Greek Research Collaboration Produces Unique Insights into Mechanisms of Benefit of Clarithromycin in Community-Acquired Pneumonia

- New research based on directly measured metrics of patients in a randomized, placebo-controlled clinical trial provides a mechanistic explanation for the clinical benefit provided by the antimicrobial agent clarithromycin in patients with community-acquired pneumonia (CAP).
- Insights argue for effects of clarithromycin on immune function and inflammation in addition to its acknowledged antimicrobial action

[Athens, Greece, Date & Time] Compelling new insights into the mechanisms of action of the macrolide antibiotic clarithromycin in community-acquired pneumonia (CAP) have emerged from the latest analysis of data from the ACCESS randomized clinical trial. The data, published on 3 April 2026 in *eBioMedicine*, part of the *Lancet Discovery Science* suite of Open Access journals, provides a unique window onto some of the pathological processes at work in CAP and the effects of clarithromycin on those processes. In doing so this research strongly supports speculation that clarithromycin, in addition to its established antimicrobial action, may exert immune- and inflammation-modulating effects that are important contributors to its clinical effectiveness in the management of CAP in hospitalized adult patients.

The new research, like the original ACCESS study, was sponsored by the Hellenic Institute for the Study of Sepsis with funding support from Abbott Products Operations (APO), Allschwil, Switzerland. APO had no role in the design of conduct of the study, or in data collection, analysis or interpretation.

Working in collaboration with the Greek Genome Center situated at the Biomedical Research Foundation Academy of Athens (BRFAA) ACCESS investigators undertook detailed studies of gene transcription and differential gene expression in 86 patients from the ACCESS study (45 in the placebo group and 41 in the clarithromycin group) and related those findings to data about cytokine production by stimulated peripheral blood mononuclear cells (PBMCs).

“In my view this manuscript breaks boundaries in pneumonia management” said Professor Evangelos Giamarellos-Bourboulis, President of the Hellenic Institute for the Study of Sepsis (HISS) and Principal Investigator of the ACCESS study.

Giamarellos-Bourboulis noted that currently published investigations into severe pneumonia exhibit three characteristic traits:

- Clinical trials are often limited to assessment of clinical improvement, with limited exploration of the mechanisms of improvement

- Analysis on the transcriptomic profile of patients relies on observational methodology and cytokine production from circulating blood cells is often not presented, leaving readers unable to ascertain if changes at the transcriptional level are accompanied by changes in cytokine production.
- They seldom provide serial blood sampling.

"In our new report we go beyond the existing paradigm and present convincing evidence with full complementarily", Giamarellos-Bourboulis commented. "We demonstrate robustly how the impact of clarithromycin treatment on the disease processes is translated into clinical benefit."

Based on their primary clinical findings that achievement of early clinical improvement (as defined by the primary endpoint) to day 4 led to the major secondary benefits of decreased progression into respiratory failure-mechanical ventilation (RF-MV) and prevention of secondary sepsis, ACCESS investigators explored the differences in the immune trajectories from baseline to day 4 between patients who were treated with clarithromycin or with placebo using both transcriptomics and cytokine production by PBMCs and other circulating blood cells involved in immune responsiveness and cross-referenced these according to whether or not the patients studied achieved the clinical primary endpoint of ACCESS. Main findings are:

- Downregulation of IL-1 cytokines and of neutrophil degranulation in response to clarithromycin are implicated in prevention of respiratory failure
- Increase of monocyte-derived pro-inflammatory cytokines and chemokines in response to clarithromycin, coupled with upregulation of antigen presentation, is linked to clinical benefits including the prevention of secondary sepsis.
- The findings strongly support the case for using clarithromycin to treat hospitalized adult CAP patients.

"These data make ACCESS the first randomized controlled trial in CAP where clinical benefit and modulation of pathophysiological mechanisms are tied and provide robust evidence of drug benefit", commented Giamarellos-Bourboulis. "We link the trajectory of attenuation of the Interleukin-1 pathway with the decrease of the risk for progression into respiratory failure or mechanical ventilation. We also link the trajectory of the increased production of chemokines/cytokines and the decreased production of anti-inflammatory cytokines by immune cells together with the improvement of antigen-presentation and the attenuation of degranulation of neutrophils with the prevention of secondary sepsis. Findings apply both for patients with bacterial and non-bacterial CAP."

About CAP

Community-acquired pneumonia (CAP) is an acute infection of the lungs acquired outside hospitals or healthcare facilities. Infections of this sort are sometimes referred to as “lower respiratory tract infections” to differentiate them from infections which affect the upper parts of the respiratory tract, such as sinusitis.

Bacterial CAP is most commonly caused by organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus*. It typically presents with acute and severe symptoms, including high fever, productive cough with purulent sputum, and localized chest findings on examination. Antibiotics are the mainstay of treatment in these cases.

CAP is a medical concern because it is a leading cause of morbidity and mortality worldwide. It is characterized by activation of inflammatory pathways and immune dysfunction and as a result is a major cause of sepsis. That in turn places a significant burden on healthcare systems due to hospitalizations and complications of organ dysfunction. Early diagnosis and appropriate treatment are critical to improving outcomes.

About the ACCESS Study

The ACCESS study (**A** randomized clinical trial of oral **C**larithromycin in **C**ommunity-acquired pneumonia to attenuat**E** inflammatory response**S** and improve outcome**S**) is a Phase III prospective, double-blind, randomized controlled trial conducted in adult patients hospitalized with community-acquired pneumonia (CAP) in 18 public Greek hospitals between January 2021 and April 2023. Participating centres represented the major geographic regions of the country (Alexandroupolis, Attiki, Ioannina, Kerkyra, Larissa and Patras). The study was registered at www.clinicaltrials.gov before the inclusion of the first patient (NCT04724044).

Patients were eligible to take part in ACCESS if they were ≥18 years of age with radiological evidence of pneumonia and at least two indicative symptoms (cough, pleuritic chest pain, sputum production or shortness of breath) *plus* at least two signs of the systemic inflammatory response syndrome *plus* total sequential organ failure assessment (SOFA) score ≥2 and blood procalcitonin (PCT) ≥0·25 ng/mL. (PCT level was used to identify patients with bacterial CAP requiring antibiotics.) Patients who had COVID-19 were excluded.

Patients were double-blind randomized in a 1:1 ratio to treatment with antibiotics chosen according to current best practice (known as “Standard-of-Care” or SoC): this included widespread use of third-generation cephalosporins and β-lactam plus β-lactamase combinations. In addition to SoC, patients in ACCESS received either placebo or oral clarithromycin at doses of 500 mg, given every 12 hours for 7 consecutive days (unless a patient was discharged earlier).

The primary endpoint of the ACCESS trial was early clinical and anti-inflammatory response assessed after the first 72 hours. This composite outcome, incorporating an at least 50% decrease of the respiratory severity symptom (RSS) score and improvement of organ dysfunction or systemic inflammation, was attained in 38.3% of patients of the SoC and placebo arm and in 67.9% of patients of the SoC and clarithromycin arm ($p < 0.0001$). Among patients treated with clarithromycin there was also a decrease of mortality by the end of treatment (8% in the clarithromycin arm versus 17% in the placebo arm) and less progression into respiratory failure requiring mechanical ventilation (6.0% versus 17.3%, $p = 0.0041$).Patients treated with clarithromycin were also significantly less likely to develop new episodes of sepsis (13% vs. 24%, $p = 0.029$).

Primary findings from the ACCESS study were published in the peer-reviewed high-impact medical science journal *Lancet Respiratory Medicine* in 2024 (doi: 10.1016/S2213-2600(23)00412-5). Responding to the findings in an accompanying Editorial, Professor Grant Waterer, University of Western Australia, Perth, Australia, stated that “Combination therapy with clarithromycin should now be considered standard of care in all hospitalized [CAP] patients, not just a treatment alternative.”

About Clarithromycin

Clarithromycin is a semi-synthetic macrolide antibiotic derived from erythromycin. Widely used to treat a range of bacterial infections, it works by primarily inhibiting bacterial protein synthesis through binding to the 50S ribosomal subunit, thereby preventing bacterial growth. It is on the World Health Organization's List of Essential Medicines.

About HISS

Hellenic Institute for the Study of Sepsis (HISS) is a leading, non-profit, non-commercial organization in medical research since 2010, supporting clinical research in sepsis and systemic inflammation. Based in Athens, Greece, HISS interfaces with infectious disease specialists through the Hellenic Sepsis Study Group to design, develop, implement and analyse complex clinical trials and other lines of research to improve the understanding and management of infectious diseases. HISS has to date initiated 34 studies into sepsis and severe infections and a further 4 studies of systemic inflammatory disorders, including ACCESS, BEYOND, EMBRACE, INSPIRE, PRECISION, POINT, and REACT.

For more details visit www.sepsis.gr.

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