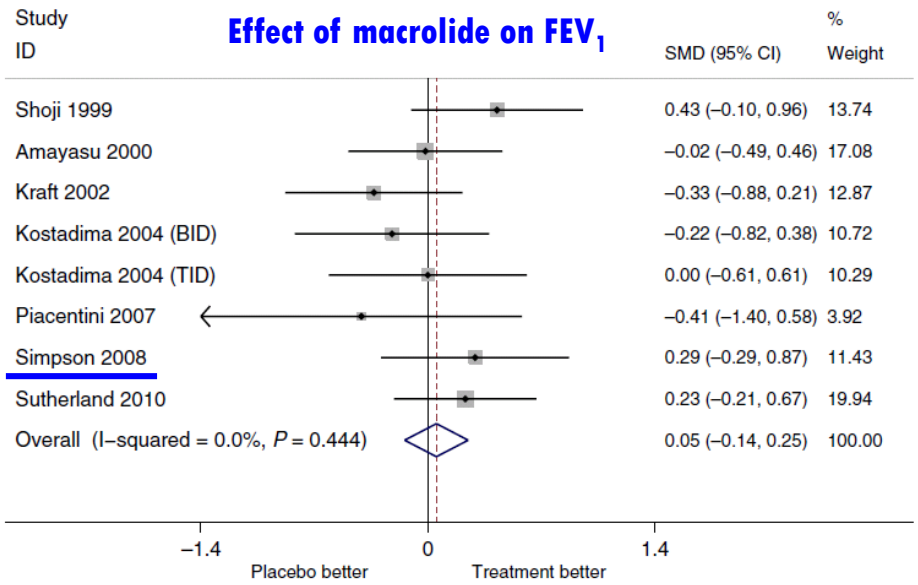
Clinic Rev Allerg Immunol published online: July 2014

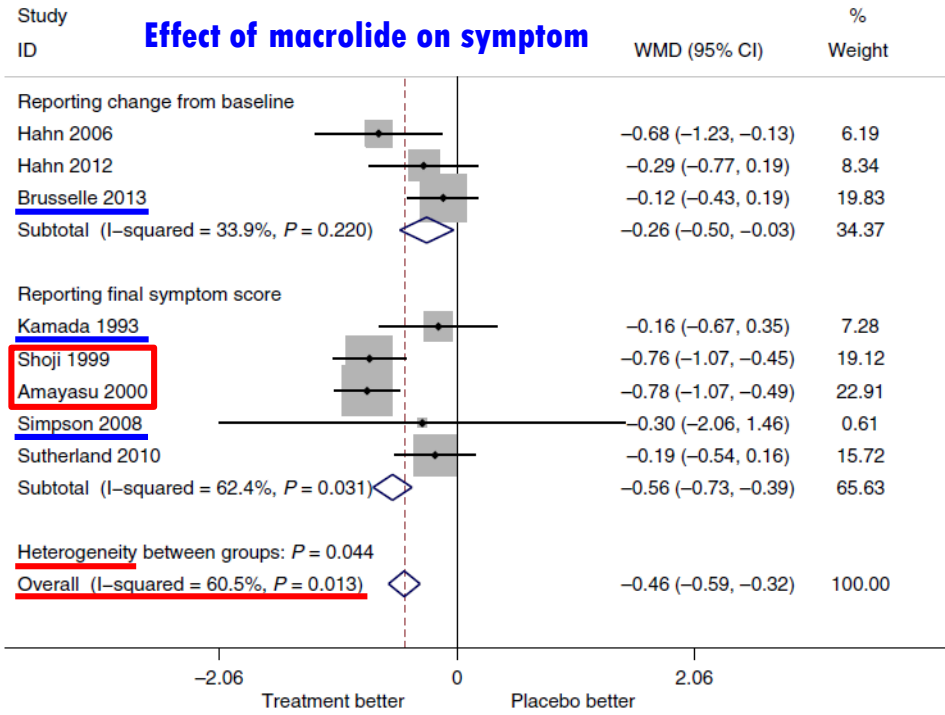
- Overall, the role of empiric antibiotic therapy without clear evidence of a bacterial trigger for an acute severe asthma exacerbation is unclear. Viral agents, particularly HRV-C, RSV, and influenza A appear to be the more prevalent and recurring threats.
- Both viral and to a lesser extent bacterial agents can play a role, and co-infection may also be present and worsen prognosis in hospitalized patients.

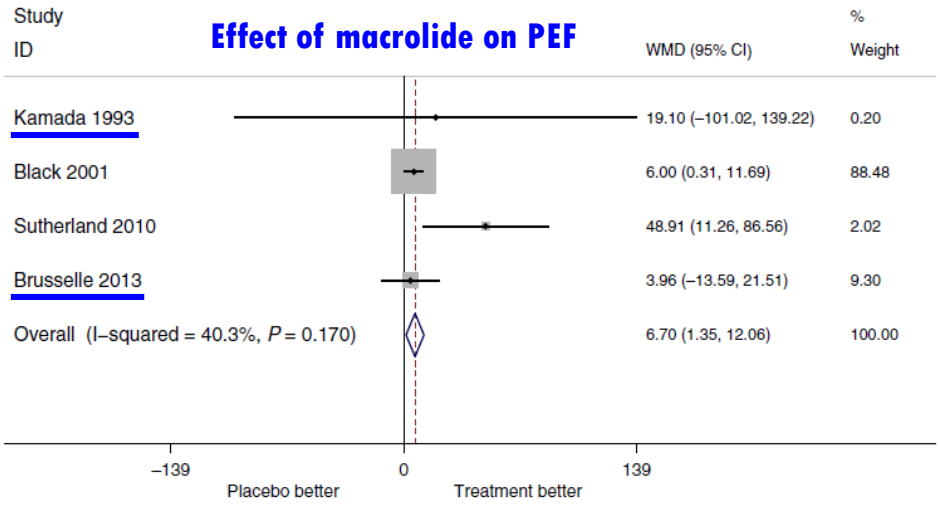
Fig. 1 The use of antibiotics and antiviral therapy in severe AEBA

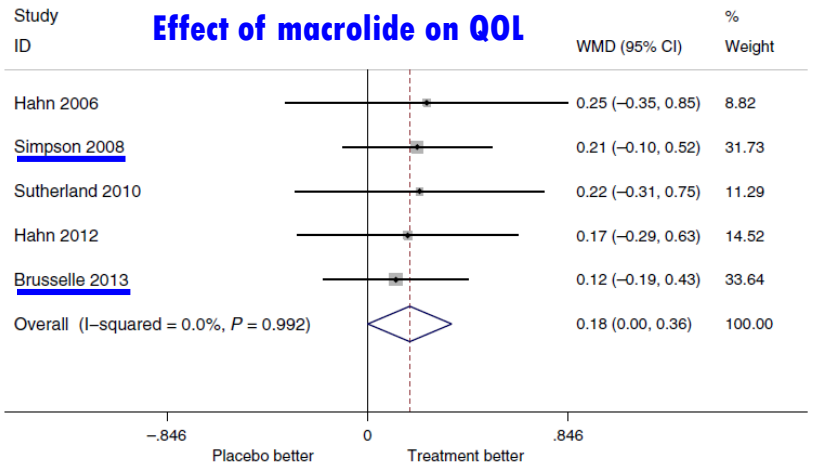


Macrolides for the treatment of asthma
Meta-analysis of RCTs, Reiter *et al*. Allergy 2013









Macrolides and asthma, severe asthma

- Macrolides for asthma
  - 환자수가 적었고, 환자군과 중증도, macrolide 종류 및 outcome measure가 heterogeneous
  - 연구기간이 짧고, 부작용 및 악화예방에 대한 평가가 부족
  - Crossover design 연구에서 positive results
  - Mild to moderate asthma → 굳이 macrolide를 사용 할 필요?

- Macrolides for **severe asthma**
  - **Very low** quality evidence