MACROLIDE & IMMUNOMODULATORY EFFECT

Bs Huỳnh Minh Thiện

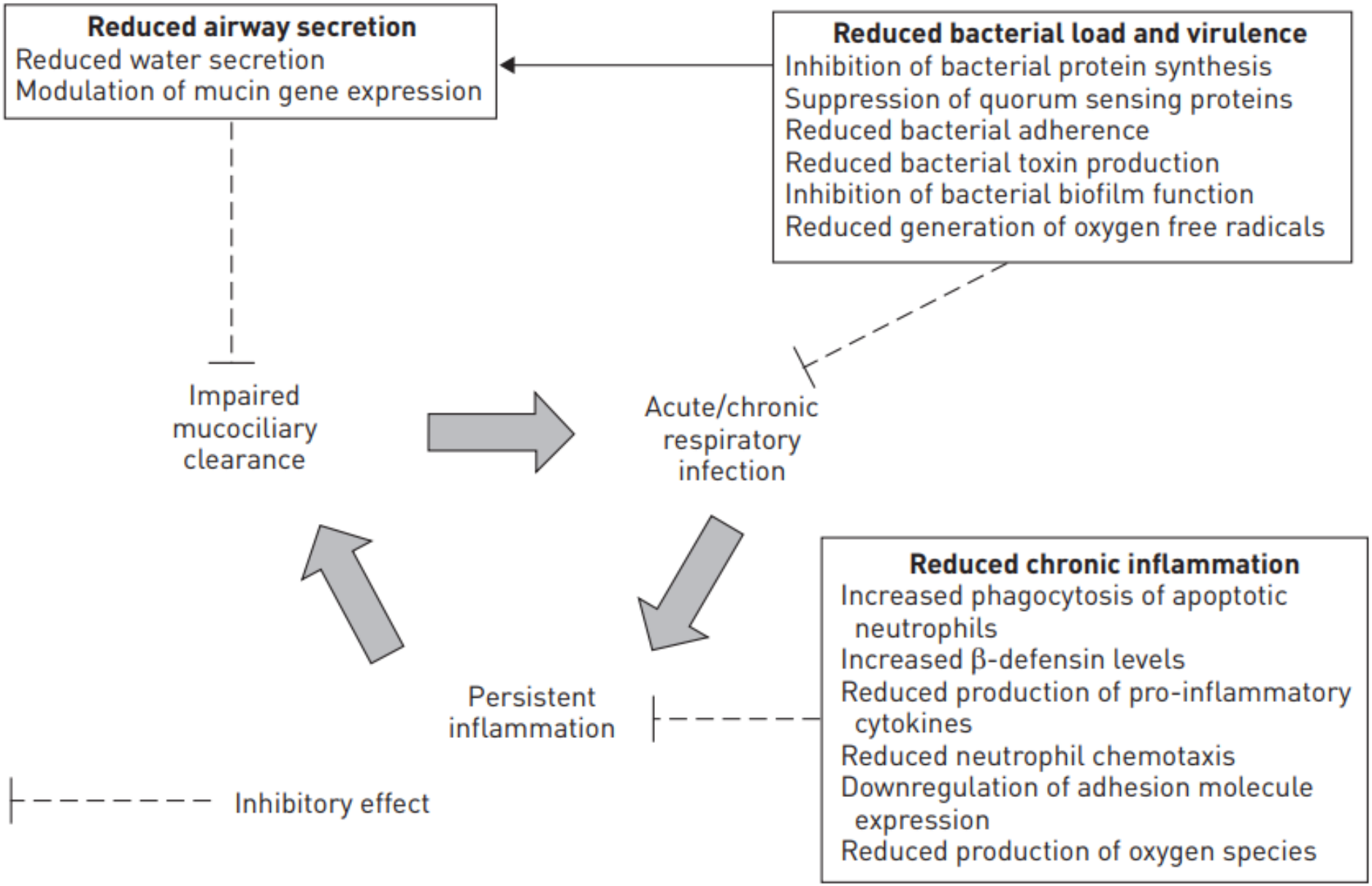
KHOA Hễ HẤP 1

CONTENT

- Immunomodulatory effect of macrolide
- Evidence of longterm use of macrolide in
  - diffuse panbronchiolitis
  - cystic fibrosis
  - COPD
  - bronchiolitis obliterans after transplant
- Evidence of longterm use of macrolide in children with
  - post infectious broncholitis obliterans
  - plastic bronchitis
- Conclusion

- Long-term macrolide was first used to treat **diffuse panbronchiolitis** (DPB) in the late 1980s
- **Anti-inflammatory** and **immunomodulatory** activity and **antimicrobial**

Paolo Spagnolo, Leonardo M. Fabbri and Andrew Bush . Longterm macrolide treatment for chronic respiratory disease. Eur Respir J 2013; 42: 239–251



Paolo Spagnolo, Leonardo M. Fabbri and Andrew Bush . Longterm macrolide treatment for chronic respiratory disease. Eur Respir J 2013; 42: 239–251

Diffuse panbronchiolitis

- progressive inflammatory airway disease reported in East Asians
- chronic airway infection, sinusitis
- often complicated by Pseudomonas aeruginosa infection
- chronic productive cough, dyspnea, airflow limitation and chronic sinusitis

Diffuse panbronchiolitis

- Benefits of using macrolides
- 10-year survival rate increasing from 12–50% (patients were infected with P. aeruginosa) to 90%
- impossible nowadays to conduct a randomised controlled trial (RCT) because **no patient agree to be randomised to placebo**

Paolo Spagnolo, Leonardo M. Fabbri and Andrew Bush . Longterm macrolide treatment for chronic respiratory disease. Eur Respir J 2013; 42: 239–251

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Diffuse panbronchiolitis

We recommend using a macrolide antibiotic in all patients diagnosed with DPB (**Grade 1B**). The agent of first choice is erythromycin 400 to 600 mg/day due to the greater clinical experience with it. For patients who are unable to tolerate erythromycin or do not improve, alternative macrolides include clarithromycin, roxithromycin, and azithromycin. (See 'Macrolide antibiotics' above.)

Cystic fibrosis

- the most common life-shortening inherited disease in white populations
- caused by mutations in the cystic fibrosis transmembrane conductance regulator gene
- characterised by neutrophilic infiltration and pro-inflammatory cytokine production

Cystic fibrosis

- 6 RCTs showing evidence of benefit
- Cochrane systematic review
  - 10 studies
  - 959 patients
  - Aged ≥ 5 years old
  - Intervention duration 2-12 months, Azithromycin 250 mg tablet 3 times per week (>40 kg, 500 mg) versus placebo

Cochrane Library

Cochrane Database of Systematic Reviews

Macrolide antibiotics for cystic fibrosis

Cochrane Systematic Review - **Intervention** | Version published: 14 November 2012 see what's new

New search

View article information

Kevin W Southern | Pierre M Barker | Arturo Solis-Moya | Latifa Patel

View authors' declarations of interest

Cystic fibrosis

- Long-term macrolide therapy
  - improves lung function
  - reduces the risk of infective exacerbations
  - decreases the requirement for additional antibiotics

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Cystic fibrosis: Overview of the treatment of lung disease

Author: Richard H Simon, MD
Section Editor: George B Mallory, MD
Deputy Editor: Alison G Hoppin, MD

- We suggest initiating chronic azithromycin therapy for children ≥6 months old at the time of the first positive culture for *P. aeruginosa* and continued regardless of whether the pseudomonas is eradicated (**Grade 2B**). We also suggest azithromycin for all patients ≥6 years old regardless of their *P. aeruginosa* status (**Grade 2B**). Test patients for nontuberculous mycobacteria prior to initiating azithromycin

COPD

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 25, 2011 VOL. 365 NO. 8

Azithromycin for Prevention of Exacerbations of COPD

Richard K. Albert, M.D., John Connett, Ph.D., William C. Bailey, M.D., Richard Casaburi, M.D., Ph.D., J. Allen D. Cooper, Jr., M.D., Gerard J. Criner, M.D., Jeffrey L. Curtis, M.D., Mark T. Dransfield, M.D., MeiLan K. Han, M.D., Stephen C. Lazarus, M.D., Barry Make, M.D., Nathaniel Marchetti, M.D., Fernando J. Martinez, M.D., Nancy E. Madinger, M.D., Charlene McEvoy, M.D., M.P.H., Dennis E. Niewoehner, M.D., Janos Porsasz, M.D., Ph.D., Connie S. Price, M.D., John Reilly, M.D., Paul D. Scanlon, M.D., Frank C. Sciurba, M.D., Steven M. Scharf, M.D., Ph.D., George R. Washko, M.D., Prescott G. Woodruff, M.D., M.P.H., and Nicholas R. Anthonisen, M.D., for the COPD Clinical Research Network

ABSTRACT

COPD

- Prospective, parallel-group, placebo-controlled design
- 1142 patients
  - 570 participants use azithromycin, dose of 250 mg daily
  - 572 participants use placebo for **1 year**
- Result
  - Reduce frequency of exacerbations (P=0.01)
  - Life quality score improve

COPD

Cochrane Library

Cochrane Database of Systematic Reviews

Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Cochrane Systematic Review - **Intervention** | Version published: 30 October 2018 **see what's new**

New search **Conclusions changed**

Am score 73 **View article information**

Samantha C Herath | Rebecca Normansell | Samantha Maisey | Phillippa Poole

View authors' declarations of interest

COPD

- 14 randomized trials
- 3932 patients with moderate-to-severe COPD
- continuous, intermittent and one pulsed arm use macrolide from 3-36 months
- Result
  - significant reduction in the number of exacerbation (OR 0.57, 95% CI 0.42-0.78)
  - improvement in quality-of-life measures
  - improvement FEV 1

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Management of infection in exacerbations of chronic obstructive pulmonary disease

Authors: John G Bartlett, MD, Sanjay Sethi, MD
Section Editor: Daniel J Sexton, MD
Deputy Editors: Sheila Bond, MD, Helen Hollingsworth, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Mar 2019. | **This topic last updated:** Nov 19, 2018.

For most patients with COPD, we suggest not administering antibiotic prophylaxis (**Grade 2B**). For patients who continue to have frequent exacerbations despite optimal therapy for COPD with bronchodilators and anti-inflammatory agents, we suggest antibiotic prophylaxis with azithromycin (**Grade 2B**). Azithromycin can be given as 250 mg daily or at a lower dose of 250 to 500 mg three times per week. We often use 250 mg three times per week to reduce adverse effects. (See 'Prophylactic antibiotics' above.)

Bronchiolitis obliterans after transplant

- A retrospective study of 107 patients with azithromycin treatment for 3-6 months, 40% patients increase FEV1 ≥10%
- Among 81 lung transplant recipients with BOS treated with azithromycin, 24 showed an improvement in FEV1, 35 patients showed progression

- 62 patients with potential BOS or grade 1 to 3 BOS treated with azithromycin for 1 year, 13 had a ≥ 10% improvement in FEV1

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Chronic lung transplant rejection: Bronchiolitis obliterans

Author: Joseph Pilewski, MD
Section Editor: Elbert P Trulock, MD
Deputy Editor: Helen Hollingsworth, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Mar 2019. | **This topic last updated:** Nov 12, 2018.

Prevention and treatment

- For patients with new onset BOS, we suggest addition of long-term azithromycin therapy rather than other therapies. The usual dose is 250 mg daily for five days, followed by 250 mg three times weekly (**Grade 2C**). In addition, the maintenance immunosuppression regimen is assessed and optimized (table 4). (See 'New onset BOS' above.)

PEDIATRICS ???

- **Cystic fibrosis**
- Post infectious bronchiolitis obliterans
- Plastic bronchitis

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POST INFECTIOUS BRONCHIOLITIS OBLITERANS

Li *et al. BMC Pediatrics* 2014, **14**:238
http://www.biomedcentral.com/1471-2431/14/238

BMC Pediatrics

RESEARCH ARTICLE Open Access

Post-infectious bronchiolitis obliterans in children: a review of 42 cases

Ya-Nan Li[1,2], Li Liu[1], Hong-Mei Qiao[1], Hang Cheng[1] and Huan-Ji Cheng[1*]

POST INFECTIOUS BRONCHIOLITIS OBLITERANS

- 42 cases
- Aged ≤ 14 years old
- The treatment protocol included oral Prednisone and Azithromycin
- Evaluated at 1, 3 and 6 months after the initiation of treatment
  - IOS/ Spirometry
  - acute exacerbations of respiratory symptoms

POST INFECTIOUS BRONCHIOLITIS OBLITERANS

- After six months of therapy:
  - 36patients (85.7%) improve
  - 6 cases (14.3%) is not effective

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Azithromycin therapy in children with postinfectious bronchiolitis obliterans

Zeynep Seda Uyan, Levent Midyat, Erkan Çakir, Yasemin Gökdemir, Nihal Sahin, Canan Baydemir, Velat Sen, Ahmet Hakan Gedik, Ela Erdem, Fazilet Karakoç, Bülent Karadag, Refika Ersu

European Respiratory Journal 2016 48: PA1602; **DOI:** 10.1183/13993003.congress-2016.PA1602

POST INFECTIOUS BRONCHIOLITIS OBLITERANS

- 19 PIBO patients (mean age:109±59 months, 21% female)
- **Methods**
  - 8 patients received Azithromycin for 6 months
  - 11 patients did not receive Azithromycin
- **Results**
  - There was a significant difference of
    - R20 and X20 results at the second month (p=0.012 and 0.012)
    - R15% and R20% and FEV1 results (p=0.033, 0.033 and 0.042) at the forth month in the azithromycin group.

PLASTIC BRONCHITIS

Hindawi Publishing Corporation
Case Reports in Pulmonology
Volume 2013, Article ID 649365, 8 pages
http://dx.doi.org/10.1155/2013/649365

Hindawi

Case Report

Pediatric Plastic Bronchitis: Case Report and Retrospective Comparative Analysis of Epidemiology and Pathology

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PLASTIC BRONCHITIS

- 14 plastic bronchitis patients were seen over a 12 years
- Treatment
  - acute cast removal
  - long-term prevention of cast recurrence
    - Inhaled mucolytics and fibrinolytics
    - Inhaled corticosteroid
    - Oral azithromycin
- 10 cases have no further casts after 2 years

Table 1: Clinical presentation, treatment, and outcomes of 14 patients with plastic bronchitis.

	Patient identification	Presentation of PB	Treatment	Gross description and histopathology	Outcome
1	3 yo M with hypoplastic left heart syndrome. Cardiac surgeries included Norwood, BT shunt, Glenn, and Fontan.	Worsening respiratory distress and expectoration of multiple casts after Fontan.	Multiple bronchoscopic cast removals, budesonide, levalbuterol, direct and inhaled t-PA, spironolactone, inhaled hypertonic saline (3%). Oral azithromycin and spironolactone.	Gross: irregular branching, spongy, soft, tan, and red-brown tissue. Largest specimen 6 × 1.5 × 0.7 cm. Histology: hypocellular fibrinous casts.	Continued small expectorated casts but without further obstructive casts 6 months after PB diagnosis.
2	3 yo M with tricuspid atresia. Cardiac surgeries included Glenn and Fontan. Course complicated by protein-losing enteropathy and chylothorax.	Presented with chronic cough; expectoration productive of branching mucoid casts.	Bronchoscopic cast removal. Inhaled steroids, albuterol, acetylcysteine, dornase alpha, and alteplase. Oral azithromycin.	Gross: 2.2 × 1.4 × 0.3 cm white fibrous tissue. Histology: hypocellular, fibrinous cast.	Continued levalbuterol and acetylcysteine with small expectorated casts daily 12 years after PB diagnosis.
3	6 yo M with d-transposition of the great arteries and asthma. Cardiac surgery included arterial switch, closure of ASD, VSD, and PDA ligation.	Respiratory distress and right lung collapse in setting of influenza B infection. Bronchoscopy followed by forceps removal of cast.	Bronchoscopic cast removal, inhaled budesonide, acetylcysteine, dornase alpha, levalbuterol, inhaled t-PA. Oral azithromycin.	Gross: thick, white, extremely viscous material adherent to bronchus wall and obstructing right mainstem bronchus. Histology: mixture of hypocellular fibrinous casts and inflammatory casts with abundant eosinophils.	Well-controlled asthma with no further casts at 3 years after PB diagnosis.
4	1 yo M with DiGeorge syndrome, tetralogy of Fallot, pulmonary atresia, and MAPCAs with chronic lung disease who was ventilator dependent. Cardiac surgeries included unifocalization to RV-to-PA conduit with VSD closure.	Repeated plugging of tracheostomy with thick mucous.	Inhaled dornase alpha, levalbuterol, albuterol, budesonide. Oral azithromycin.		Continued on inhaled dornase alpha, budesonide, levalbuterol, and albuterol at discharge, which was 2 months after initial diagnosis of PB.
5	2 yo M with tricuspid atresia. Cardiac surgeries included Glenn and Fontan. Course complicated by chylothorax.	Presented with significant cough which improved after expectoration of cast with delicate strands.	Budesonide, levalbuterol, spironolactone.		Fontan was fenestrated after PB diagnosis and no further casts at 9 months after PB diagnosis.

PLASTIC BRONCHITIS

Pediatric Pulmonology 35:139–143 (2003)

Case Reports

Treatment of Cast Bronchitis With Low-Dose Oral Azithromycin

Karen D. Schultz, MD* and Christopher M. Oermann, MD

Summary. Cast or plastic bronchitis is an unusual disorder that is rarely encountered in the pediatric population. It is characterized by the expectoration of large, branching plugs of airway debris. These "casts" conform to the shape of portions of the tracheobronchial tree, and give the disorder its name. Cast bronchitis is typically seen in association with several primary pulmonary disorders and cyanotic congenital heart disease. It can be classified as inflammatory or acellular, based on the histologic characteristics of the casts. The presence of large, obstructive plugs filling the airways of lobes or entire lungs can result in a variety of clinical signs and symptoms, and may ultimately lead to respiratory failure and death. Conventional treatment of cast bronchitis

PLASTIC BRONCHITIS

- 15 years old boy with 1-year history of productive cough
- He was treated for 12 months with oral corticosteroids, oral antibiotics, inhaled steroids, beta-agonists, and guaifenesin
- The patient developed acute worsening clinical status: dyspnea, altered mental status, expectoration of a 4-cm-long branching cast
- He was transfered to hospital for airway clearance by rigid bronchoscopy. Copious quantities of yellow-white, thick, tenacious mucus originating in his left lower lobe

PLASTIC BRONCHITIS

- 6 weeks later, the patient continued expectoration of small casts
- Empiric treatment with low-dose azithromycin was initiated
- The patient has been symptom-free on a regimen of azithromycin and inhaled fluticasone-salmeterol.
- He has not had any cast production for 5 months, the longest interval without expectoration of plugs in 2 years.

CONCLUSION

- Longterm use of macrolide is effective in Diffuse panbronchiolitis, Cystic fibrosis, COPD, Bronchiolitis obliterans after transplant
- In children, post infectious broncholitis obliterans, plastic bronchitis treated with longterm low dose of macrolide have some potential result.