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Updates on Lower Respiratory Tract Infection Management

Naim Aoun MD
American Board
Pulmonary, Critical Care and Sleep Medicine

24 April 2024

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Management of Lower Respiratory Track Infections

Naim Aoun MD

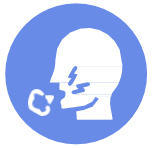
American Board

Pulmonary, Critical Care and Sleep Medicine

Lower respiratory tract infections

- Lower respiratory tract infections (LRTIs) include:
  - Bronchitis
  - Pneumonia
- Acute illness (present for 21 days or less), usually with cough as main symptom
- At least 1 other symptom

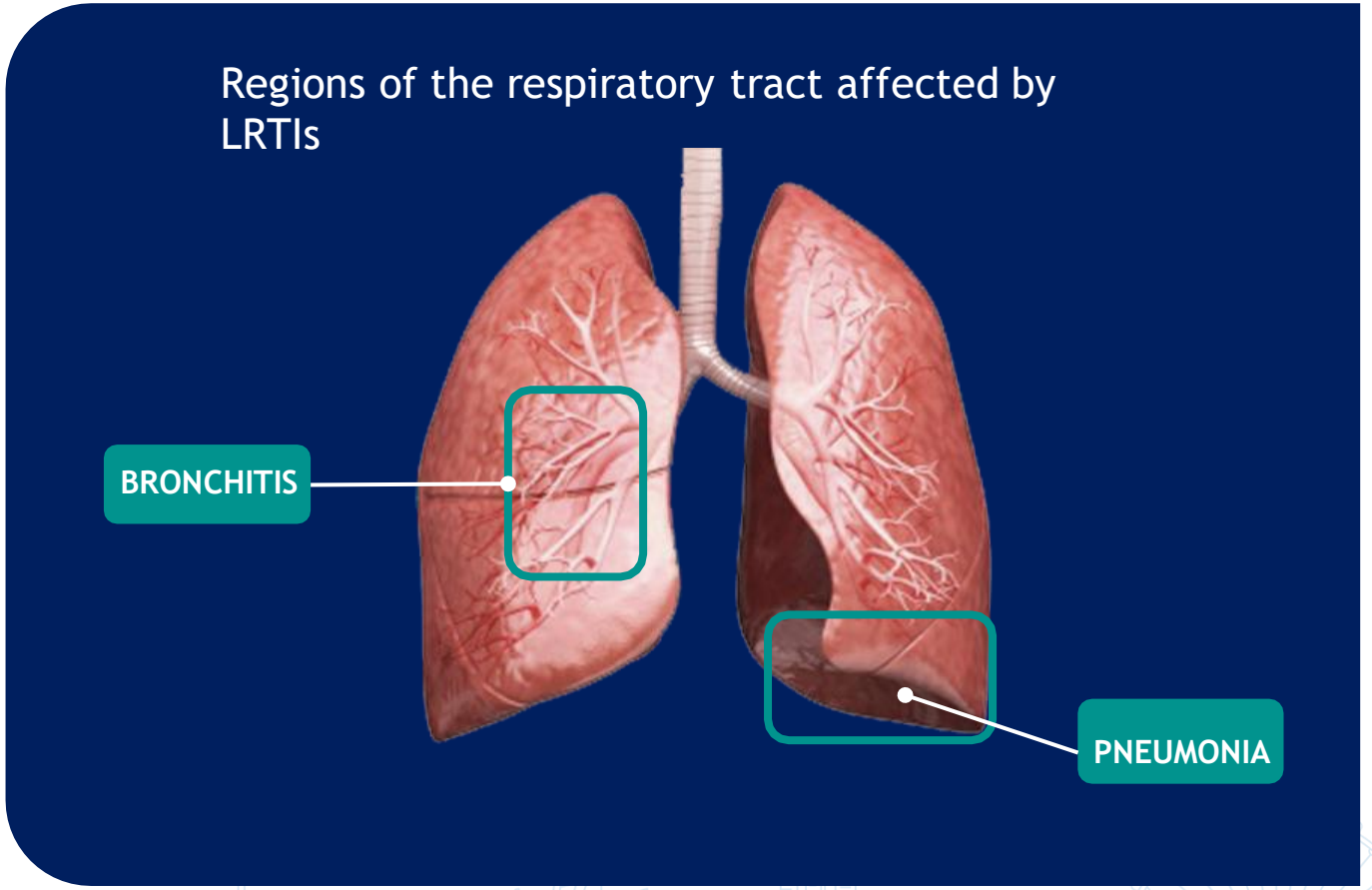

Sputum production


Wheeze


Dyspnoea


Chest pain


Fever



Bronchitis: Commonly encountered around the world

Annual Estimated Incidence of Acute Bronchitis

PER 1000
INDIVIDUALS

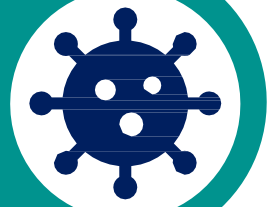
Incidence of acute bronchitis varies by age:

In **younger men**, the incidence is estimated at **36 per 1000.**

In **people older than 85,** the incidence is much higher: **225 per 1000.**

Bronchitis: Viruses are the primary cause

Viruses are the primary cause of acute bronchitis, with approximately 10% of cases attributable to bacterial pathogens.



Patients with no comorbidities usually improve **spontaneously** within 4 to 8 days.

Bronchitis: Some Cases Are Caused by Bacteria

- **Bacterial infections** are more likely to occur in:
  - Smokers
  - People with chronic obstructive pulmonary disease (COPD)
  - People with previous respiratory viral infections

- **Types of bacteria** associated with acute bronchitis:
  - *Mycoplasma pneumoniae*
  - *Chlamydia pneumoniae*
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
  - *Bordetella pertussis*

Antibiotics Not Associated with Shorter Duration or Reduced Severity of Acute Lower Respiratory Tract Infection

Original Research | Published: 15 April 2024

(2024) Cite this article

Journal of General Internal Medicine

Aims and scope →

Submit manuscript →

1.Study Population

1. **Total Patients**: 718 with baseline data
2. **Antibiotics Prescribed**: 29% at baseline

2.Most Common Antibiotics

1. Amoxicillin-Clavulanate, Azithromycin, Doxycycline, Amoxicillin
2. Prescribed in 85% of cases where antibiotics were used

3.Effects on Cough (Duration and Severity)

1. **Finding**: No significant effect on duration or overall severity of cough

4. Impact on Healthcare Utilization

1. **Follow-Up Visits Reduced**: 14.1% vs 8.2%
2. **Possible Reason**: Reduced motivation to seek follow-up for additional antibiotic prescription

5.Other Medications

1. **Systemic Corticosteroids**: More likely in antibiotic recipients (31.9% vs 4.5%, $p < 0.001$)
2. **Albuterol Inhaler**: More likely in antibiotic recipients (22.7% vs 7.6%, $p < 0.001$)

Pneumonia: Infection of the lung parenchyma

Pneumonia is usually classified by the setting in which the patient has contracted the infection.

Community setting

- Community-acquired pneumonia
  - Pneumonia acquired outside the hospital in individuals who have not been hospitalised during the month prior to symptom onset.

Healthcare/institutional setting

- Hospital-acquired pneumonia (HAP)
- Ventilator-associated pneumonia (VAP)
- Healthcare-associated pneumonia (HCAP)

Community-acquired pneumonia: Major morbidity & mortality

- CAP is the **leading infectious cause of death** in the US.

People Affected Annually

Hospital Admissions

will require admission to the hospital intensive care unit.

- Mortality may be as high as 36.5% among ICU patients.
- Mortality rates are even higher in patients with bacteremia.

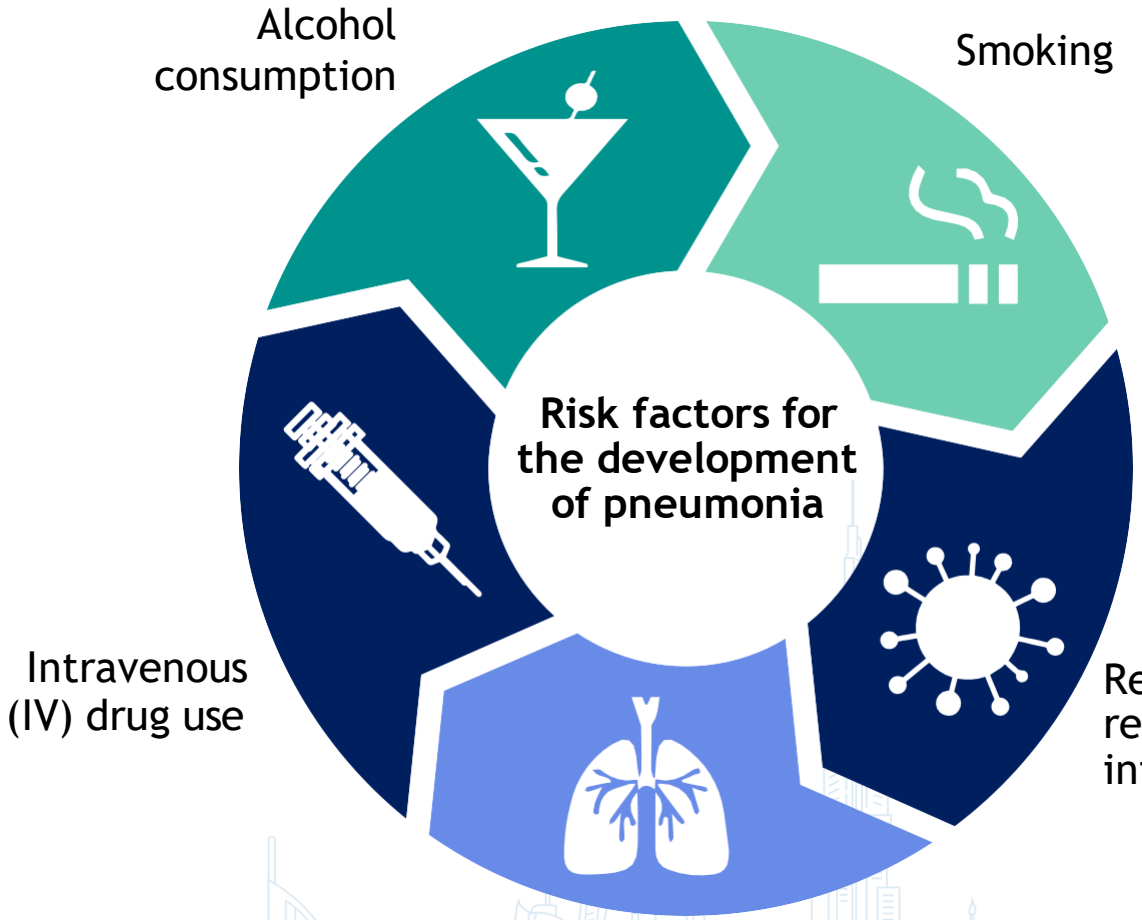
- Inpatient management can increase the cost of care for CAP up to 25-fold compared to outpatient management.

UP
TO
25
X
MORE
$$$

Pneumonia: Risk Factors

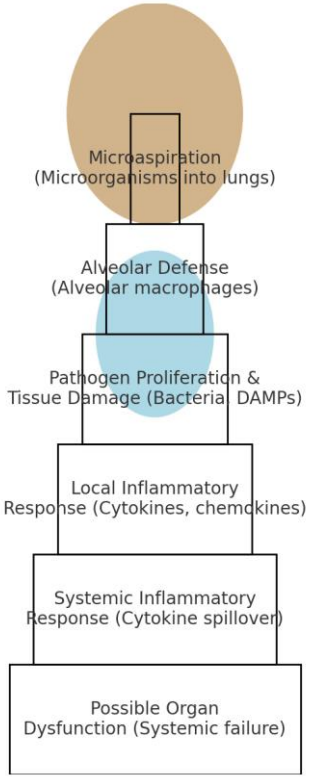
Risk Factors:

- Advanced Age
- Chronic Lung Disease
- Chronic Heart Disease
- Cardiovascular Disease
- DM
- Malnutrition
- Immunocompromising Conditions



Pathophysiology

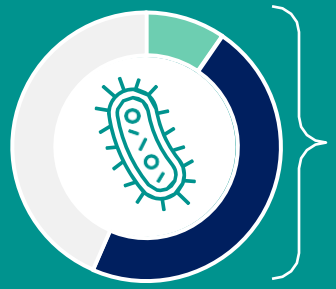
- Microaspiration
- Pathogens overcomes the defenses
- Multiply and cause local tissue damage
- Local inflammatory response
- Cytokine spill over and cause SIR



The inflammatory responses explain most of the host patient's signs and symptoms as well as laboratory and imaging abnormalities

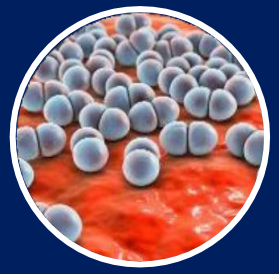
Microbiology of community-acquired pneumonia

- **Bacteria** are the sole cause of 11% to 65% of CAP cases*.
- **Gram-negative** bacteria are less common (2-10% of cases).



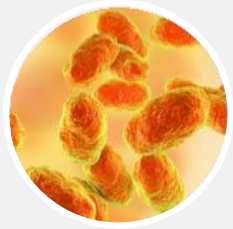
*Depending on the region.

- ***Streptococcus pneumoniae*** is the most common infectious bacteria (~19-34% of cases).
- USA: 10-15% of inpatients
- Pre-Abx era represented 95%.



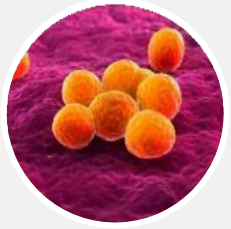
Streptococcus pneumoniae

OTHER COMMON BACTERIA



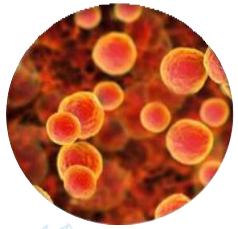
Haemophilus influenzae/ Klebsiella

Moraxella catarrhalis

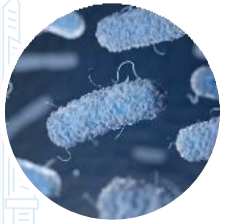


Staphylococcus aureus

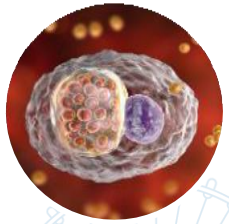
ATYPICAL PATHOGENS



Mycoplasma pneumoniae



Legionella pneumophila



Chlamydia species

22% of cases in some studies

Pneumonia diagnosis: Symptoms and signs

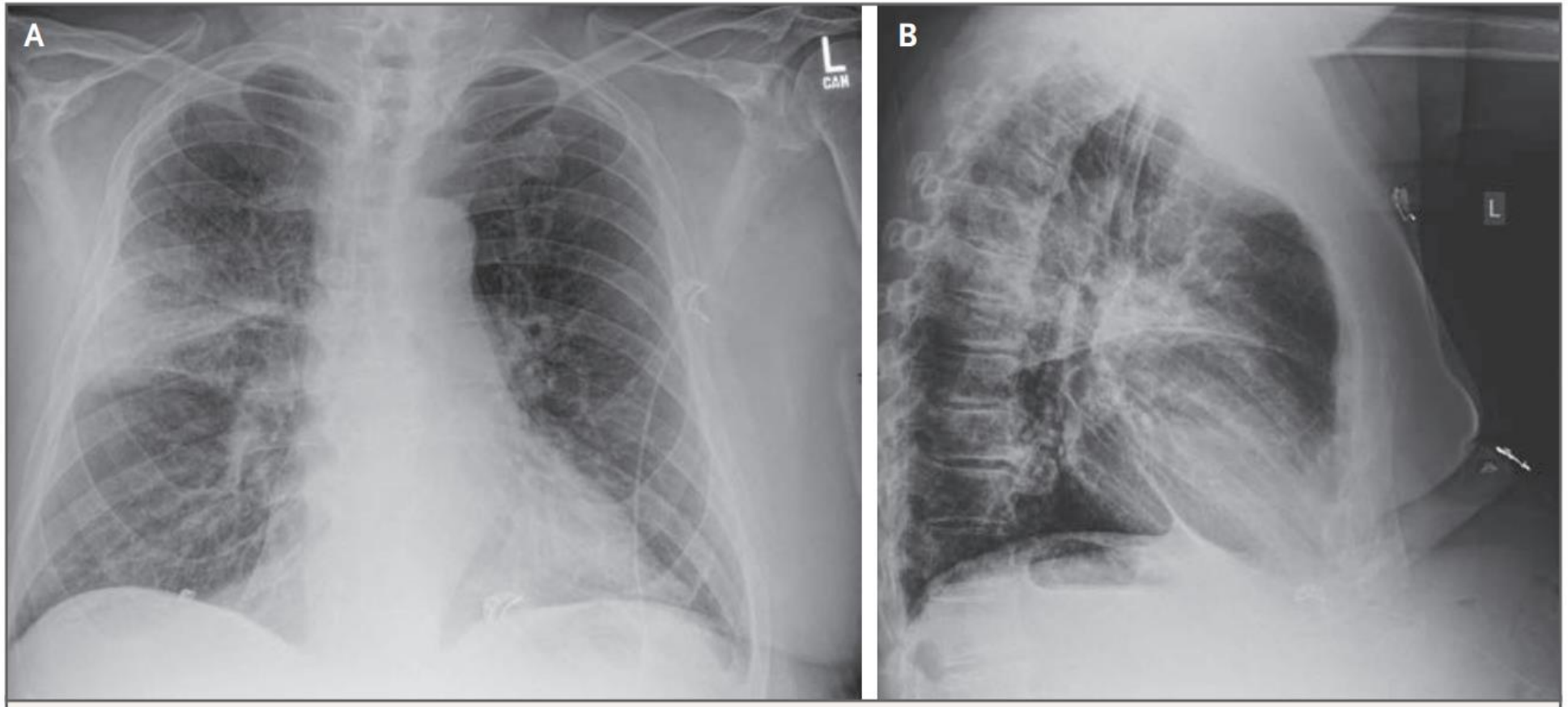


Figure 1. Chest Radiographs.

Posteroanterior (Panel A) and lateral (Panel B) views show right upper-lobe infiltrate.

Pneumonia diagnosis: Symptoms and signs

According to guidelines from the European Respiratory Society (ERS) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), **pneumonia should be suspected when 1 of the following symptoms is present.**

- **New focal chest signs** such as:
  - Decreased chest expansion
  - Dullness on percussion
  - Decreased air entry
  - Bronchial breathing or crackles

Cough/Sputum/ Dyspnea

Pulse rate >100

Tachypnea

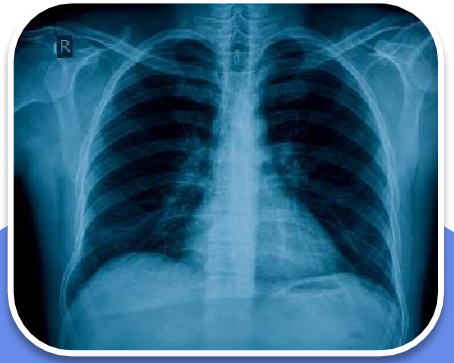
Chills/Fever/Malaise

30% no fever

Pneumonia diagnosis: CRP levels, X-rays, and other testing

C-reactive protein (CRP) testing can help rule out other acute respiratory illnesses:

- Pneumonia is highly unlikely with a CRP level of <20 mg/L.
- Pneumonia is likely with a CRP level of >100 mg/L.

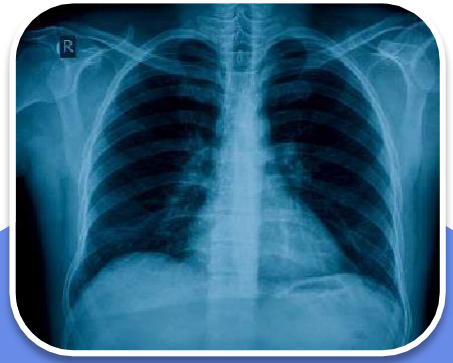


- A definitive diagnosis of pneumonia requires evidence of consolidation on **chest X-ray.**
- **Covid and Influenza PCR**
- **How about Procalcitonin level?**

- The European groups <u>do not recommend:</u>
  - **Cultures** or Gram stains for LRTIs without the presence of pneumonia.
  - **Use of biomarkers** to assess the presence of bacterial pathogens.

Pneumonia diagnosis: Inpatients

- Gram Stain and Cx
- Blood Cx
- Legionella and Strep Ag.
- PCR
- Procal (<0.1).



- A definitive diagnosis of pneumonia requires evidence of consolidation on **chest X-ray.**

- Gram is + in 80% of Strep P.
- Blood Cx + only in 20-25% of Strep P.
- Blood Cx unlikely to be + in H-Flu, Pseudomonas, Moraxella.
- Strep Ag: 77-88% +
- Legionella Serotype 1: 74%.

Site of Care

Depends on many variables:

- **Severity of illness**
- **Associated disease**
- **Presence of hypoxemia**
- **Adequacy of home support**
- **Probability of adherence to treatment.**

Table 4. CURB-65 Severity Score

Clinical Criteria	Points
Confusion	1
Blood Urea nitrogen >20 mg/dL	1
Respiratory rate ≥30 breaths/min	1
Blood pressure (systolic <90 mmHg *or* diastolic ≤60 mmHg)	1
Age ≥65 y	1
Total Score	**Recommendations**
0-1	Low risk; outpatient treatment
2	Moderately severe; short inpatient hospitalization or closely supervised outpatient treatment
3-5	Severe pneumonia; hospitalization required; consider ICU admission

Source: Reference 11.

Treatment

- Should be initiated promptly and at the point of care where the diagnosis of pneumonia was first made.
- Outpa
- For o ents, IDSA 25%) +/- Amox
- For outpatients with coexisting illnesses or recent use of antimicrobial agents: Respiratory Quinolones alone or a beta-lactam (e.g., amoxicillin–clavulanate) plus a macrolide.

UpToDate:

- **For most patients in this category, we treat with amoxicillin-clavulanate plus a macrolide (ie, azithromycin, clarithromycin) or doxycycline.**
- **In general, we prefer macrolides over doxycycline; improved outcomes in patients with more severe CAP (possibly due to their immunomodulatory effect)**

Pneumonia (community-acquired): antimicrobial prescribing

Choice of antibiotic: adults aged 18 years and over

LOW SEVERITY PNEUMONIA

(community-acquired) based on clinical judgement and guided by CRB65 score 0 or CURB65 score 0 or 1

Amoxicillin	Doxycycline	Clarithromycin	Erythromycin (in pregnancy)
500mg three times a day (higher doses can be used – see BNF) for 5 days	200 mg on first day, then 100 mg once a day for 4 days (5-day course in total)	500 mg twice a day For 5 days	500 mg four times a day For 5 days

Alternative oral antibiotics if low severity, for penicillin allergy or if amoxicillin unsuitable (for example, atypical pathogens suspected)

MODERATE SEVERITY PNEUMONIA

(community-acquired) based on clinical judgement and guided by CRB65 score 1 or 2 or CURB65 score 2; guided by microbiological results when available

Amoxicillin with (if atypic pathogens suspected) with	Clarithromycin or	Erythromycin (in pregnancy)	Doxycycline	Clarithro -mycine
500mg three times a day (higher doses can be used – see BNF) for 5 days	500mg twice a day for 5 days	500 mg four times a day for 5 days	200 mg on first day, then 100 mg once a day for 4 day (5-day course in total)	500 mg Twice a day for 5 days

Alternative oral antibiotics if moderate severity, for penicillin allergy; guided by microbiological results when available

HIGH SEVERITY PNEUMONIA

(community-acquired) based on clinical judgement and guided by CRB65 score 3 or 4 or CURB65 score 3-5; guided by microbiological results when available

Co Amoxiclav with	Clarithromycin or	Erythromycin (in pregnancy)	Levofloxacin (consider safety issues)
500/125 mg three times a day orally or 1.2 g three times a day IV for 5 days	500 mg twice a day orally or IV for 5 days	500 mg four times a day orally for 5 days	500 mg twice a day orally or IV for 5 days

Alternative oral antibiotics if high severity, for penicillin allergy; guided by microbiological results when available

NICE National Institute for Health and Care Excellence

NICE guideline 2019

GOV.UK Topics Government activity

Home > Drug Safety Update

Fluoroquinolone antibiotics: new restrictions and precautions for use due to very rare reports of disabling and potentially long-lasting or irreversible side effects

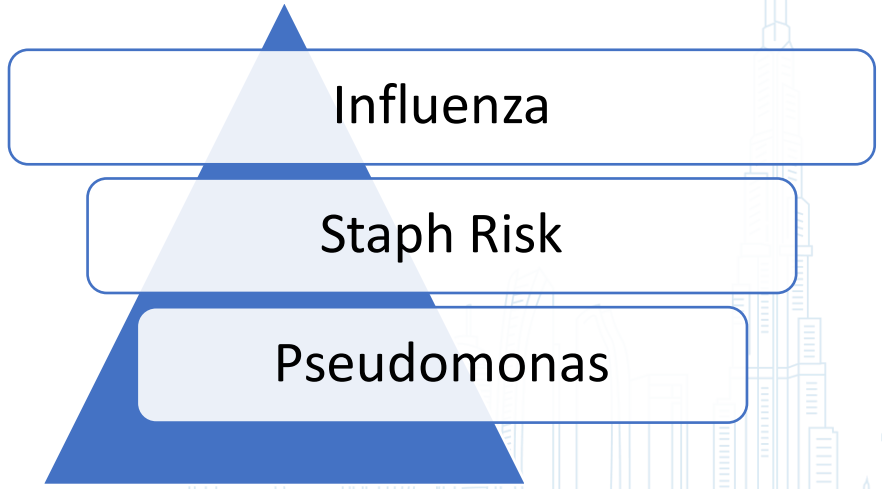
Disabling, long-lasting or potentially irreversible adverse reactions affecting musculoskeletal and nervous systems have been reported very rarely with fluoroquinolone antibiotics. Fluoroquinolone treatment should be discontinued at the first signs of a serious adverse reaction, including tendon pain or inflammation.

From: Medicines and Healthcare products Regulatory Agency

Published 21 March 2019

In Hospital Treatment

- In patients requiring hospitalization and in whom no cause of infection is immediately apparent, IDSA/ATS guidelines recommend empirical therapy with either a beta-lactam plus a macrolide or a quinolone alone.
- ICU Admission
  - Special Considerations:



Duration of therapy

- 5- 7 days in outpatient
- 5-7 days in inpatient who are improving

- Staph might need 2 weeks and if hematogenous: 4 weeks.

- Cavitating pneumonia and lung abscesses are usually treated for several weeks; some experts continue treatment until cavities have resolved.

Steroids….

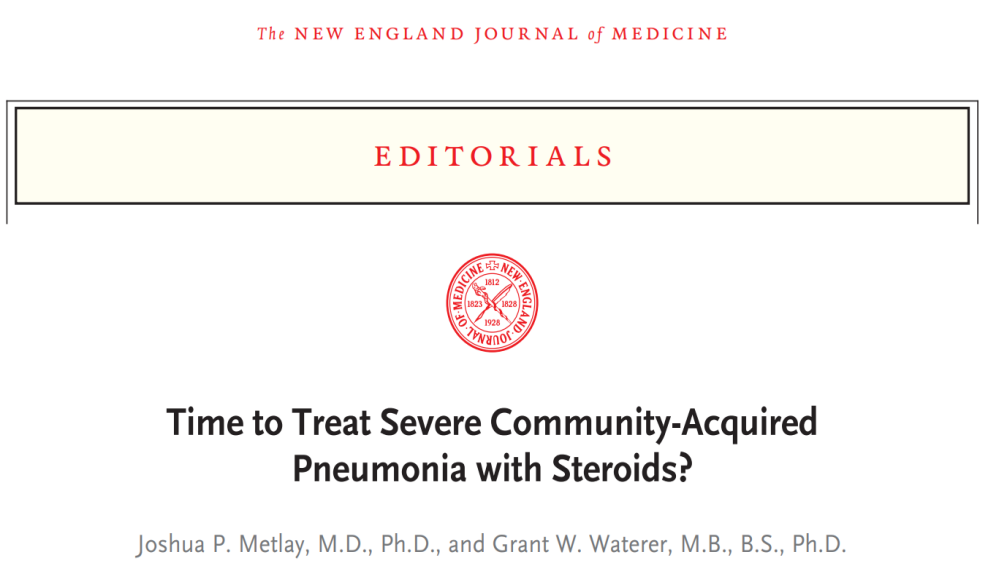
ORIGINAL ARTICLE

Hydrocortisone in Severe Community-Acquired Pneumonia

Pierre-François Dequin, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-Pierre Quenot, M.D., Ph.D., Toufik Kamel, M.D., Jean-Damien Ricard, M.D., Ph.D., Julio Badie, M.D., Jean Reignier, M.D., Ph.D., Nicholas Heming, M.D., Ph.D., Gaëtan Plantefève, M.D., Bertrand Souweine, M.D., Ph.D., Guillaume Voiriot, M.D., Ph.D., Gwenhaël Colin, M.D., et al., for the CRICS-TriGGERSep Network*

May 25, 2023
N Engl J Med 2023; 388:1931-1941
DOI: 10.1056/NEJMoa2215145

Recommendations:



The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Time to Treat Severe Community-Acquired Pneumonia with Steroids?

Joshua P. Metlay, M.D., Ph.D., and Grant W. Waterer, M.B., B.S., Ph.D.

From the Department of Medicine, Massachusetts General Hospital and Harvard Medical School — both in Boston (J.P.M.); and Royal Perth Hospital and University of Western Australia — both in Perth, Australia (G.W.W.).

* Early < 24 hours initiation

- Respiratory failure needing at least high flow.
- ICU admission

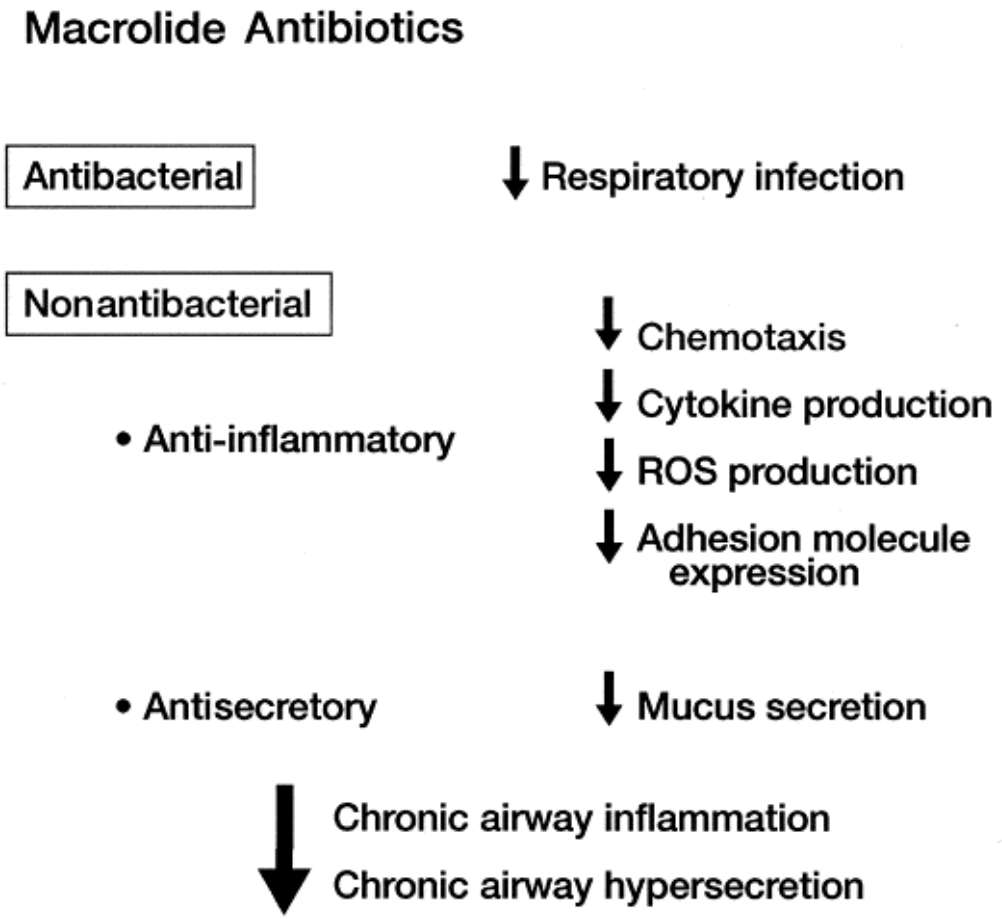
- **Excluding:**
  - Influenza
  - Septic Shock

Lack of Response:

Table 4. Reasons for a Lack of Response to Treatment of CAP.

Correct organism but inappropriate antibiotic choice or dose
Resistance of organism to selected antibiotic
Wrong dose (e.g., in a patient who is morbidly obese or has fluid overload)
Antibiotics not administered
Correct organism and correct antibiotic but infection is loculated (e.g., most commonly empyema)
Obstruction (e.g., lung cancer, foreign body)
Incorrect identification of causative organism
No identification of causative organism and empirical therapy directed toward wrong organism
Noninfectious cause
Drug-induced fever
Presence of an unrecognized, concurrent infection

Immunomodulatory Effects of Macrolides



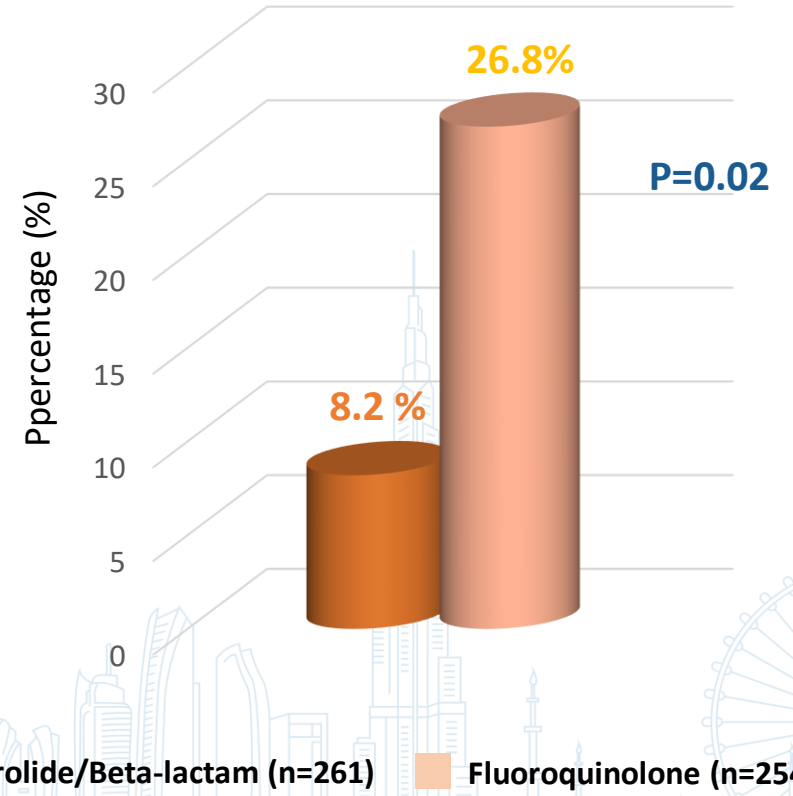
Jun Tamaoki, Junichi Kadota, Hajime Takizawa,
Clinical implications of the immunomodulatory effects of macrolides,
The American Journal of Medicine Supplements, Volume 117, Issue 9, Supplement 1,

2004, Pages 5-11, ISSN 1548-2766,

Clarithromycin Beta Lactam combination reduces mortality in Community Acquired Pneumonia in hospitalized patients

Mortality at 14 days
was significantly lower following a macrolide-beta-lactam combination than fluoroquinolone monotherapy for the treatment of CAP in 515 hospitalized patients[1]

14-Day Mortality following at least 48 hours of treatment for CAP[1]



1. Lodise TP, Kwa A, Cosler L, et al. Comparison of β-lactam and macrolide combination therapy versus fluoroquinolone monotherapy in hospitalized veterans affairs patients with community-acquired pneumonia. Antimicrob Agents Chemother 2007;51(11):3977–3982.

Access Study 2024

Articles

Clarithromycin for early anti-inflammatory responses in community-acquired pneumonia in Greece (ACCESS): a randomised, double-blind, placebo-controlled trial

Evangelos J Giamarellos-Bourboulis, Athanasios Siampanos, Amalia Bolanou, Sarantia Doulou, Nikolaos Kakavoulis, Konstantinos Tsiakos, Sokratis Katopodis, Georgios Schinas, Lamprini Skorda, Zoi Alexiou, Konstantinos Armenis, Paraskevi Katsaounou, George Chrysos, Aikaterini Masgala, Garyphalia Poulakou, Nikolaos Antonakos, Asimina Safarika, Miltiades Kyprianou, Konstantina Dakou, Styliani Gerakari, Ilias C Papanikolaou, Haralampos Milionis, Markos Marangos, George N Dalekos, Vasiliki Tzavara, Karolina Akinosoglou, Eryfilli Hatziaggelaki, Styliani Sympardi, Theano Kontopoulou, Maria Mouktaroudi, Antonios Papadopoulos, Michael S Niederman

Summary

Background Addition of macrolide antibiotics to β-lactam antibiotics for the treatment of patients in hospital with community-acquired pneumonia is based on results from observational studies and meta-analyses rather than randomised clinical trials. We investigated if addition of the macrolide clarithromycin to treatment with a β-lactam antibiotic in this population could improve early clinical response—the new regulatory endpoint for community-acquired pneumonia—and explored the possible contribution of modulation of the inflammatory host response to that outcome.

Lancet Respir Med 2024

Published Online
January 3, 2024
https://doi.org/10.1016/S2213-2600(23)00412-5

This online publication has been corrected.

Study Design

- ACCESS was conducted at multiple public hospitals within Greece from 2021 to 2023
- Pneumonia plus 2 signs of SIRS
- A total of 278 patients were enrolled in the trial and randomized to standard care with or without oral clarithromycin (500 mg tablets every 12 hours for a week).
  - Over 60% of the patient population were men, and all of the patients were white.

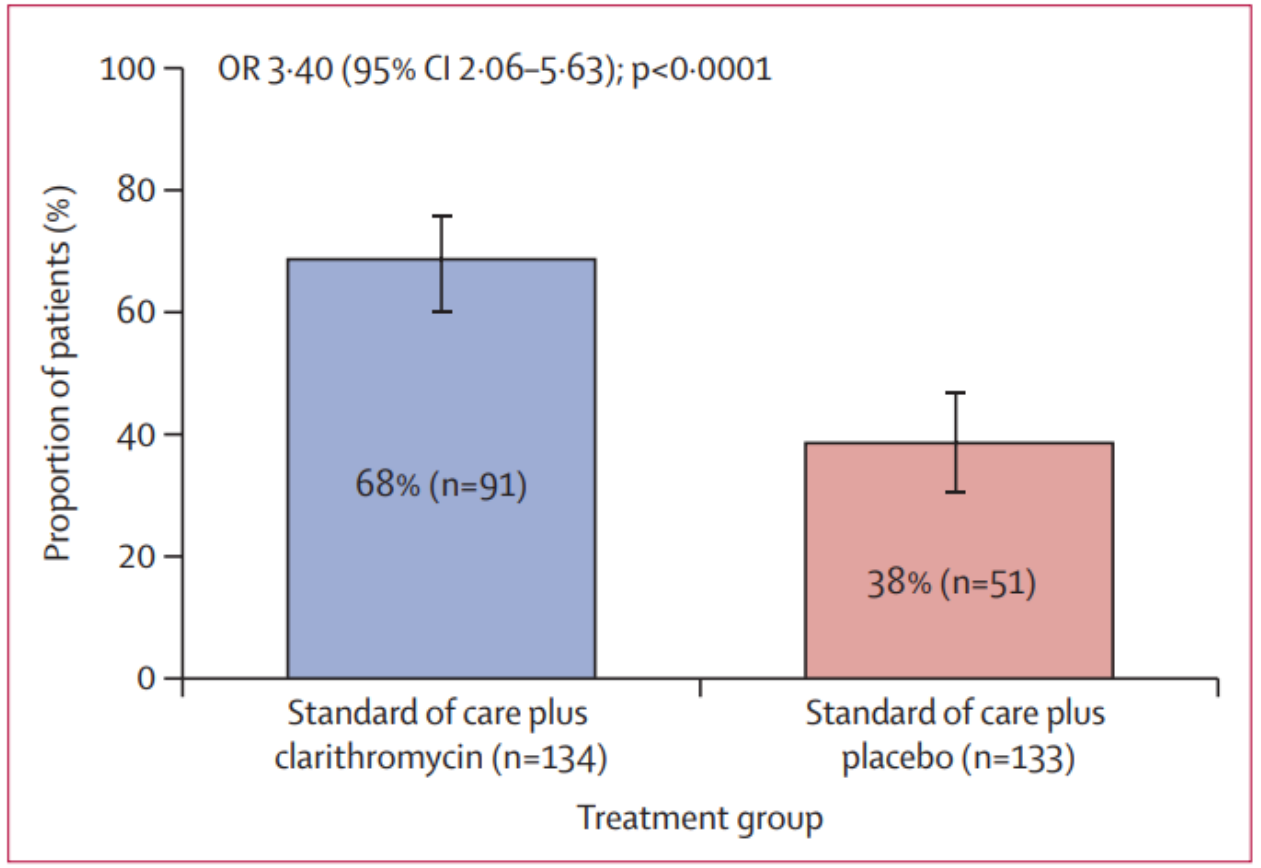
Primary Endpoint

- The composite primary endpoint is assessed at day 4 of treatment and requires two components to be met:
  - (1) early clinical response as defined by the European Medicines Agency and the US Food and Drug Administration (any 50% or more decrease in respiratory symptom severity score compared with visit 1

AND

  - (2) any 30% or more decrease in Sequential Organ Failure Assessment score or favorable change in procalcitonin kinetics (defined as ≥80% decrease in procalcitonin compared with visit 1 or blood procalcitonin

Primary composite study endpoint



Results

- Individual components of the primary endpoint all favored the clarithromycin group over controls:
  - Decreases in respiratory symptom severity scores of at least 50% from baseline: 72% vs 48% (OR 2.83, 95% CI 1.70-4.70)
  - Decrease of 30% or more in SOFA score: 68% vs 41% (OR 3.10, 95% CI 1.88-5.11)
  - Favorable change in procalcitonin kinetics: 69% vs 54% (OR 1.86, 95% CI 1.12-3.06)

Results

	Standard of care plus clarithromycin (n= 134)	Standard of care plus placebo (n=133)	Difference, % (95% CI)	Odds ratio (95% CI)	p value
Primary study endpoint					
Composite* primary endpoint met by day 4	91 (68%; 60 to 75)	51 (38%; 31 to 47)	29·6% (17·7 to 40·3)	3·40 (2·06 to 5·63)	<0·0001
Secondary study endpoints					
≥50% decrease in respiratory symptom severity score at day 4	97 (72%; 64 to 79)	64 (48%; 40 to 57)	24·3% (12·6 to 35·1)	2·83 (1·70 to 4·70)	<0·0001
≥30% decrease in SOFA score at day 4	91 (68%; 60 to 75)	54 (41%; 33 to 49)	27·3% (15·4 to 38·1)	3·10 (1·88 to 5·11)	<0·0001
Favourable procalcitonin kinetics† at day 4	92 (69%; 60 to 79)	72 (54%; 46 to 62)	14·5% (2·8 to 25·7)	1·86 (1·12 to 3·06)	0·017
Favourable procalcitonin kinetics† at end-of-treatment visit (day 8)	104 (78%; 70 to 84)	88 (66%; 58 to 74)	11·5% (0·6 to 21·9)	1·77 (1·03 to 3·05)	0·042
≥50% decrease in SOFA score at end-of-treatment visit (day 8)	84 (63%; 54 to 70)	66 (50%; 41 to 58)	13·1% (1·2 to 24·5)	1·70 (1·05 to 2·78)	0·036
Clinical success at end-of-treatment visit (day 8)	43 (32%; 25 to 40)	23 (17%; 12 to 25)	14·8% (4·5 to 24·8)	2·26 (1·27 to 4·03)	0·0067
Clinical success at test-of-cure visit (day 14)	92 (69%; 60 to 76)	71 (53%; 45 to 62)	15·3% (3·6 to 26·4)	1·91 (1·16 to 3·15)	0·012
Clinical success at day 28	83 (62%; 54 to 70)	66 (50%; 41 to 58)	12·3% (0·4 to 49·6)	1·65 (1·02 to 2·69)	0·049
Progression to organ dysfunction by day 28‡	8 (6%; 3 to 11)	23 (17%; 12 to 25)	11·3% (3·7 to 19·2)	0·30 (0·13 to 0·71)	0·0041
Development of new sepsis by day 28‡	18 (13%; 9 to 20)	32 (24%; 18 to 32)	10·6% (1·2 to 19·8)	0·49 (0·26 to 0·93)	0·029
Discharge alive by day 90	106 (79%; 72 to 85)	83 (62%; 54 to 70)	16·7% (5·8 to 27·1)	2·28 (1·32 to 3·93)	0·031
Mortality by day 28§	27 (20%; 14 to 28)	35 (26%; 20 to 34)	6·2% (–3·9 to 16·2)	0·70 (0·39 to 1·25)	0·25
Mortality by day 90§	46 (34%; 27 to 43)	50 (38%; 30 to 46)	3·3% (–8·2 to 14·6)	0·87 (0·52 to 1·43)	0·61
Hospital readmission by day 90	11 (8%; 5 to 14)	20 (15%; 10 to 22)	6·8% (–0·9 to 14·7)	0·51 (0·23 to 1·10)	0·089

Data are n (%; 95% CI) unless otherwise stated. SOFA=Sequential Organ Failure Assessment. *Composite primary endpoint was (1) a 50% or more decrease in respiratory symptom severity score compared with visit 1; and (2) a 30% or more decrease in SOFA score compared with visit 1 or favourable change in procalcitonin kinetics (defined as ≥80% decrease in procalcitonin compared with visit 1 or blood procalcitonin <0·25 ng/mL), or both. †For definition of favourable procalcitonin kinetics, see previous footnote. ‡According to the protocol, this endpoint was scheduled at day 90. However, data were censored at day 28 because no new events occurred after day 28. §Includes patients dying early.

Table 2: **Primary and secondary study endpoints**

Conclusion:

- **Diagnosis Criteria**
  - Confirmed through symptomology and clinical signs consistent with pneumonia.
  - Evidence of a new lung infiltrate visible on radiological imaging.

- **Outpatient Treatment**
  - Mild cases typically managed with empirical therapy, without specific bacterial identification.
  - Consider testing for SARS-CoV-2 and influenza as part of the diagnostic workup.

- **Hospitalized Patient Management**
  - In-depth microbiological testing is advised to identify causative pathogens and tailor therapy accurately.

- **Antimicrobial Therapy Selection**
  - Based on the severity of the illness, existing comorbidities, and potential for antimicrobial resistance.
  - All international guidelines recommend the addition of a macrolide.