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Management of the reemergence of respiratory tract infections

Zahia Chahine Elsett, MD

Reemergence???

Decrease in the viral and bacterial respiratory infections during confinement for Covid pandemia

Cross-sectional study

February 1, 2022

Prevalence of Common Infectious Diseases After COVID-19 Vaccination and Easing of Pandemic Restrictions in Israel

Shimon Amar, MD[1,2]; Yonat Shemer Avni, PhD[3]; Norm O'Rourke, PhD[4]; et alTal Michael, MPH[5]
Author Affiliations Article Information

JAMA Netw Open. 2022;5(2):e2146175.
doi:10.1001/jamanetworkopen.2021.46175

Cross-sectional study

386 711 patients in community clinics in Israel

- increase in incidence rates of various infections ,viral and bacterial , among all age groups during 3 months after the easing of COVID-19–related social restrictions.

NB: viral infections will predispose to bacterial superinfections

Research Article | Open Access
Volume 2022 | Article
ID 4915678 | https://doi.org/10.1155/2022/4915678

Resurgence of Respiratory Viruses after Relaxation of COVID-19 Containment Measures: A Real-World Data Study from a Regional Hospital of Italy

findings

extremely low prevalence of influenza virus among hospitalized patients and outpatients during the first two COVID-19 winter seasons, with a reemergence of respiratory syncytial virus in the late 2021.

WHO

Case numbers for infections like Strep A, flu and RSV have risen since the pandemic

BJCP British Journal of Clinical Pharmacology

Changes in antibiotic prescribing following COVID-19 restrictions: Lessons for post-pandemic antibiotic stewardship

Malcolm B. Gillies, David P. Burgner, Lorraine Ivancic, Natasha Nassar, Jessica E. Miller, Sheena G. Sullivan, Isobel M. F. Todd, Sallie-Anne Pearson, Andrea L. Schaffer, Helga Zoega

First published: 17 August 2021

RESULTS

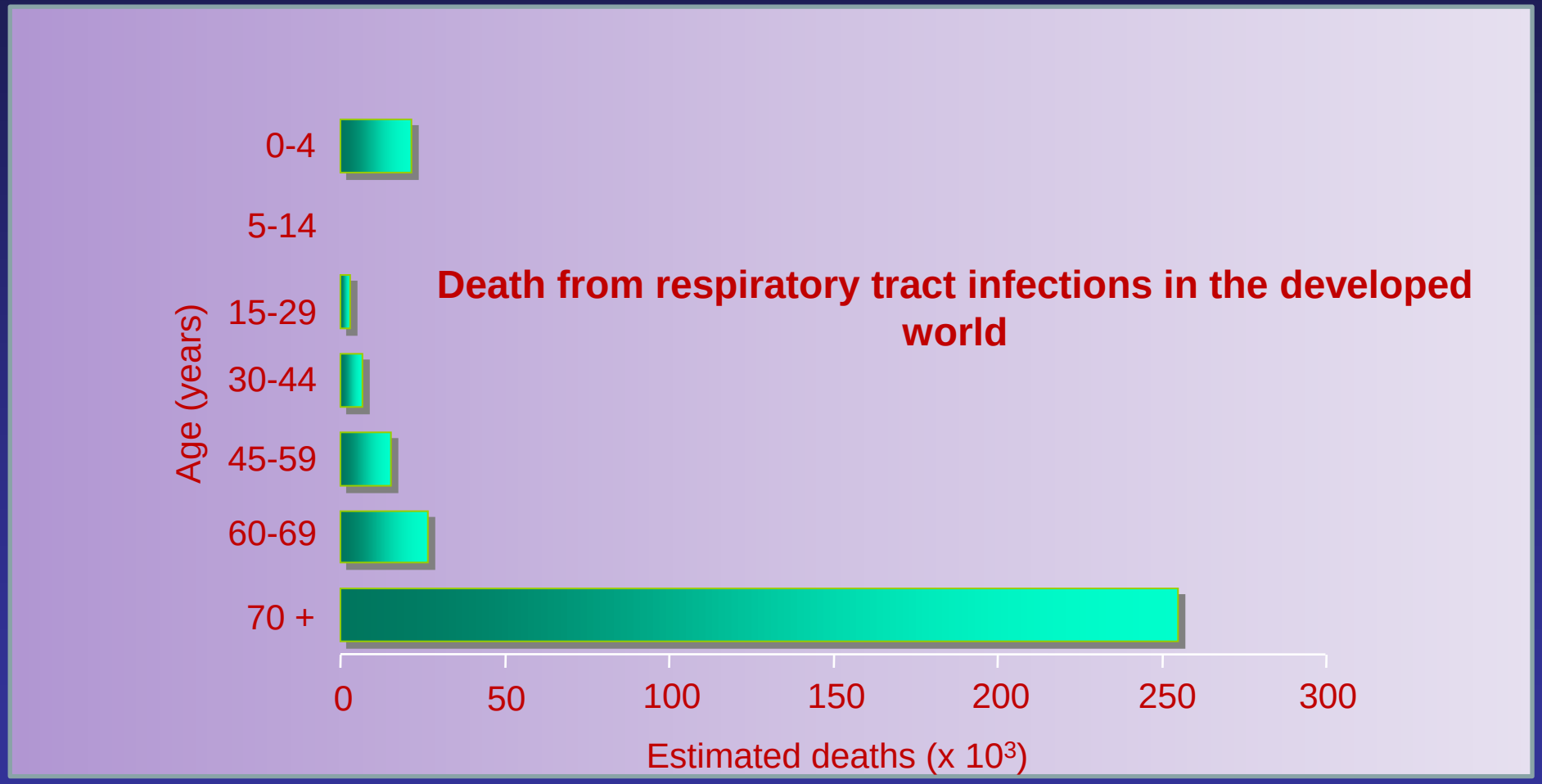
- *community antibiotic use fell dramatically in many countries several months into the COVID-19 pandemic.*

Antibiotics recommended for treatment of respiratory tract infections showed large reductions (range 51–69%),

Antibiotics for non-respiratory infections were unchanged.

Respiratory Tract Infections

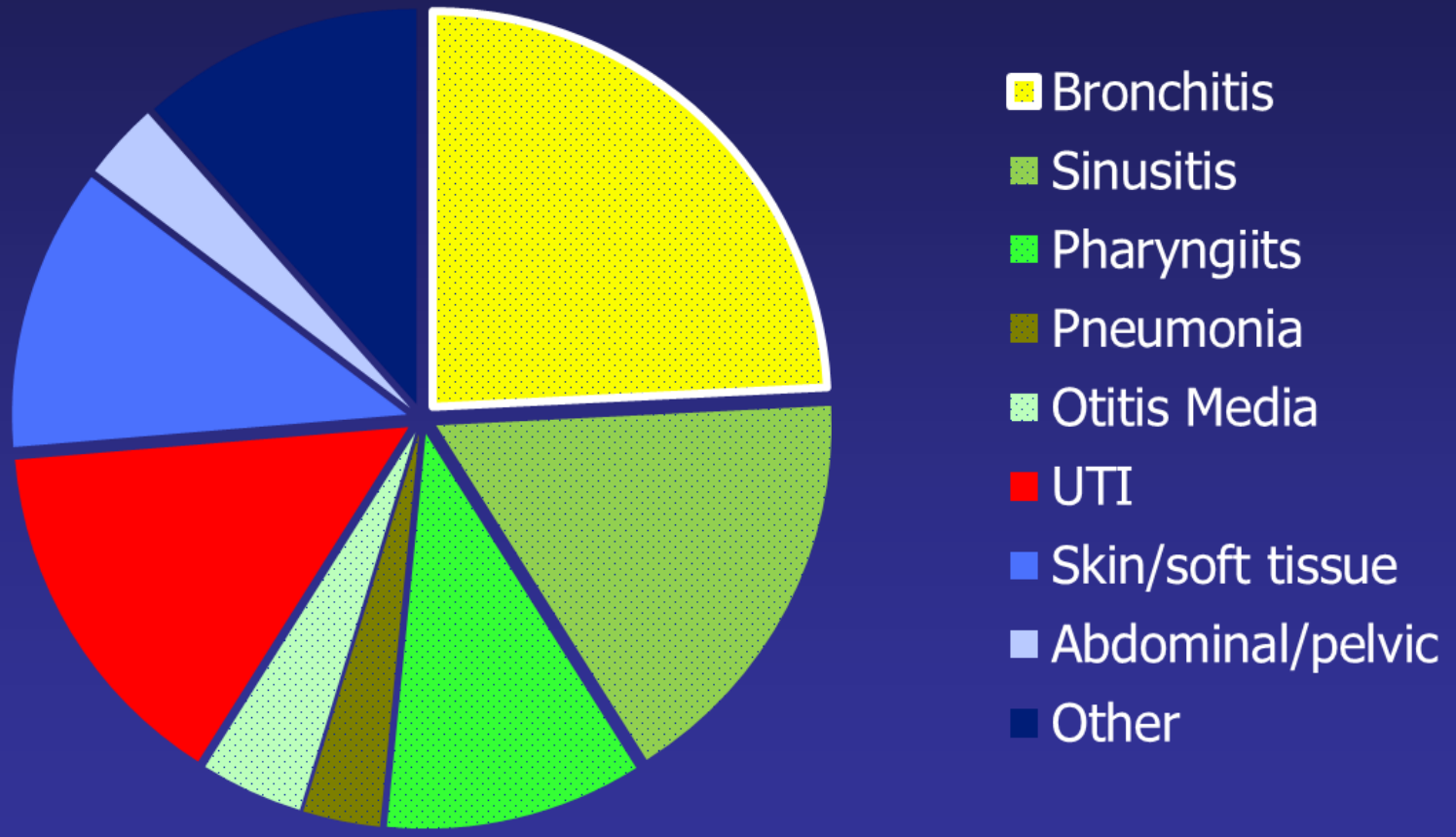
A major cause of mortality



Murray & Lopez. Bull World Health Organ 1994 ; 72 : 447-80

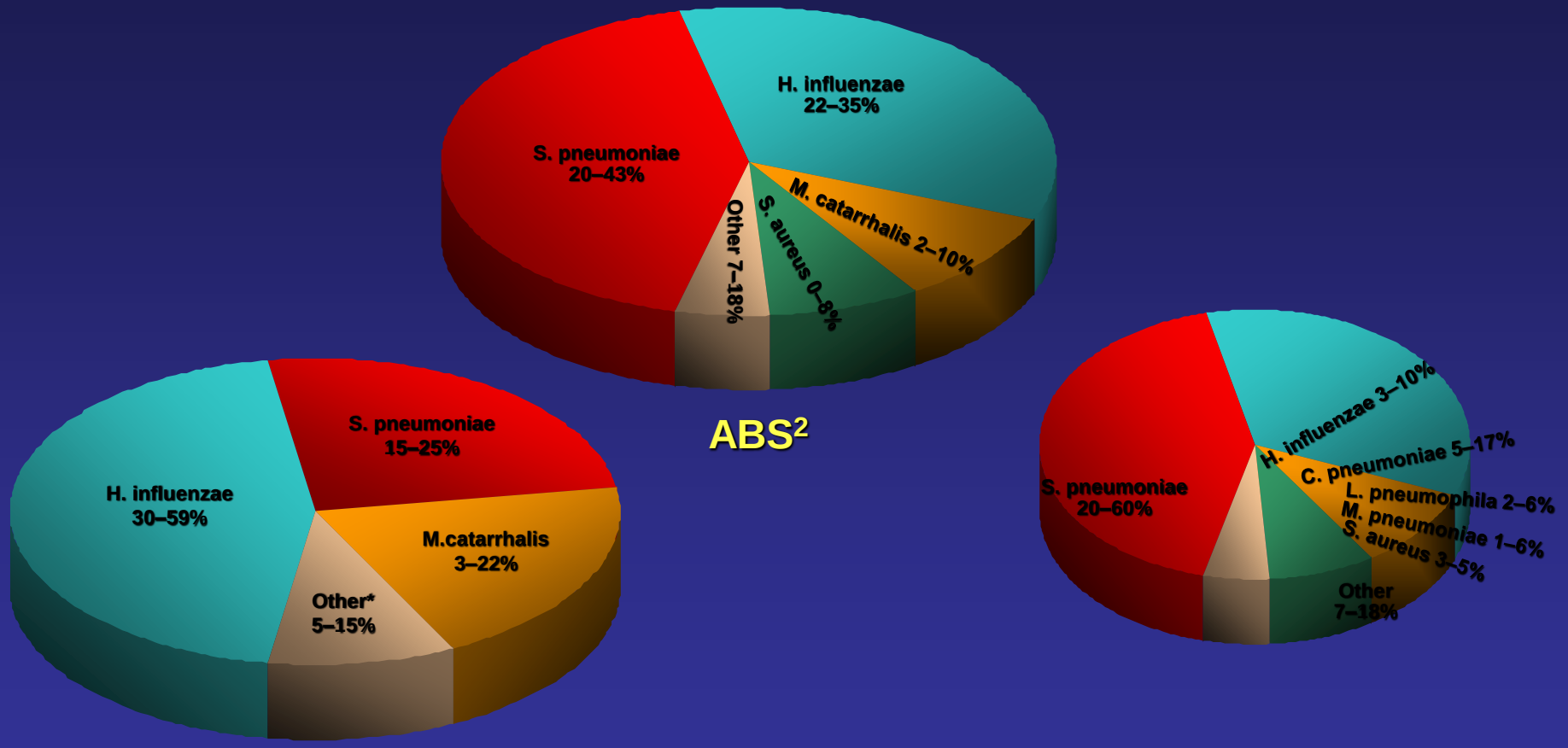
Over half of Antibiotic Use in Adults is for Respiratory Tract Infections

Adult Oral Antibiotic Use by Diagnosis



2004-2005 Physician Drug & Diagnosis Audit (PDDA)

Bacterial Etiology in RTIs



AECB = Acute Exacerbation of Chronic Bronchitis; ABS = Acute Bacterial Sinusitis; CAP = Community-Acquired Pneumonia
*Other pathogens include Staphylococcus aureus, Pseudomonas aeruginosa

1. Guthrie R. Chest 2001; 2. Sinus and Allergy Health Partnership. Otolaryngol Head Neck Surg 2004; 3. Bartlett JG, Mundy LM. N Engl J Med 1995

World Health Organization
report based on data from 87 countries in 2020 -----
Antimicrobial resistance is high

Increased drug resistance in bacteria causing bloodstream infections, including against last-resort antibiotics, was seen in the first year of the coronavirus pandemic,

The overuse and/or misuse of antibiotics has helped microbes to become resistant to many treatments, while the pipeline of replacement therapies in development is alarmingly sparse,

WHO

-Warns of too few new drugs for deadly superbugs

-We have arrived in the post-antibiotic era

MACROLIDES

- The macrolides (macrocyclic lactones) are a group of *bacteriostatic* antibiotics
- Erythromycin is the first member discovered in the 1950s.
- Oleandomycin, troleandomycin, spiramycin, josamycin, tilmicosin, and tylosin.
- Roxithromycin, Clarithromycin and Azithromycin are the later additions.

Ref. Dr Kumari Anjana – Macrolides and Lincosamides

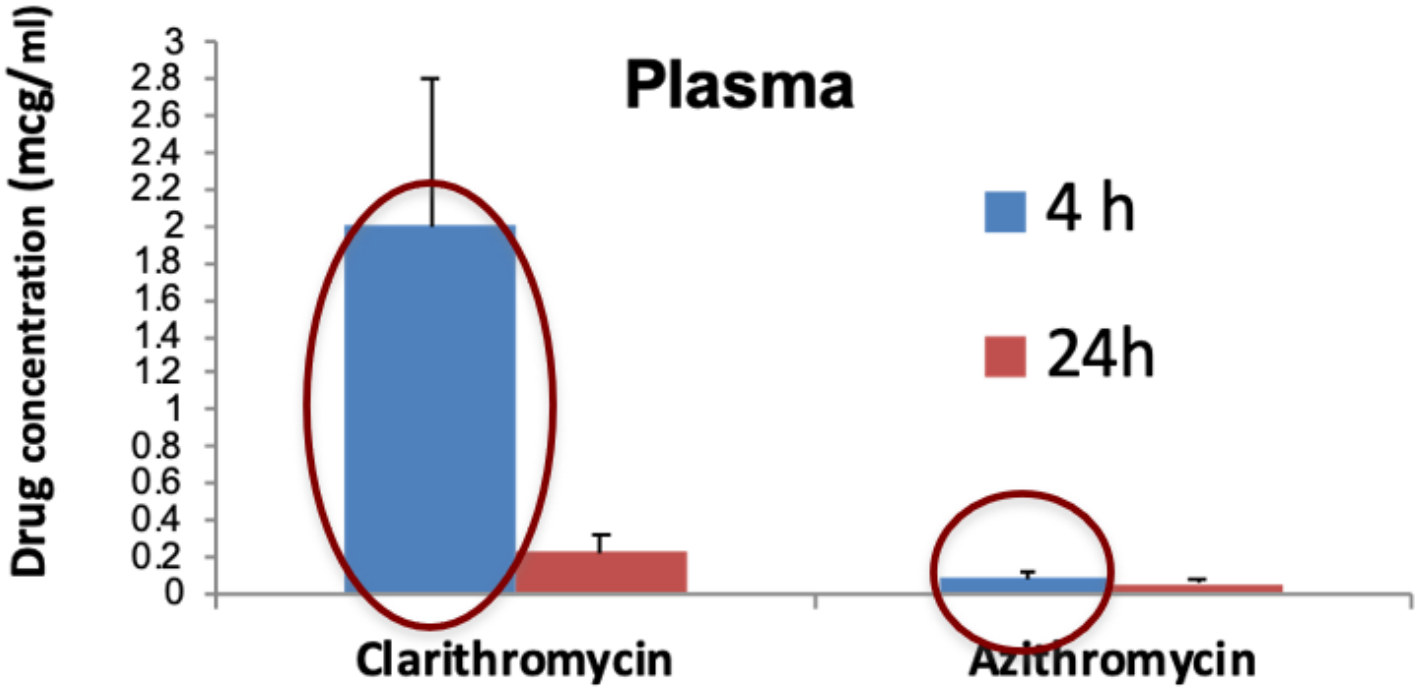
NEWER MACROLIDES

- To overcome the limitations of erythromycin:
  - narrow spectrum activity,
  - poor tissue penetration,
  - gastric acid liability,
  - low oral bioavailability, and
  - short half life.

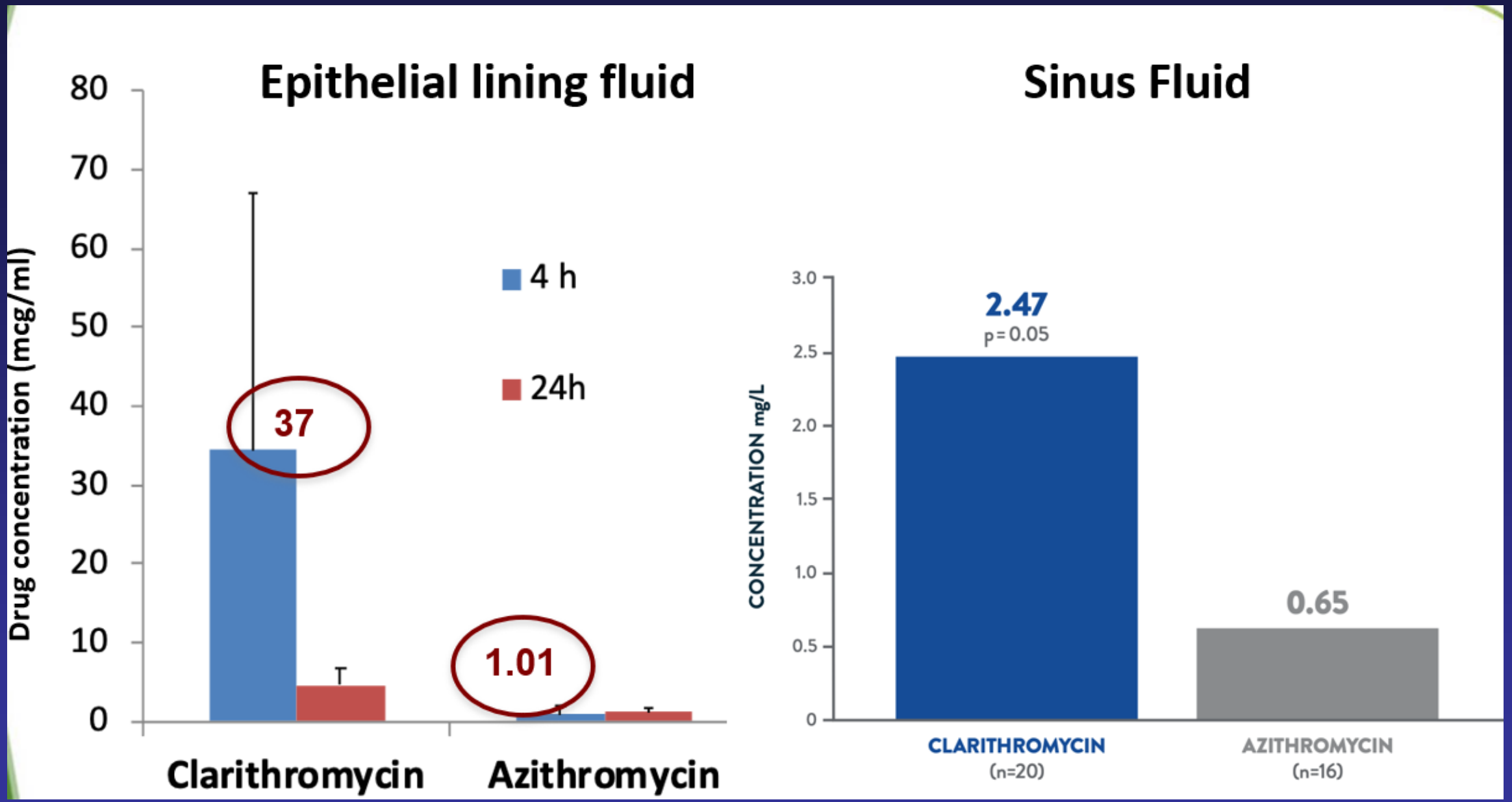
Ref. Dr Kumari Anjana – Macrolides and Lincosamides

Pharmacokinetics

Parameter	Azithromycin	Clarithromycin	14-Hydroxy-clarithromycin
C_{max} (µg/ml)	0.1 - 0.4	2.1 – 2.4	0.6 – 1.0
Half – life (hrs)	68	4.6	6.0

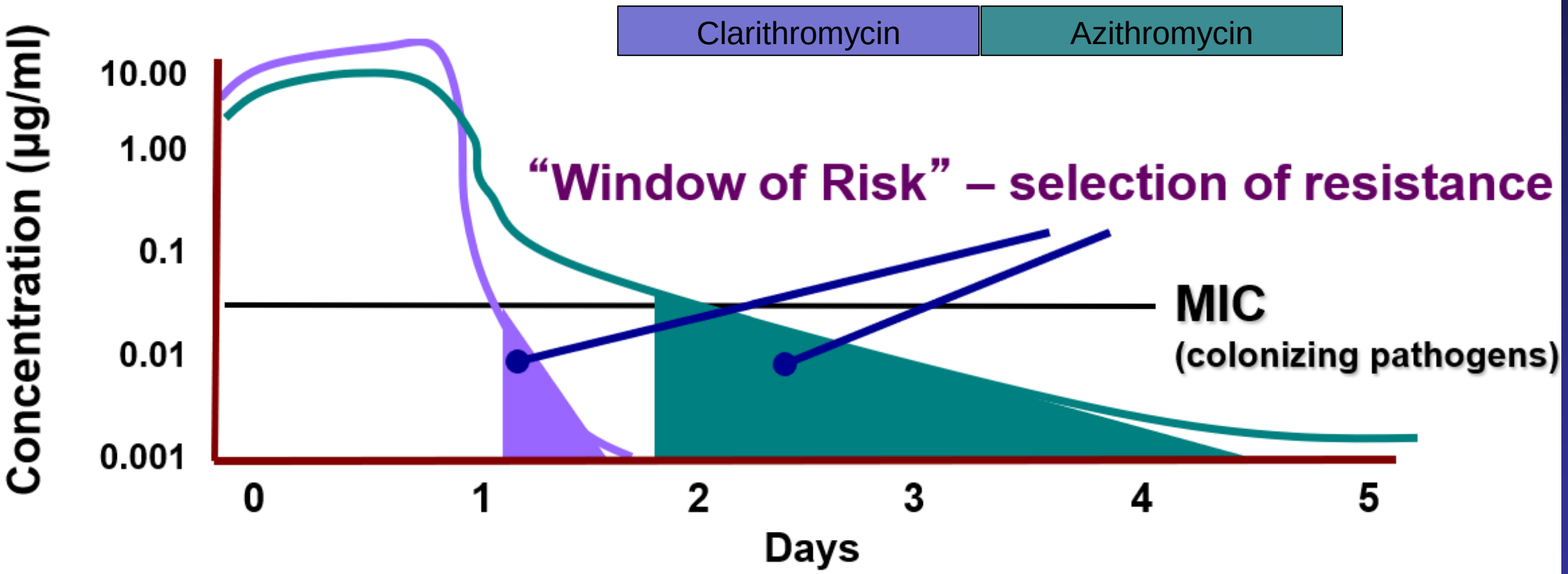


Infection and Drug Resistance 2019:12 585–596



Infection and Drug Resistance 2019:12 585–596

Antimicrobial Half-Life



Antibiotics with a long half life (Azithromycin) may preferentially select resistant organisms due to exposure of colonizing bacteria to sub-therapeutic antimicrobial levels for a sustained period of time.

Infection and Drug Resistance 2019:12 585–596

Active metabolite= 14-hydroxyclarithromycin

- act synergistically both in vitro and in vivo with its parent molecule, enhancing the anti-*Haemophilus* activity of the macrolide.

- Bergeron et al and Hoover et al were able to demonstrate synergy between clarithromycin and 14-HC against some strains of *Haemophilus*, as well as *Enterococcus* and *Staphylococci*.

bactericidal effect of clarithromycin and 14-HC combinations was additive in 92% of all strains of H. influenzae and synergistic in the other 8%, with no evidence of influence from the presence/absence of a beta-lactamase.

Infection and Drug Resistance 2019:12 585–596

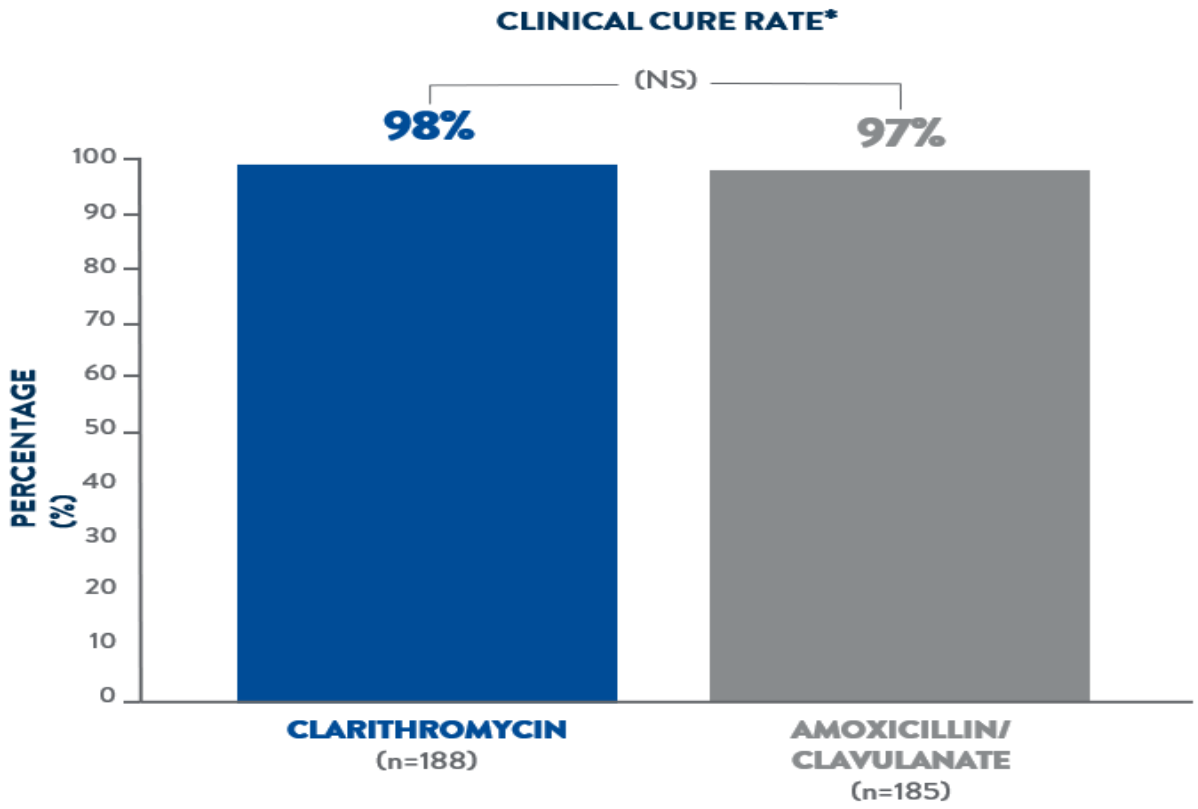
CLARITHROMYCIN IN ADULTS

SINUSITIS

LEV2273159

CLARITHROMYCIN IS COMPARABLE

WITH AMOXICILLIN/CLAVULANATE FOR CLINICAL CURE RATE



DOSE REGIMEN:

CLARITHROMYCIN 1000 mg OD FOR 14 DAYS
(n=188) TOTAL NUMBER OF PATIENTS

AMOXICILLIN/CLAVULANATE 875/125 mg BID FOR 14 DAYS
(n=185) TOTAL NUMBER OF PATIENTS

Adapted from Riffer *et al.* 2005.

*Conducted up to 10 days following the completion of treatment.

BID, twice daily; NS, not significant; OD, once daily.

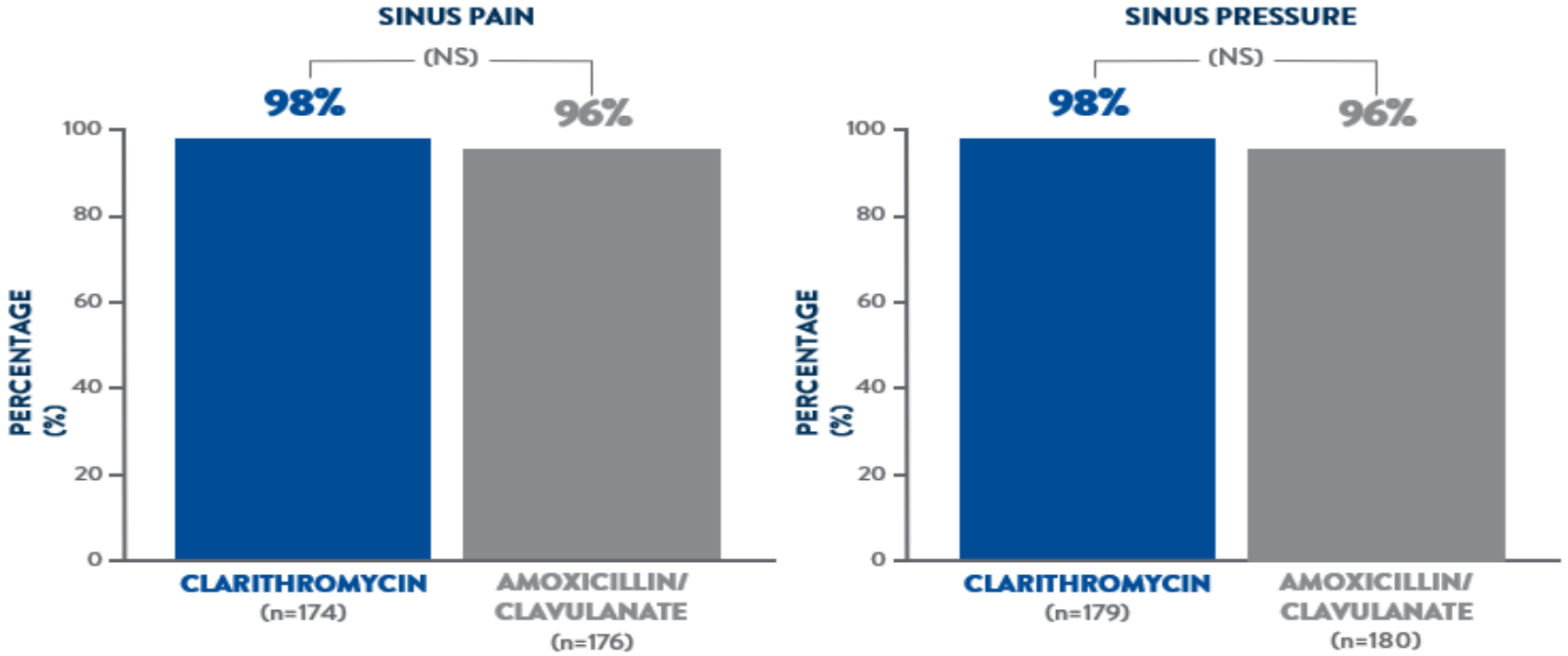
Study design: multicentre, randomised, investigator-blinded. 437 patients (aged ≥12 years) with signs/symptoms and radiographic findings of uncomplicated acute bacterial sinusitis were randomised to receive clarithromycin 1000 mg OD for 14 days or amoxicillin/clavulanate 875/125 mg BID for 14 days. Study objective: to compare the efficacy and tolerability of clarithromycin versus amoxicillin/clavulanate for the treatment of acute bacterial sinusitis.

REFERENCES

Riffer E, Spiller J, Palmer R, *et al*. Once daily clarithromycin extended-release vs twice-daily amoxicillin/clavulanate in patients with acute bacterial sinusitis: a randomized, investigator-blinded study. *Curr Med Res Opin*. 2005;21(1):61–70.-2

CLARITHROMYCIN IS AT LEAST AS EFFECTIVE AS AMOXICILLIN/CLAVULANATE FOR RESOLUTION OR IMPROVEMENT OF SINUS PAIN AND SINUS PRESSURE

Rate of resolution or improvement of pre-treatment symptoms at Test-of-Cure visit of clinically evaluable patients*



DOSE REGIMEN:

CLARITHROMYCIN 1000 mg OD FOR 14 DAYS (n=188 total number of patients)

AMOXICILLIN/ CLAVULANATE 875/125 mg BID FOR 14 DAYS (n=185 total number of patients)

Adapted from Riffer *et al.* 2005.

*Conducted up to 10 days following the completion of treatment

BID, twice daily; NS, not significant; OD, once daily.

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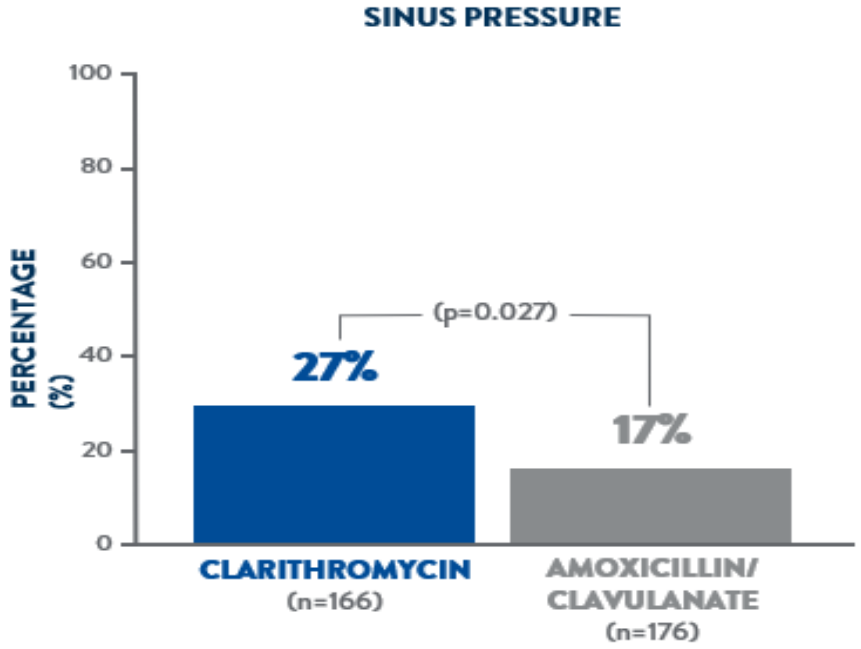
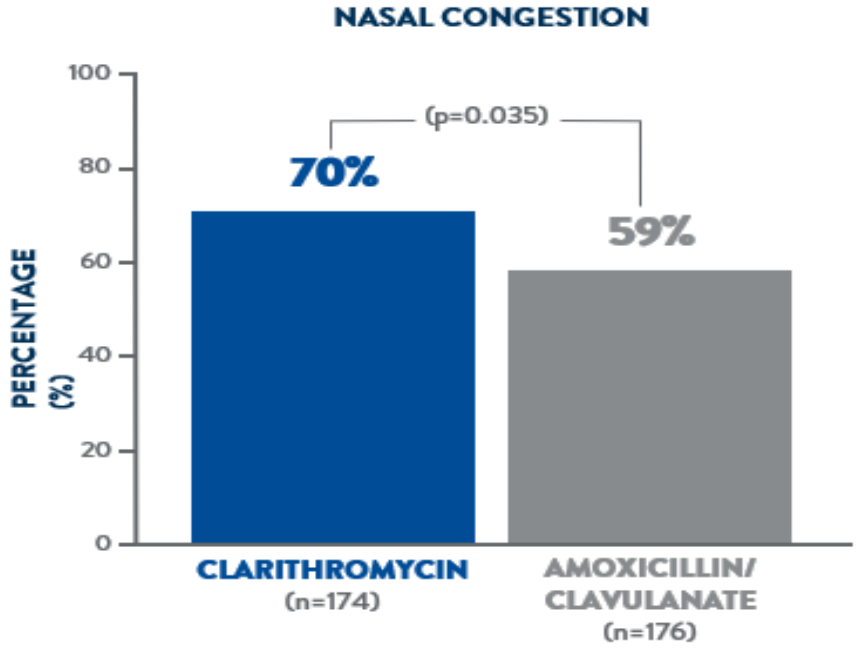
CLARITHROMYCIN SHOWED SIGNIFICANT SYMPTOMATIC IMPROVEMENT & RELIEF COMPARED TO AMOXICILLIN/CLAVULANATE AS EARLY AS 2-5 DAYS5 WITH HIGHER RESOLUTION RATE OF SINUS PRESSURE & IMPROVEMENT /RESOLUTION RATE OF NASAL CONGESTION

Difference in resolution of Sinus Pressure 2-5 days after study drug initiation



Rate of resolution or improvement of Nasal Congestion 2-5 days after study drug intitiation



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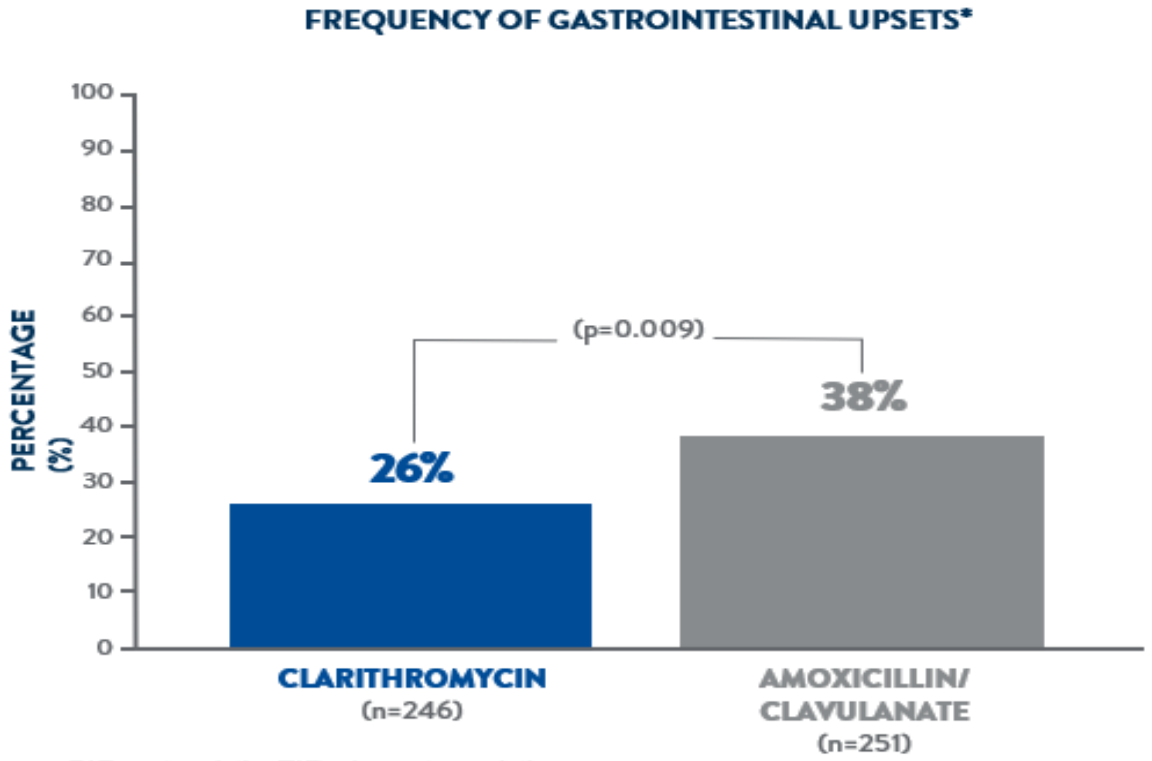
CLARITHROMYCIN IS AS EFFECTIVE AS AMOXICILLIN/CLAVULANATE WITH SIGNIFICANTLY FEWER GASTROINTESTINAL UPSETS IN ACUTE SINUSITIS



BID, twice daily; TID, three times daily.

*Most adverse events were mild or moderate in severity.

CLARITHROMYCIN
demonstrated comparable clinical success to amoxicillin/clavulanate (97% versus 93% respectively)[6]

DOSING REGIMEN:
CLARITHROMYCIN 500 mg BID
AMOXICILLIN/CLAVULANATE 500 mg TID

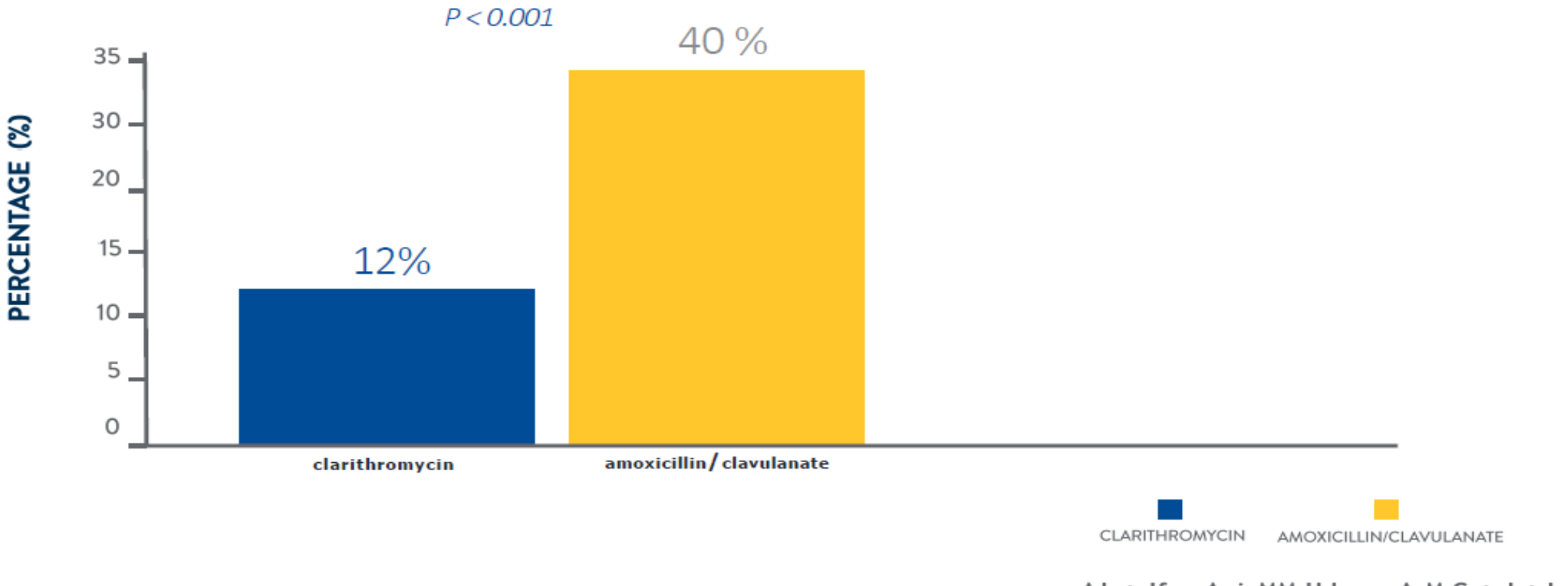
Adapted from Dubois *et al.* 1993.

Study design: single-blind (investigator-blind), randomised, multicentre trial. 497 patients (aged ≥12 years) with a diagnosis of acute maxillary sinusitis were randomised to receive clarithromycin 500 mg BID or amoxicillin/clavulanate 500 mg TID for a maximum of 14 days. Study objective: to compare the efficacy of clarithromycin with that of amoxicillin/clavulanate.

REFERENCES
Dubois J, Saint-Pierre C, Tremblay C. Efficacy of clarithromycin vs. amoxicillin/clavulanate in the treatment of acute maxillary sinusitis. *Ear Nose Throat J.* 1993;72(12):804–810.

CLARITHROMYCIN was WELL tolerated than amoxicillin/ clavulanate with a lower incidence of gastrointestinal side effects[9]

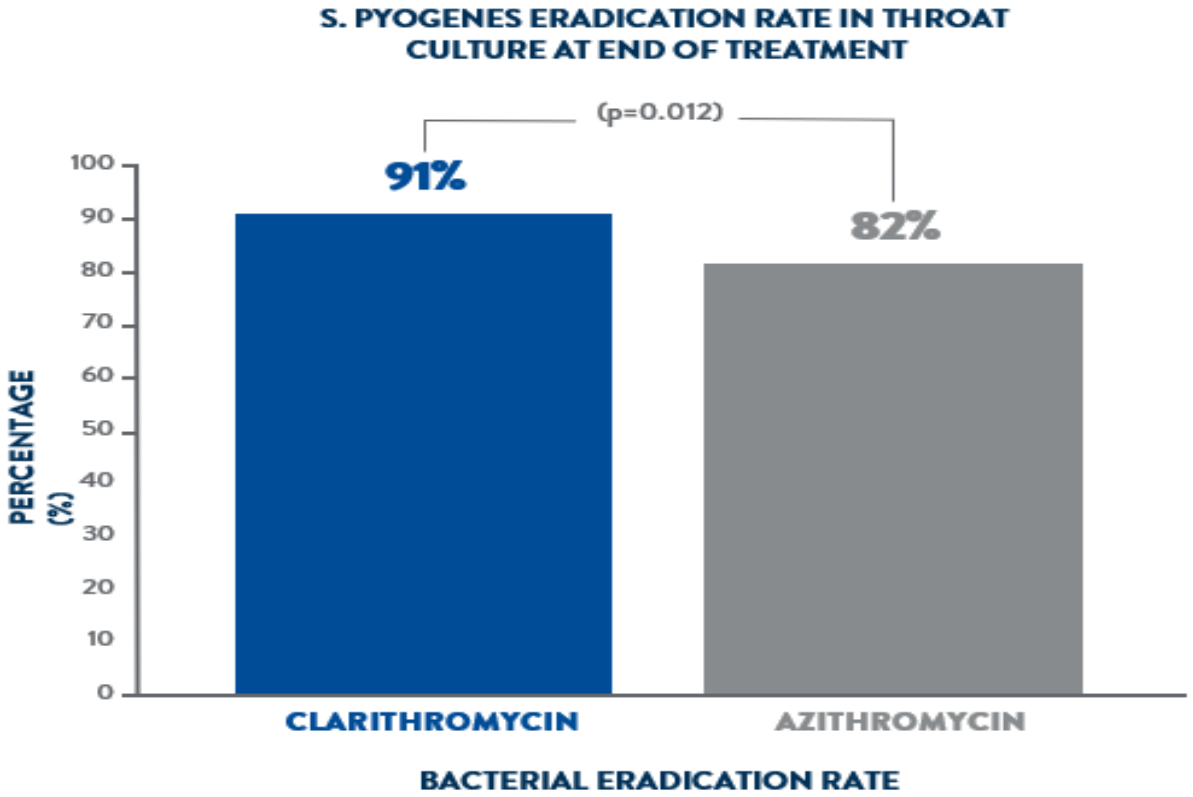
DIARRHEA



Adapted from Aspin MM, Hoberman A, McCarty J et al.

Aspin et al. Comparative study of the safety and efficacy of clarithromycin and amoxicillin-clavulanate in the treatment of acute otitis media in children

CLARITHROMYCIN 10-DAYS IS MORE EFFECTIVE THAN AZITHROMYCIN 5-DAYS IN STREPTOCOCCAL PHARYNGITIS



* Alternative to penicillin or amoxicillin.
BID, twice daily; OD, once daily

CLARITHROMYCIN
is recommended
for the treatment of Group A Streptococcal pharyngitis*

Infectious Diseases
Society of America

DOSING REGIMEN:[7]
CLARITHROMYCIN 250 mg BID 10 DAYS (n=260)
AZITHROMYCIN 500 mg DAY 1 PLUS 250 mg OD FOR NEXT 4 DAYS (n=265)

Adapted from Kaplan *et al.* 2001.

Study design: investigator-blinded, randomised, parallel-group, multicentre study. 525 patients (aged ≥12 years) with signs and symptoms of acute-onset pharyngitis from whom *S. pyogenes* was recovered were randomised to receive clarithromycin 250 mg BID for 10 days or azithromycin 500 mg OD for 1 day then 250 mg OD for 4 days. Study objective: to compare the bacteriologic streptococcal eradication rate of clarithromycin versus azithromycin.[7]

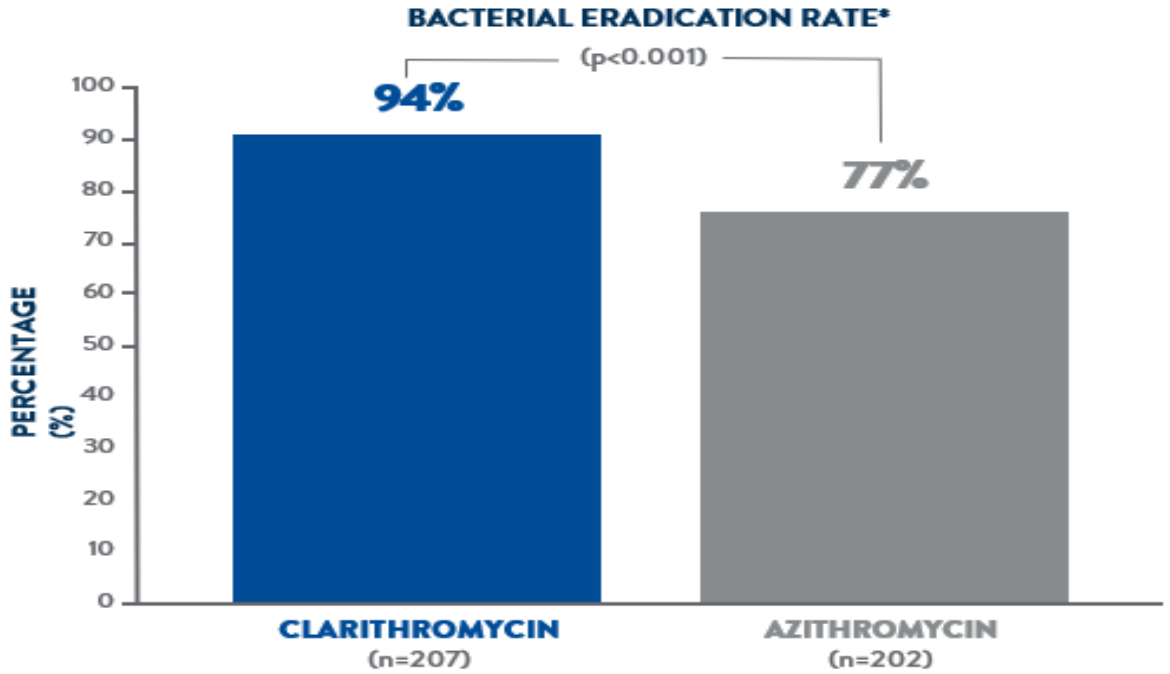
REFERENCES

Kaplan EL, Gooch III WM, Notario GF, Craft JC. Macrolide therapy of group A streptococcal pharyngitis: 10 days of macrolide therapy (clarithromycin) is more effective in streptococcal eradication than 5 days (azithromycin). *Clin Infect Dis.* 2001;32(12):1798–1802.

Shulman ST, Bisno AL, Clegg HW. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. Clin Infect Dis. 2012;55(10):e86–e102.

CLARITHROMYCIN RESULTED IN HIGHER STREPTOCOCCAL ERADICATION FOR THE TREATMENT OF PHARYNGITIS/TONSILLITIS COMPARED WITH AZITHROMYCIN

Clarithromycin demonstrated higher *Streptococcal* eradication to azithromycin in pharyngitis/tonsillitis



DOSING REGIMEN:

CLARITHROMYCIN 250 mg BID FOR 10 DAYS
AZITHROMYCIN 250 mg BID DAY 1, THEN 250 mg OD DAYS 2-5

BID, twice daily; OD, once daily.

Adapted from Chang *et al.* 1999.

Study design: randomized, multicentre, investigator-blind, parallel comparative control study. 525 patients (aged ≥12 years) with symptoms of streptococcal pharyngitis/tonsillitis and S. pyogenes positive were randomised to clarithromycin 250 mg BID for 10 days or azithromycin 250 mg BID for 1 day then 250 mg OD for days 2-5. Study objective: to compare additional antibiotic usage for patients using clarithromycin or azithromycin for the treatment of S. pyogenes pharyngitis/tonsillitis.

REFERENCES
Chang RJ, Busman T, Ryan J, et al. Additional antibiotic utilization in a randomized trial of clarithromycin (clari) compared with azithromycin (azi) for the treatment of S. pyogenes pharyngitis/tonsillitis. *Value Health.* 1999;2(3):134–135.

IDSA/ATS Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults

Lionel A. Mandell,a Richard G. Wunderink, Antonio Anzueto, John G. Bartlett, G. Douglas Campbell, Nathan C. Dean, Scott F. Dowell, Thomas M. File, Jr.Daniel M. Musher,
Michael S. Niederman, Antonio Torres, and Cynthia G. Whitney

IDSA/ATS Guidelines for CAP in Adults • CID 2007:44 (Suppl 2)

Treatment of pneumonia

Ideal

Detection of the causative pathogen by a rapid test (e.g. *Legionella* in urine)

Pathogen-directed antimicrobial therapy

Reality

Even with extensive diagnostic testing the causative pathogen can be identified in only 50% of cases

Empirical therapy

Individual expertise

Guidelines

Outpatient treatment

IDSA/ATS Guidelines for CAP in Adults •

1. Previously healthy and no use of antimicrobials within the previous 3 months

   A macrolide (strong recommendation; level I evidence).

   Doxycyline (weak recommendation; level III evidence)

2. Presence of comorbidities, or use of antimicrobials within the previous 3 months (*in which case an alternative from a different class should be selected*)

   A respiratory fluoroquinolone (levofloxacin (750 mg, moxifloxacin or gemifloxacin,) (strong recommendation; level I evidence)

   A β-lactam plus a macrolide (strong recommendation level I evidence)

Inpatients, non-ICU treatment

IDSA/ATS Guidelines for CAP in Adults

A respiratory fluoroquinolone

(strong recommendation; level I evidence)

A β-lactam* **plus** a macrolide

(strong recommendation; level I evidence)

Inpatient treatment (ICU)

IDSA/ATS Guidelines for CAP in Adults • **2007:44 (Suppl 2)**

A β-lactam

(cefotaxime, ceftriaxone, or ampicillin-sulbactam)

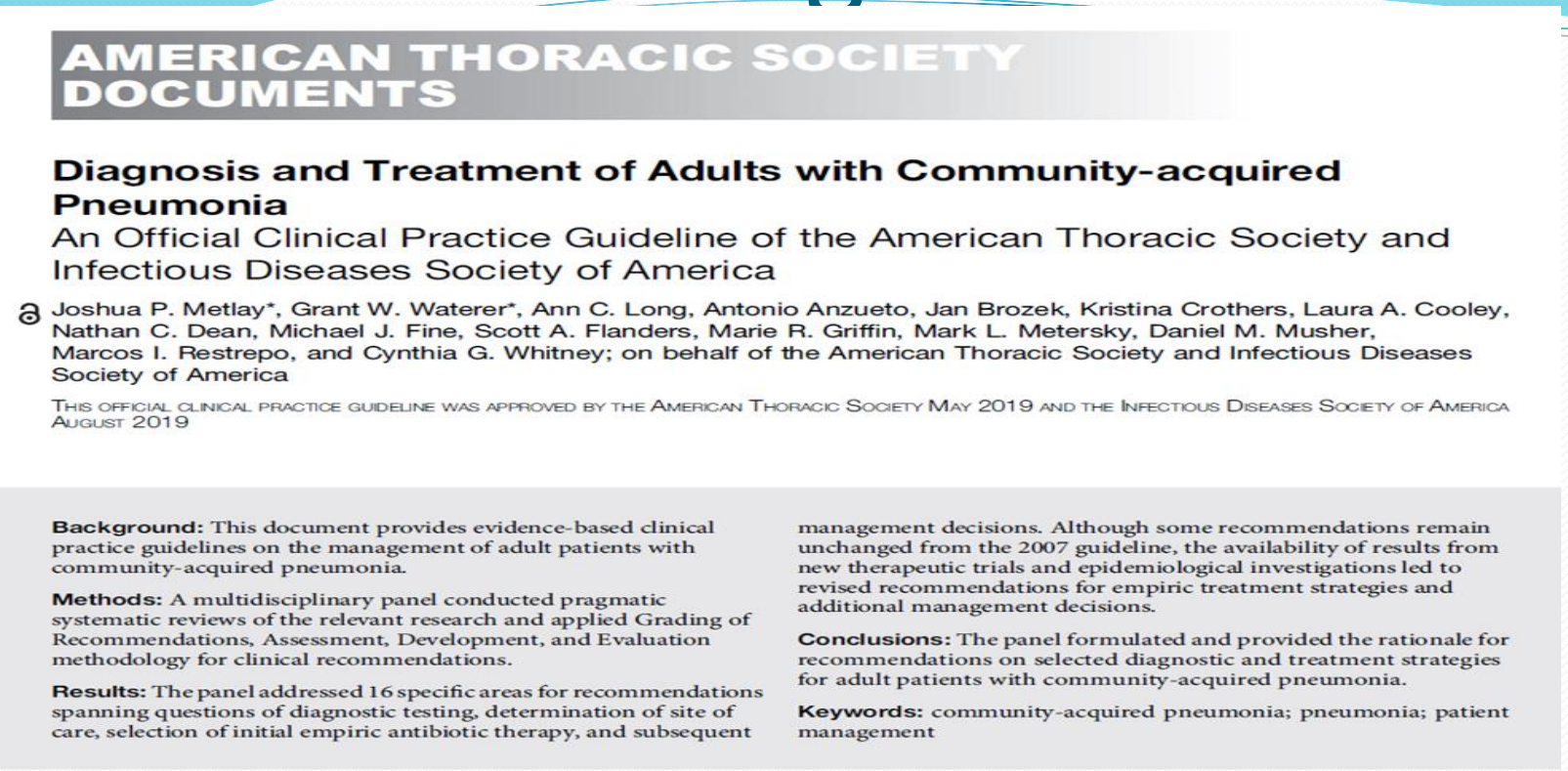
plus either azithromycin (level II evidence)

or

a respiratory fluoroquinolone (level I evidence strong recommendation)

(for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended)

2019 ATS CAP guideline



AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis and Treatment of Adults with Community-acquired Pneumonia

An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America

Joshua P. Metlay*, Grant W. Waterer*, Ann C. Long, Antonio Anzueto, Jan Brozek, Kristina Crothers, Laura A. Cooley, Nathan C. Dean, Michael J. Fine, Scott A. Flanders, Marie R. Griffin, Mark L. Metersky, Daniel M. Musher, Marcos I. Restrepo, and Cynthia G. Whitney; on behalf of the American Thoracic Society and Infectious Diseases Society of America

This official clinical practice guideline was approved by the American Thoracic Society May 2019 and the Infectious Diseases Society of America August 2019

Background: This document provides evidence-based clinical practice guidelines on the management of adult patients with community-acquired pneumonia.

Methods: A multidisciplinary panel conducted pragmatic systematic reviews of the relevant research and applied Grading of Recommendations, Assessment, Development, and Evaluation methodology for clinical recommendations.

Results: The panel addressed 16 specific areas for recommendations spanning questions of diagnostic testing, determination of site of care, selection of initial empiric antibiotic therapy, and subsequent management decisions. Although some recommendations remain unchanged from the 2007 guideline, the availability of results from new therapeutic trials and epidemiological investigations led to revised recommendations for empiric treatment strategies and additional management decisions.

Conclusions: The panel formulated and provided the rationale for recommendations on selected diagnostic and treatment strategies for adult patients with community-acquired pneumonia.

Keywords: community-acquired pneumonia; pneumonia; patient management

- (ATS) / (IDSA) updated clinical guideline 2019 for community-acquired pneumonia (CAP) recommend both β-Lactam / macrolide and β-lactam / fluoroquinolone combinations for treatment **but** remarks that there is **stronger evidence favoring a β-lactam/macrolide combination**

2.Metlay JP, et al. Am J Respir Crit Care Med Vol 200, Iss 7, pp e45–e67, Oct 1, 2019

LEV2273159

CLARITHROMYCIN PLUS A ß-LACTAM IS THE STRONGLY RECOMMENDED STANDARD INITIAL TREATMENT FOR PATIENTS WITH COMMUNITY ACQUIRED PNEUMONIA10

The difference between the 2019 and 2007 American Thoracic Society/ Infectious Diseases Society of America Community-acquired Pneumonia Guidelines

Recommendation

Standard empiric therapy for severe CAP

2007 ATS/IDSA Guideline
ß-lactam/macrolide and ß-lactam/ fluoroquinolone
combinations given equal weight

2019 ATS/IDSA Guideline Both accepted but stronger evidence in favor of ß-lactam/ macrolide combination

ATS, American Thoracic Society; CAP, community-acquired pneumonia; IDSA, Infectious Diseases Society of America. The American Thoracic Society (ATS) / Infectious Diseases Society of America (IDSA) updated clinical guideline 2019 for community-acquired pneumonia (CAP) recommends both ß-Lactam / macrolide and ß-lactam / fluoroquinolone combinations for treatment but remarks that there is **stronger evidence favoring a ß-lactam/macrolide combination.**

Metlay JP, Waterer GW, Long AC, *et al.* Diagnosis and treatment of adults with community-acquired pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med.* 2019;200:e45–e67.

n

2019 ATS CAP guideline

Recommendation 9.1: In inpatient adults with nonsevere CAP: combination therapy with a β-lactam and macrolide (strong recommendation, high quality of evidence)

Nie et al. and Horita et al. demonstrated that β-lactam/macrolide combinations may decrease all-cause death, but mainly for patients with CAP.

Recommendation 9.2: In inpatient adults with severe CAP: a β-lactam plus a macrolide (strong recommendation, moderate quality of evidence)

A mortality benefit from macrolides has been observed mainly in cohorts with a large number of patients with severe CAP. In a systematic review, Vardakas et al. found that combination of β-lactam/fluoroquinolone therapy was associated with higher mortality than β-lactam/macrolide combination therapy for the treatment of patients with CAP.

2. Metlay JP, et al. Am J Respir Crit Care Med Vol 200, Iss 7, pp e45–e67, Oct 1, 2019

Guidelines cannot always account for individual variation among patients.

The IDSA considers adherence to these guidelines to be voluntary, with

application to be made by the physician in the light of each patient's individual circumstances

Early administration of antibiotics: is it important?

Meehan et al. *JAMA* 1997; **278**: 2080–84

4 hours

Houck et al. *Arch Intern Med* 2019; **164**: 637–44

2hours – 1 HOUR

Assessment of non-responders

Wrong organism

Drug resistant

Other organism than isolated

Wrong diagnosis

Atelectasis

Pulmonary embolus

ARDS

Neoplasm

Complications

Empyema

Lung abscess

Survival benefit associated with clarithromycin in severe community-acquired pneumonia: A matched comparator study

1. Kyriazopoulou et al., Survival benefit associated with clarithromycin in severe community-acquired pneumonia: A matched comparator study. *International Journal of antimicrobial agents 55 (2020)*

Study design

- Inclusion criteria: (a) age ≥18 years; (b) both genders; (c) at least two signs of SIRS (Systemic Inflammation Response Syndrome) ; and (d) acute pyelonephritis, CAP, intra-abdominal infection, primary bacteremia, ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia. Only patients with CAP were included in the present analysis.
- CAP was defined as the presence of at least two signs or symptoms compatible with CAP (i.e. cough, sputum production, dyspnea, auscultatory rales) and new infiltrate on chest x-ray in a patient without any history of contact with the hospital environment or healthcare facilities in the preceding 90 days

1.Kyriazopoulou et al., Survival benefit associated with clarithromycin in severe community-acquired pneumonia: A matched comparator study. *International Journal of antimicrobial agents 55 (2020)*

Pre-defined analysis plan

- Only patients with CAP and sepsis classified according to the new Sepsis-3 criteria were analyzed
- 4 treatment groups were formed:

✓ clarithromycin group, comprising all available patients treated with a combination of clarithromycin and one β-lactam;

✓ azithromycin group, comprising patients treated with a combination of azithromycin and one β-lactam;

✓ respiratory fluoroquinolone group, comprising patients treated with moxifloxacin or levofloxacin alone;

✓ β-lactam group, comprising patients treated with β-lactam monotherapy.

1.Kyriazopoulou et al., Survival benefit associated with clarithromycin in severe community-acquired pneumonia: A matched comparator study. *International Journal of antimicrobial agents 55 (2020)*

Study Endpoints

- The primary study endpoint was comparative 28-day mortality between the clarithromycin group and the β-lactam group.
- The secondary study endpoints were: (a) impact of clarithromycin intake on 28-day mortality in comparison with the other groups; (b) time to development of new organ dysfunction between the clarithromycin group and the β-lactam group; and (c) impact of clarithromycin intake on ***Resolution of CAP*** in comparison with the other groups.
- ***Resolution of CAP*** *was defined as resolution of the signs of SIRS and the symptoms compatible with CAP (cough, sputum production, dyspnea, auscultatory rales) at the completion of 7 days of treatment.*

1.Kyriazopoulou et al., Survival benefit associated with clarithromycin in severe community-acquired pneumonia: A matched comparator study. *International Journal of antimicrobial agents 55 (2020)*

Matching process

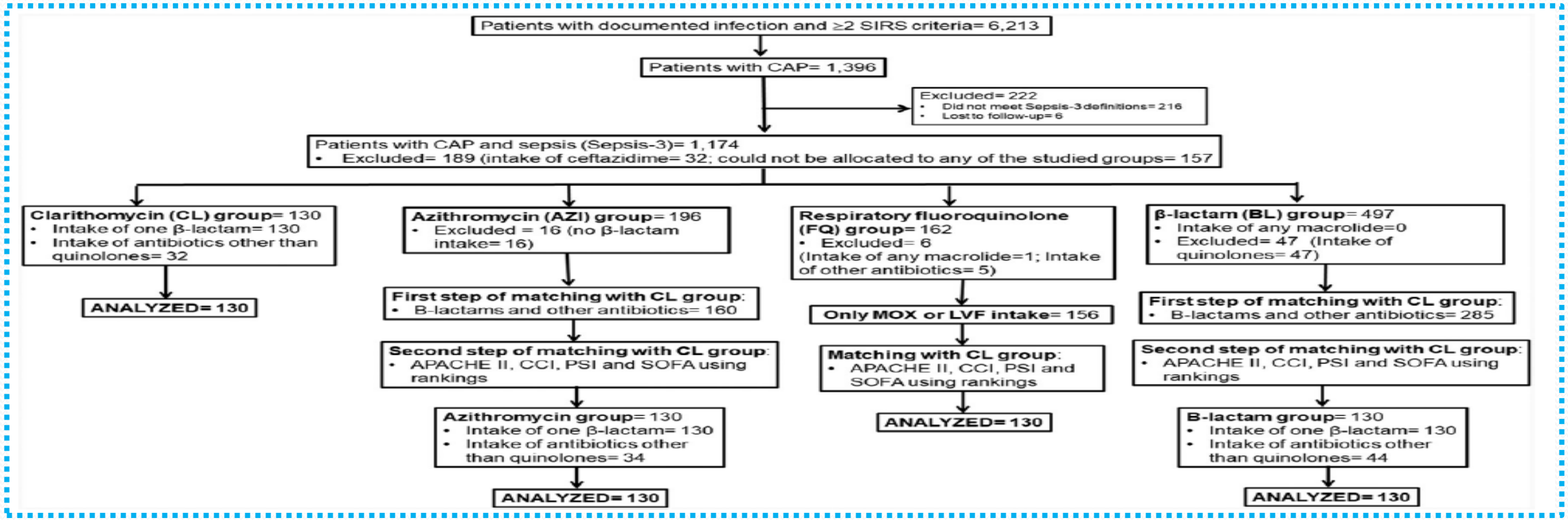


Fig. 1. *Matching process to define the β-lactam and fluoroquinolone groups. APACHE, Acute Physiology and Chronic Health Evaluation; CAP, community-acquired pneumonia; CCI, Charlson's Comorbidity Index; PSI, Pneumonia Severity Index; Sepsis-3, 2016 proposed definitions for sepsis; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.*

1.Kyriazopoulou et al., Survival benefit associated with clarithromycin in severe community-acquired pneumonia: A matched comparator study. *International Journal of antimicrobial agents 55 (2020)*

Four well-matched treatment groups were identified from 1174 patients with CAP and sepsis.[1]

Group 1:	Group 2:	Group 3:	Group 4:
Clarithromycin 500 mg BID (i.v.) + β-lactam¥ (n=130)	Azithromycin 500 mg OD (i.v.): 7 days + β-lactam¥ (n=130)	Fluoroquinolone* (i.v.) (n=130)	β-lactam (n=130)

RESULTS

PRIMARY STUDY ENDPOINT

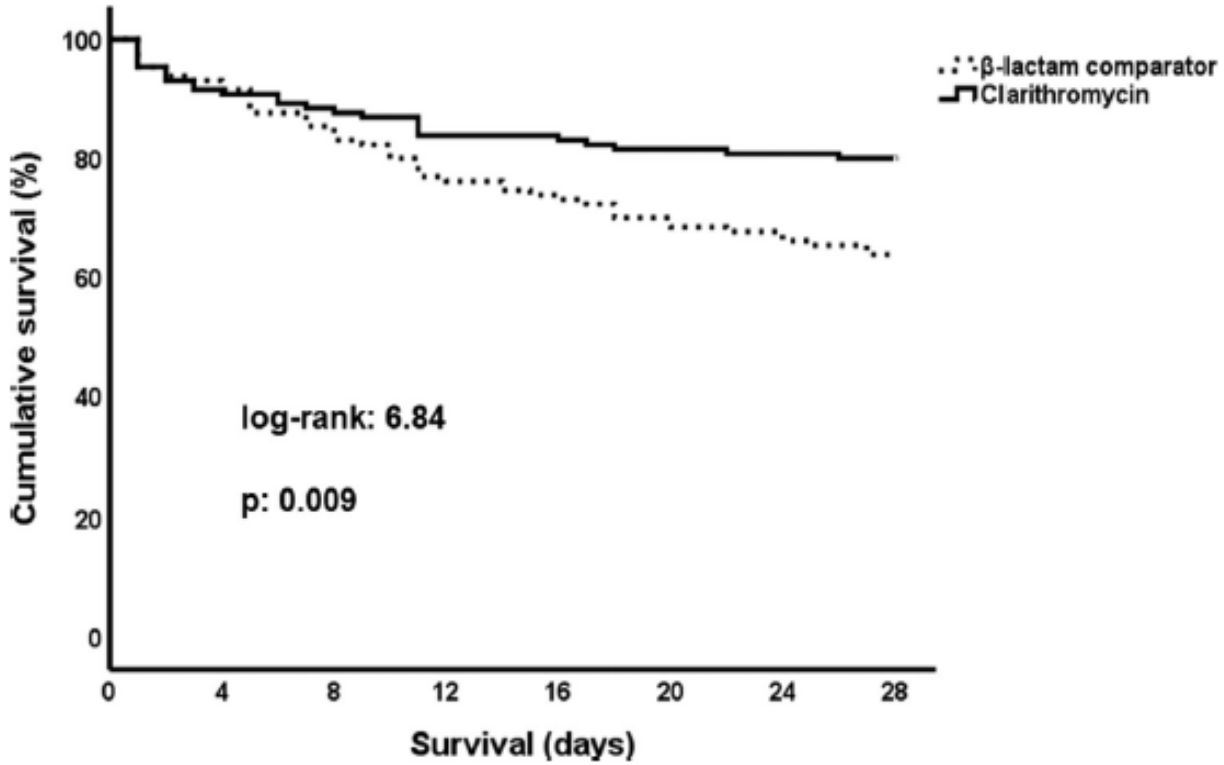


Fig.1 *Primary study endpoint. Comparative survival of 130 patients treated with clarithromycin and 130 comparators treated with β-lactams.*

During the first 28 days, there were 47 deaths in the β-lactam group (36.2%) and 27 deaths (20.8%) in the clarithromycin group (*P* = 0.009, Fisher's exact test).

The OR for death after 28 days for those treated with clarithromycin was 0.46 (95% CI 0.27–0.81; *P* = 0.006, Mantel–Haeszelstatistics).

Survival of patients treated with clarithromycin was significantly prolonged.

1.Kyriazopoulou et al., Survival benefit associated with clarithromycin in severe community-acquired pneumonia: A matched comparator study. *International Journal of Antimicrobial Agents, 55 (2020)*

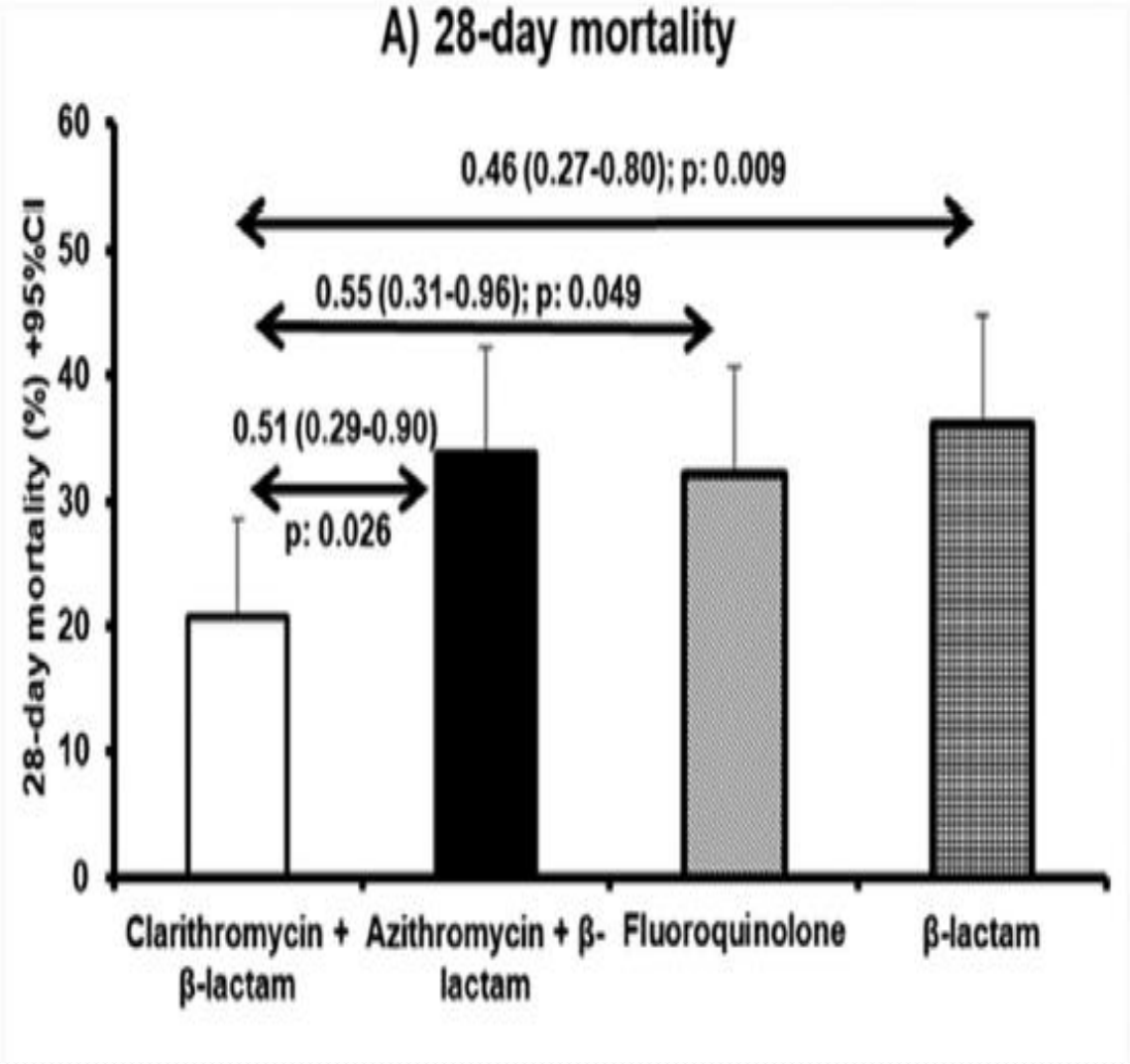


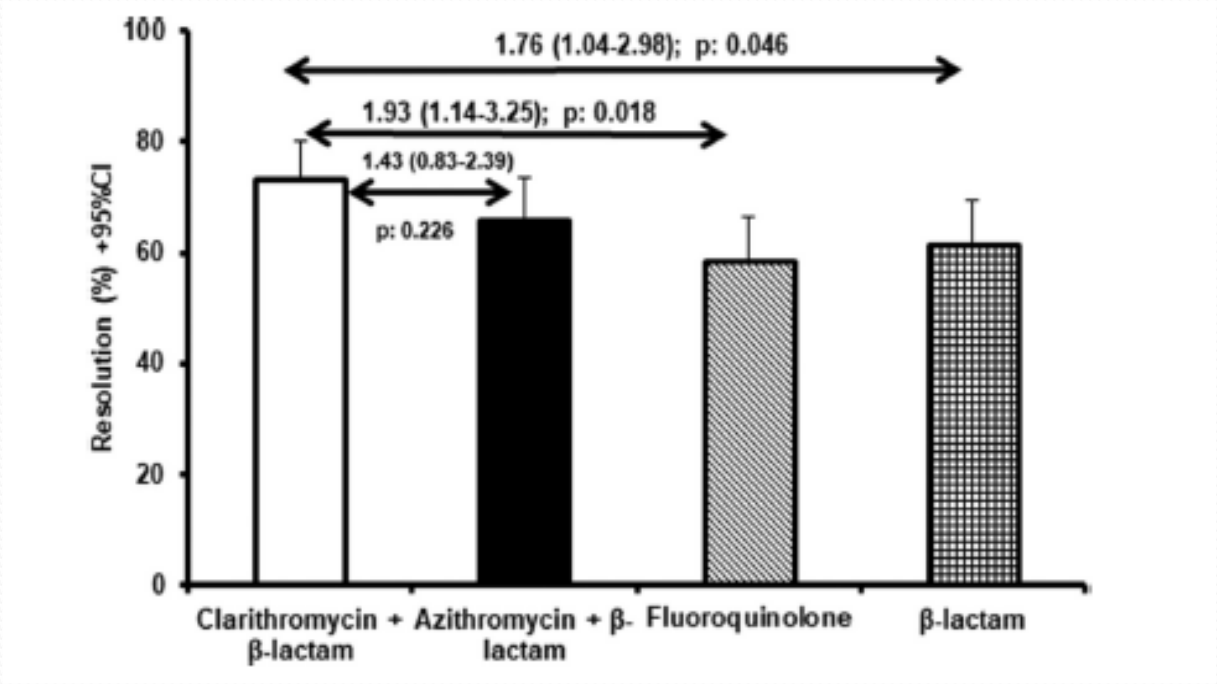
Fig.2 *Comparative 28-day mortality of patients treated with the combination of clarithromycin and one β-lactam vs the other groups. The values above the arrows indicate the odds ratio and 95% confidence intervals (CI) of death under clarithromycin for the indicated comparisons; the respective P -value is also provided.*

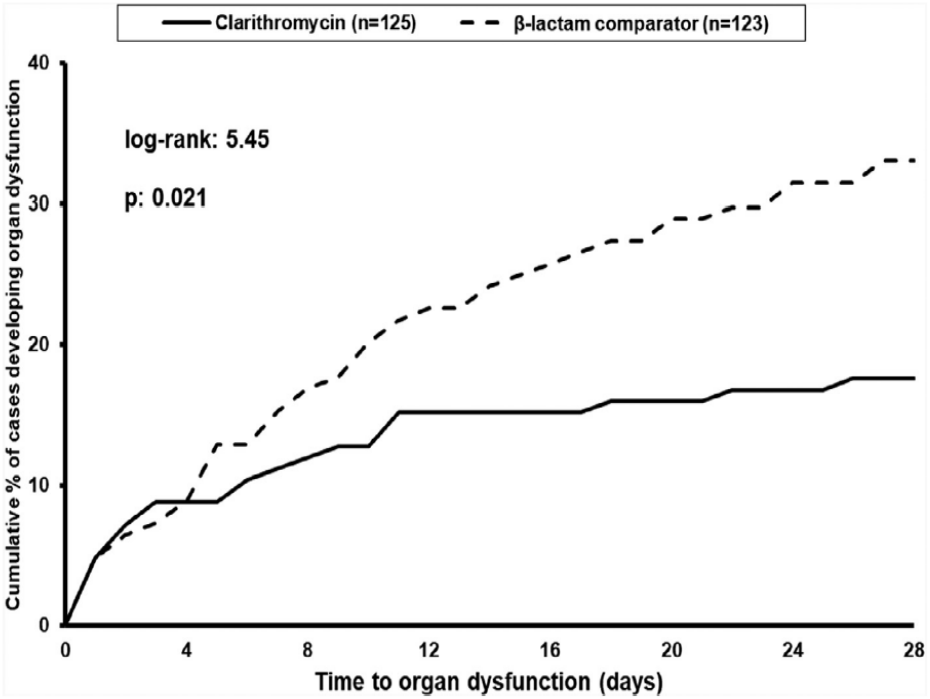
Kyryiazopoulou et al, concluded that **addition of clarithromycin to the treatment regimen of patients with severe CAP leads to better survival rates** than the other study treatments[1].

This finding reinforces the 2019 recommendations from the ATS and IDSA which suggests stronger evidence for use of macrolides + β-lactam versus fluoroquinolone, or β-lactam alone for severe CAP.

1.Kyriazopoulou et al., Survival benefit associated with clarithromycin in severe community-acquired pneumonia: A matched comparator study. *International Journal of antimicrobial agents 55 (2020)*

2.Metlay et al. Am J Respir Crit Care Med Vol 200, Iss 7, pp e45–e67, Oct 1, 2019





- Other secondary endpoints demonstrated that new organ dysfunction accumulated more quickly with β-lactam than clarithromycin + β-lactam and that **resolution of CAP was greater with clarithromycin + β-lactam** than fluoroquinolone, or β-lactam alone

1.Kyriazopoulou et al., Survival benefit associated with clarithromycin in severe community-acquired pneumonia: A matched comparator study. *International Journal of antimicrobial agents 55 (2020)*

- This retrospective analysis using well-matched comparators showed that administration of clarithromycin with one β-lactam provided significant survival benefit over β-lactam monotherapy for severe CAP

- This survival benefit was also superior to that for azithromycin in combination with one β-lactam, and respiratory fluoroquinolone monotherapy

- **This is the first study to show that the survival benefit is due to the administration of clarithromycin and not azithromycin**

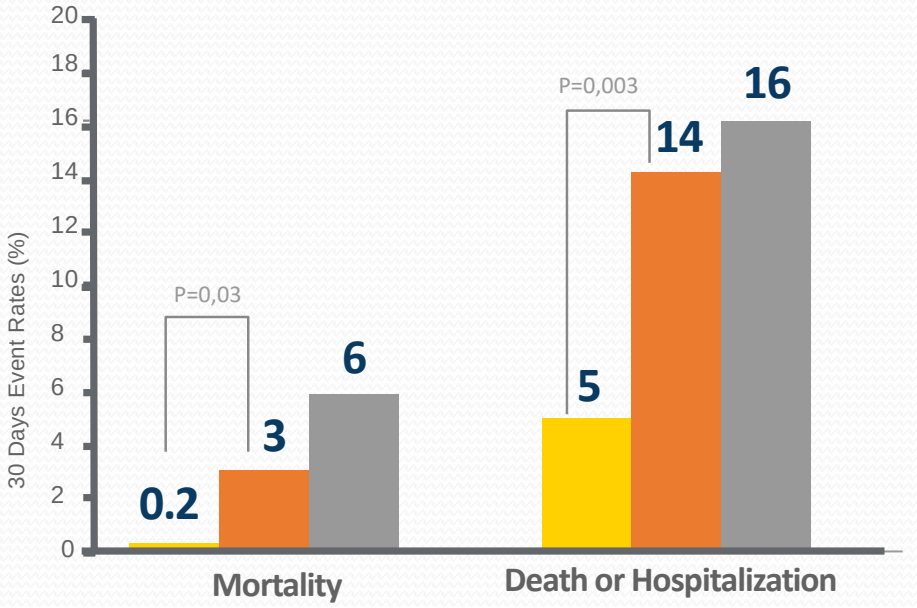
- The current study, despite its retrospective nature, showed that the addition of clarithromycin, rather than azithromycin, to the treatment regimen of patients with severe CAP led to better outcomes

1.Kyriazopoulou et al., Survival benefit associated with clarithromycin in severe community-acquired pneumonia: A matched comparator study. *International Journal of antimicrobial agents 55 (2020)*

GUIDELINE ADHERENCE & MACROLIDES REDUCED MORTALITY IN OUTPATIENTS WITH PNEUMONIA[15]

In terms of **30-day mortality**,
3% fluoroquinolone users died versus
0.2% macrolides p= 0.030

There was also a statistically significant reduction for the composite endpoint of death or hospitalization within 30-days:
5% with macrolides versus 14% for Fluoroquinolones P=0.003



Adapted from Ref 15.

Macrolides Respiratory Fluoroquinolones Guideline-Discordant Antibiotics

REFERENCES:

Asadi et al, Guideline adherence and macrolides reduced mortality in outpatients with pneumonia. Elsevier 2011

Mortality in patients with community-onset pneumonia at low risk of drug-resistant pathogens: Impact of β-lactam plus macrolide combination therapy

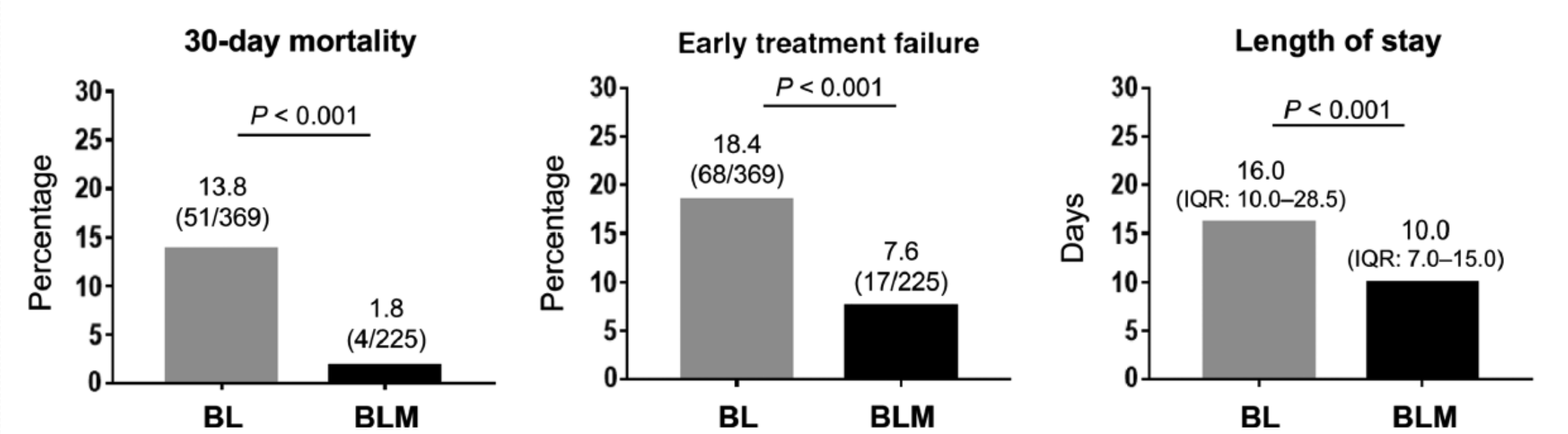
JUNYA OKUMURA,1 et al (Respirology – 2018)

- **Methods**: Post hoc analysis using a prospective multicentre study cohort of community-onset pneumonia was performed to **assess 30-day differences in mortality between non-antipseudomonal β-lactam monotherapy (BL) and BLM groups.** Logistic regression analysis was performed to assess the therapeutic effect and risk factors for mortality in patients at low DRP risk.

- **Results**: In total, **594 patients with community-onset pneumonia at low DRP risk (369 BL and 225 BLM) were analysed. The 30-day mortality in BL and BLM was 13.8% and 1.8%, respectively (P < 0.001).**

- **Conclusion**: **In patients with community-onset pneumonia at low DRP risk, BLM treatment reduced 30-day mortality compared with BL.**

3.Okumara et al, Mortality in patients with community-onset pneumonia at low risk of drug-resistant pathogens: Impact of β-lactam plus macrolide combination therapy - Respirology 2018



- The 30-day mortality proportion was lower in the BLM group than in the BL group (1.8% vs 13.8%, respectively).
- Compared with the BL group, the BLM showed a lower proportion of early treatment failure.
- The median length of hospital stay was also shorter in the BLM than that in the BL group.

3.Okumara et al, Mortality in patients with community-onset pneumonia at low risk of drug-resistant pathogens: Impact of β-lactam plus macrolide combination therapy - Respirology 2018

Macrolide therapy is associated with lower mortality in community acquired bacteraemic pneumonia

Forest W. Arnold et al – ELSEVIER 2018

- **Objective:** To define the clinical outcomes of patients with CAP and bacteremia treated with and without a macrolide.

- **Materials and methods**: Secondary analysis of the Community-Acquired Pneumonia Organization database of hospitalized patients with CAP. Patients with a positive blood culture were categorized based on the presence or absence of a macrolide in their initial antimicrobial regimen, and severity of their CAP. Outcomes included in-hospital all-cause mortality, 30-day mortality, length of stay, and time to clinical stability.

- **Results:** Among 549 patients with CAP and bacteremia, 247 (45%) were treated with a macrolide and 302 (55%) were not. The primary pathogen was Streptococcus pneumoniae (74%).
  - ✓ **The unadjusted 30-day mortality was 18.4% in the macrolide group, and 29.6% in the non-macrolide group** (adjusted relative risk (aRR)0.81; 95% confidence interval (CI)0.50–1.33; P=0.41).
  - ✓ **Unadjusted in-hospital all-cause mortality was 7.3% in the macrolide group, and 18.9% in the non-macrolide group** (aRR 0.54, 95% CI 0.30–0.98; P=0.043).
  - ✓ Length of stay and time to clinical stability were not significantly different.

- **Conclusions**: **In-hospital mortality was significantly better in the macrolide group. Our data support the use of a macrolide in hospitalized patients with CAP and bacteraemia.**

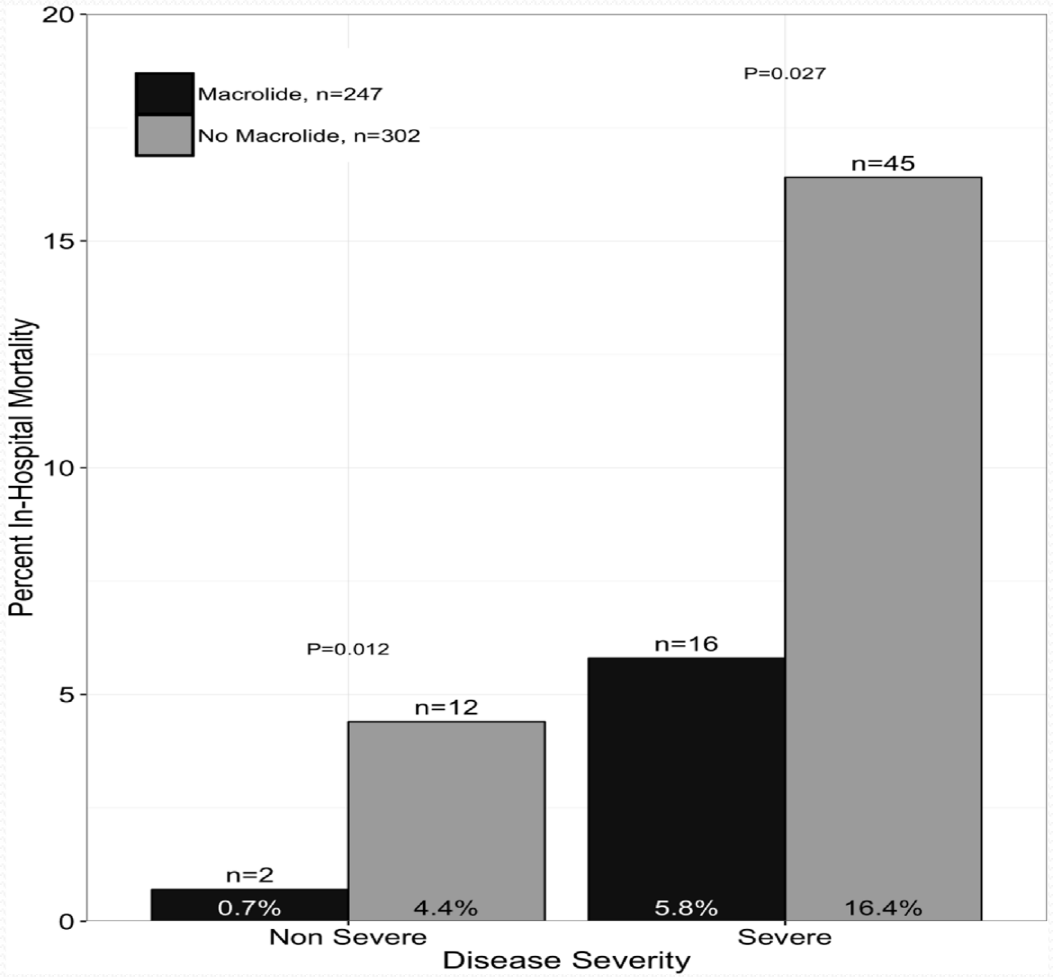


Fig. 1. In hospital mortality for severe and non-severe community-acquired pneumonia patients treated with and without a macrolide.

- **In-hospital mortality for the macrolide group was 7.3%, and for the non-macrolide group was 18.9%; P < 0.001**. Data are presented for severe and non-severe patients (Fig. 1).
- **The adjusted risk of in-hospital mortality was 46% lower for patients with a macrolide compared to those without**; RR 0.54, 95% CI 0.30–0.98; P=0.043.
- Those who received a macrolide had significantly decreased in-hospital mortality regardless of severity.

4.Forest W Arnold et al Macrolide therapy is associated with lower mortality in community acquired bacteraemic pneumonia ELSEVIER 2018

Effect of Combined ß-Lactam/Macrolide Therapy on Mortality According to the Microbial Etiology and Inflammatory Status of Patients With Community-Acquired Pneumonia

Ceccato et al CHEST 2019

- In patients with CAP and known microbial cause we aimed to evaluate 30-day mortality of a ß-lactam plus macrolide (BL+ M) compared with a fluoroquinolone alone or with a ß-lactam (FQ±BL).

- **METHODS:** We analyzed a prospective observational cohort of patients with CAP admitted to the Hospital Clinic of Barcelona between 1996 and 2016. We included only patients with known microbial cause.

- **RESULTS:** Of 1,715 patients (29%) with known etiology, a total of 932 patients (54%) received BL+M. **The combination of a ß-lactam with a macrolide was associated with decreased mortality in patients with pneumococcal CAP and in patients with high systemic inflammatory response.** **When both factors occurred together, BL+M was protective for mortality in the multivariate analysis**.

CLARITHROMYCIN IN ADULTS

Acute Exacerbations of Chronic Bronchitis

LEV2273159

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE)

Public Health England, UK

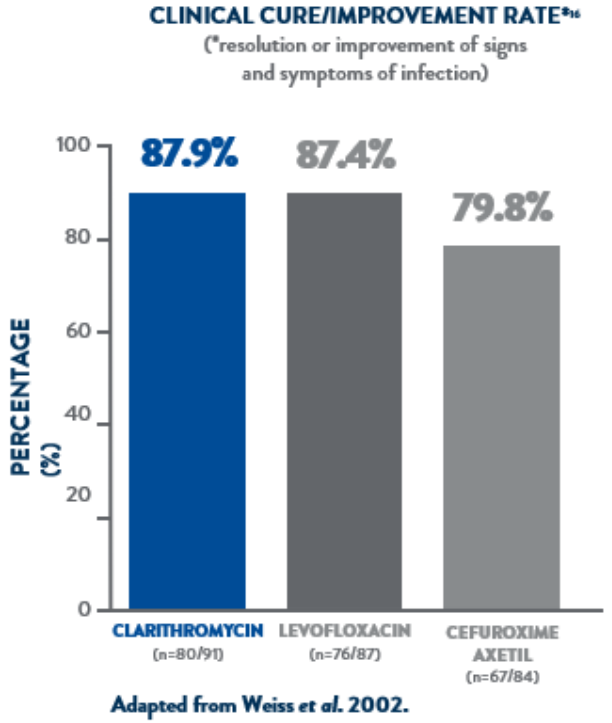
First-line monotherapy for empiric treatment of acute exacerbations of bronchiectasis.*
Dosing regimen: clarithromcyin 500 mg twice a day for 7 to 14 days.

* in the absence of current susceptibility data (guided by most recent sputum culture and susceptibilities where possible).

REFERENCES
National Institute for Health and Care Excellence. Bronchiectasis (non-cystic fibrosis), acute exacerbation: antimicrobial prescribing. NICE guideline [NG117]. 18 December 2018. Available at: https://www.nice.org.uk/guidance/ng117/resources/bronchiectasis-noncystic-fibrosis-acute-exacerbation-antimicrobial-prescribing-pdf-66141603457477 (accessed April 2021).

CLARITHROMYCIN IS AS EFFICACIOUS AS LEVOFLOXACIN AND CEPHALOSPORIN CEFUROXIME FOR THE TREATMENT OF AECB

Clarithromycin is as effective as Levofloxacin and Cefuroxime for the treatment of AECB



Adapted from Weiss *et al.* 2002.

DOSE REGIMEN:

CLARITHROMYCIN 500 mg BID FOR 10 DAYS (n=97);
LEVOFLOXACIN 500 mg OD FOR 10 DAYS (n=94);
CEFUROXIME AXETIL: 250 mg BID FOR 10 DAYS (n=92)

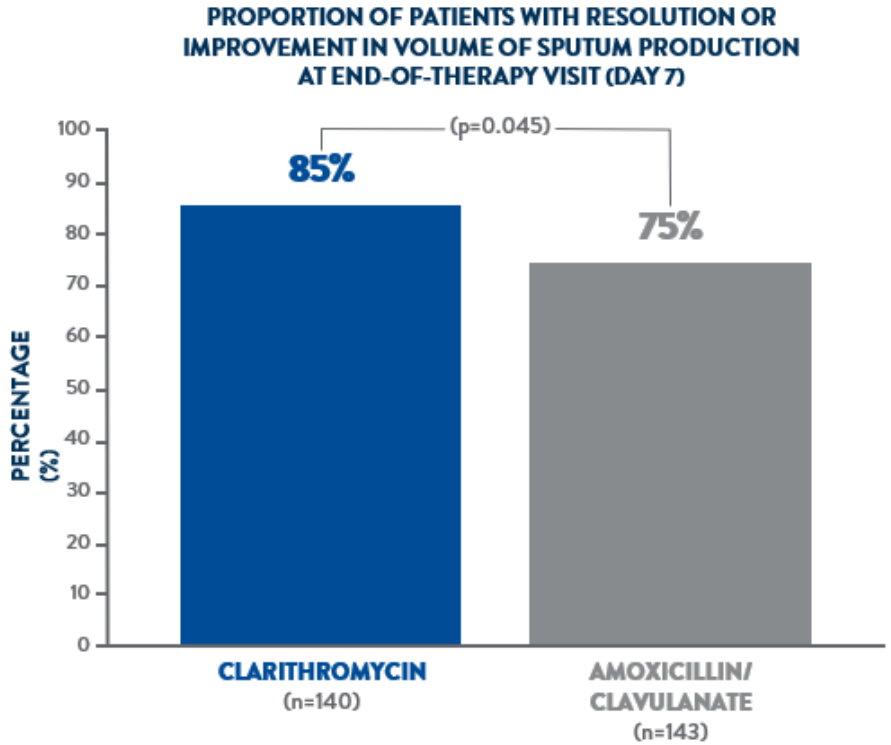
AECB, acute exacerbations of chronic bronchitis; BID, twice daily; ITT, intention to treat; OD, once daily.

Study design: two-centre, randomised, prospective, open-label study. 283 patients (aged ≥18 years) with a history of chronic bronchitis (cough and sputum production for >2 years with symptoms present on most days for 3 consecutive months) were randomised to receive clarithromycin 500 mg BID, levofloxacin 500 mg OD, or cefuroxime axetil 250 mg BID, administered with food, each for 10 days. Study objective: to compare the efficacy and tolerability of clarithromycin, levofloxacin and cefuroxime for the treatment of AECB in adult outpatients.[16]

REFERENCES

Weiss LR. Open-label, randomized comparison of the efficacy and tolerability of clarithromycin, levofloxacin, and cefuroxime axetil in the treatment of adults with acute bacterial exacerbations of chronic bronchitis. *Clin Ther.* 2002;24(9):1414–1425.

CLARITHROMYCIN LEADS TO BETTER CLINICAL OUTCOMES THAN AMOXICILLIN/CLAVULANATE IN AECB



Adapted from Anzueto *et al.* 2001.

- In a double-blind study of 283 intent-to-treat patients in the treatment of AECB, significantly more patients treated with extended-release clarithromycin (1000 mg OD for 7 days) compared with amoxicillin/clavulanate (875/125 mg BID for 10 days) reported feeling excellent or very good by study days 10-12 (48% vs 29%; p= 0.044).

DOSE REGIMEN:

CLARITHROMYCIN 1000 mg OD FOR 7 DAYS (n=140)
AMOXICILLIN/CLAVULANATE 875 mg BID FOR 10 DAYS (n=143)

AECB, acute exacerbations of chronic bronchitis; BID, twice daily; ER, extended release; OD, once daily.

Study design: phase IIIB, multicentre, randomised, investigator-blinded, parallel-group study. 287 patients (aged ≥40 years) with a presumptive diagnosis of AECB (Anthonisen type 1 criteria: increased dyspnoea, sputum volume, or sputum purulence) plus ≥1 of the following: • Fever ≥38°C not attributable to another cause. • Increased wheezing. • Increased respiratory rate. Patients were randomised to receive clarithromycin 1000 mg OD for 7 days or amoxicillin/clavulanate 875 mg BID for 10 days. Study objective: to compare the efficacy and safety of clarithromycin and amoxicillin/clavulanate for the treatment of AECB.[1]

REFERENCES

Anzueto A, Fisher CL, Jr., Busman T, et al. Comparison of the efficacy of extended-release clarithromycin tablets and amoxicillin/clavulanate tablets in the treatment of acute exacerbation of chronic bronchitis. *Clin Ther.* 2001;23:72–86.
Bishai WR. Macrolide immunomodulatory effects and symptom resolution in acute exacerbation of chronic bronchitis and acute maxillary sinusitis: a focus on clarithromycin. *Expert Rev Anti Infect Ther.* 2006;4:405–416.

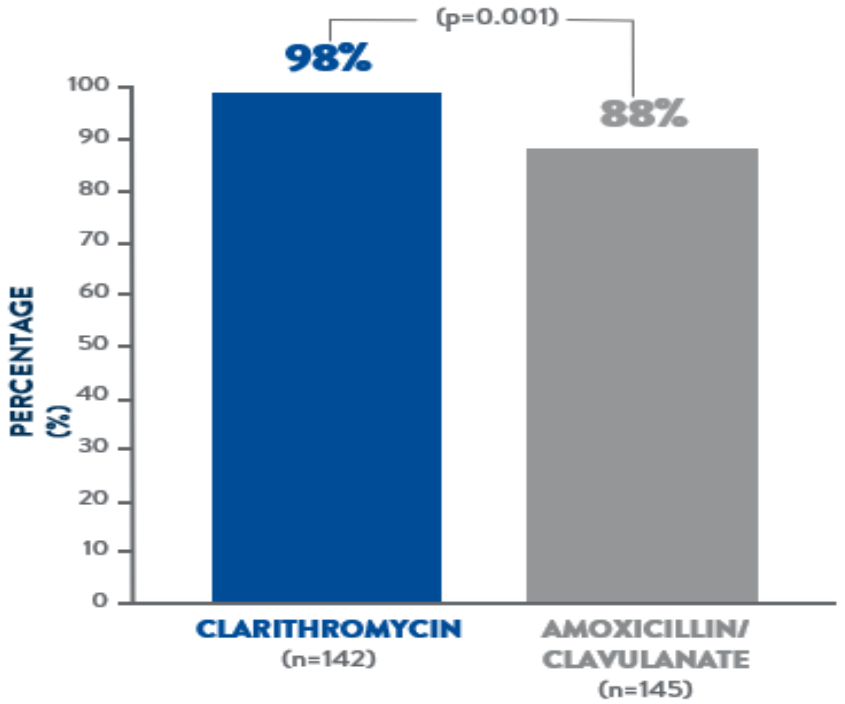
CLARITHROMYCIN IS ASSOCIATED WITH IMPROVED TOLERABILITY AND COMPLIANCE COMPARED WITH AMOXICILLIN/CLAVULANATE IN AECB

PROPORTION OF PATIENTS WHO DISCONTINUED TREATMENT
(p=0.005)

- Significantly fewer patients discontinued treatment with clarithromycin than with amoxicillin/clavulanate
- The proportion of patients who took ≥80% of prescribed medication was significantly greater with clarithromycin than with amoxicillin/clavulanate

DOSE REGIMEN:
CLARITHROMYCIN 1000 mg OD FOR 7 DAYS (n=142)
AMOXICILLIN/CLAVULANATE 875 mg BID FOR 10 DAYS (n=145)

PROPORTION OF PATIENTS WHO TOOK ≥80% OF PRESCRIBED MEDICATION



Adapted from Anzueto *et al.* 2001.

AECB, acute exacerbations of chronic bronchitis; BID, twice daily; ER, extended release; OD, once daily.

Study design: phase IIIB, multicentre, randomised, investigator-blinded, parallel-group study. 287 patients (aged ≥40 years) with a presumptive diagnosis of AECB (Anthonisen type 1 criteria: increased dyspnoea, sputum volume, or sputum purulence) plus ≥1 of the following: • Fever ≥38°C not attributable to another cause. • Increased wheezing. • Increased respiratory rate. Patients were randomised to receive clarithromycin 1000 mg OD for 7 days or amoxicillin/clavulanate 875 mg BID for 10 days. Study objective: to compare the efficacy and safety of clarithromycin and amoxicillin/clavulanate for the treatment of AECB.

REFERENCES
Anzueto A, Fisher CL, Jr., Busman T, et al. Comparison of the efficacy of extended-release clarithromycin tablets and amoxicillin/clavulanate tablets in the treatment of acute exacerbation of chronic bronchitis. Clin Ther. 2001;23:72–86.

- Macrolides =antibacterial as well as immunomodulatory properties

Arnold et al. Macrolide therapy is associated with lower mortality in community-acquired bacteraemic pneumonia – Elsevier 2018

Always refer to the locally approved PIL

Macrolide Therapy for CRS: Chronic Rhino sinusitis

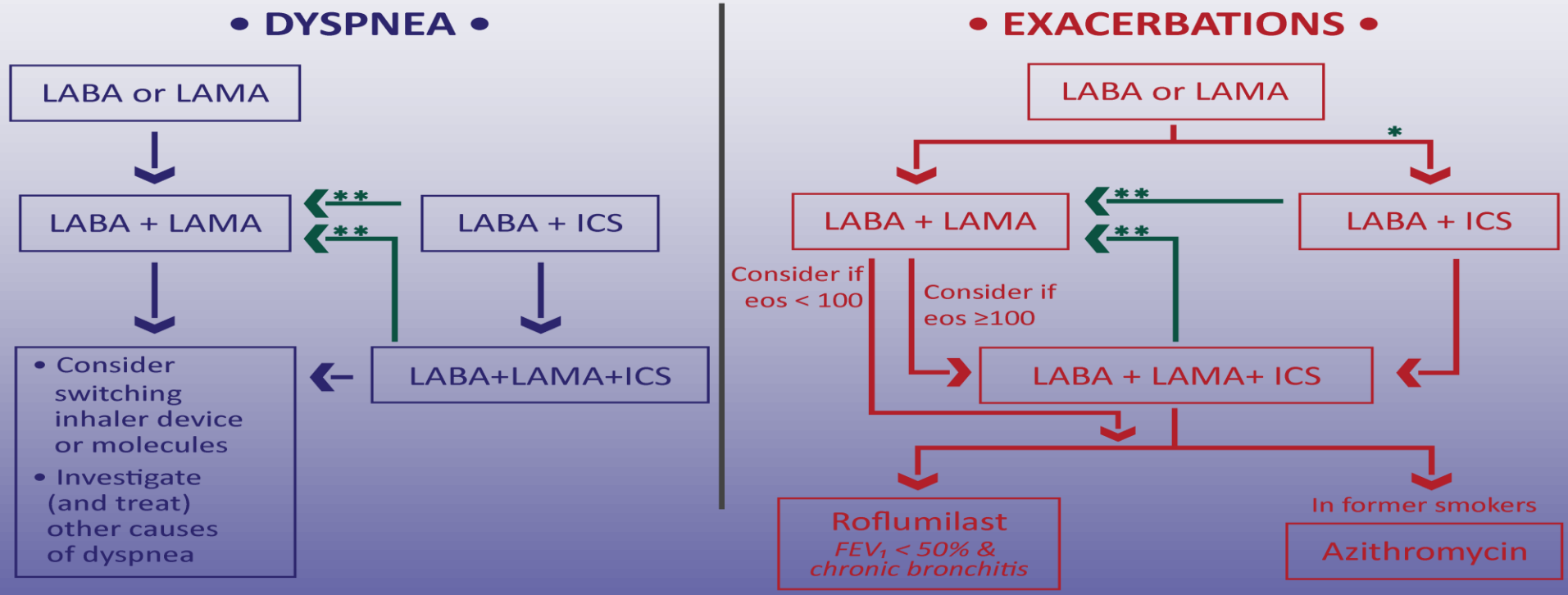
-inhibit inflammatory mediators such as IL-1B, IL-8, and intercellular adhesion molecule-1

-Protect bioactive phospholipids, reducing the number of neutrophils by accelerated apoptosis, and increasing mucociliary transport .

Always refer to the locally approved PIL

FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. **IF NOT:**
   - ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - ✓ Place patient in box corresponding to current treatment & follow indications
   - ✓ Assess response, adjust and review
   - ✓ These recommendations do not depend on the ABCD assessment at diagnosis



eos = blood eosinophil count (cells/µL)
** Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization*
*** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*

FIGURE 4.3

Treatment with macrolide antibiotics has been reported to prevent COPD exacerbations and improve patient quality of life and symptoms, especially in those patients who have frequent exacerbations.

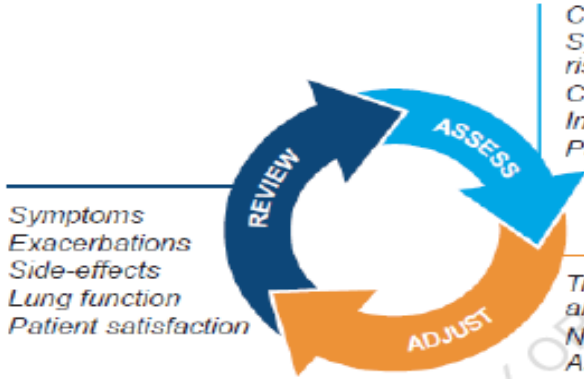
In addition to their antimicrobial effects

-macrolides have a variety of physiological functions, such as anti-inflammatory and anti-viral effects

- reduced sputum production,
- inhibition of biofilm formation
- inhibition of bacterial virulence factor production.

Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications (adjust down/up/between tracks)
Education & skills training

CONTROLLER and PREFERRED RELIEVER (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-formoterol
RELIEVER: As-needed low-dose ICS-formoterol			

CONTROLLER and ALTERNATIVE RELIEVER (Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-LABA
RELIEVER: As-needed short-acting β2-agonist				

Other controller options for either track				
	Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA; add low dose OCS but consider side-effects*

HDM: house dust mite; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist; SLIT: sublingual immunotherapy. For recommendations about *initial* asthma treatment in adults and adolescents, see Box 3-4A (p.53) and 3-4B (p.54).

American Journal of Respiratory and Critical Care Medicine

Home>All AJRCCM Issues>**Vol. 177, No. 2 | Jan 15, 2008**

Refractory Asthma

-Clarithromycin Targets Neutrophilic Airway Inflammation

-modulate IL-8 levels and neutrophil accumulation and activation in the airways

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Other Indications of Macrolides :

long-term use in treating neutrophil-dominated inflammation in

diffuse panbronchiolitis,

bronchiectasis,

cystic fibrosis.

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CONCLUSIONS:

prolonged treatment of CF patients with a 14-membered ring macrolide antibiotic clarithromycin

- *down-regulation of the inflammatory response,*
- *immunological changes including the switch from Th2 to Th1 type response.*

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Take home messages

- **Kriazopoulo et al. reinforces 2019 recommendations from the ATS and IDSA which suggests stronger evidence for use of macrolides + β-lactam versus fluoroquinolone, or β-lactam alone for severe CAP**

- **We concluded that addition of clarithromycin to the treatment regimen of patients with severe CAP leads to better survival rates than the other study treatments(Azi+ β-lactam or Quinolones monotherapy)**

THANK YOU

LEV2273159