Clinical Outcomes Associated With Procalcitonin Algorithms to Guide Antibiotic Therapy in Respiratory Tract Infections

Clinical Question In patients with respiratory tract infection, is measurement of procalcitonin to guide antibiotic prescriptions associated with reduced antibiotic exposure without increases in all-cause mortality or treatment failure?

Bottom Line The measurement of procalcitonin to guide initiation and duration of antibiotic treatment in patients with respiratory tract infections of varying severity is associated with lower antibiotic exposure without increasing all-cause mortality or treatment failure.

Philipp Schuetz, MD, MPH
Matthias Briel, MD, MSc
Beat Mueller, MD

THE MOST FREQUENT INDICATION for antibiotic use is respiratory tract infections, ranging in severity from self-limited acute bronchitis to life-threatening bacterial pneumonia.[1] Antibiotic prescriptions for nonpneumonia respiratory tract infections and prolonged courses for pneumonia contribute to antibiotic overuse, which potentially leads to the development of antibiotic resistance and increased risk of *Clostridium difficile* infection.

Procalcitonin, a biomarker for bacterial infections, is released ubiquitously in response to bacterial toxins and bacteria-specific proinflammatory mediators.[2] Previous trials investigated the effects of procalcitonin al-

Author Affiliations: Medical University Department, Kantonsspital Aarau, Tellstrasse, Aarau, Switzerland (Drs Schuetz and Mueller); Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Switzerland (Dr Briel); and Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada (Dr Briel).
Corresponding Author: Philipp Schuetz, MD, MPH, Medical University Department, Kantonsspital Aarau, Tellstrasse, CH-5001 Aarau, Switzerland (schuetzph@gmail.com).
JAMA Clinical Evidence Synopsis Section Editor: Mary McGrae McDermott, MD, Contributing Editor. We encourage authors to submit papers for consideration as a JAMA Clinical Evidence Synopsis. Please contact Dr McDermott at mdm608@northwestern.edu.

Table. Summary of Results for Measuring Procalcitonin to Guide Antibiotic Use in Respiratory Tract Infections[a]

	No. of Trials	Procalcitonin Group	Control Group	Adjusted Odds Ratio or Mean Difference (95% CI)
All patients with respiratory tract infections	14	**(n = 2085)**	**(n = 2126)**	
Mortality, No. (%)		118 (5.7)	134 (6.3)	0.94 (0.71 to 1.23)
Treatment failure, No. (%)		398 (19.1)	466 (21.9)	0.82 (0.71 to 0.97)[c]
Total antibiotic exposure, median (IQR), d		4 (0 to 8)	8 (5 to 12)	−3.47 (−3.78 to −3.17)[b]
Patients treated in primary care	2	**(n = 507)**	**(n = 501)**	
Mortality, No. (%)		0	1 (0.2)	NA
Treatment failure, No. (%)		159 (31.4)	164 (32.7)	0.95 (0.73 to 1.24)
Total antibiotic exposure, median (IQR), d		0 (0 to 0)	6 (0 to 7)	−3.06 (−3.48 to −2.65)[b]
Patients treated in the emergency department	7	**(n = 1291)**	**(n = 1314)**	
Mortality, No. (%)		61 (4.7)	59 (4.5)	1.03 (0.7 to 1.5)
Treatment failure, No. (%)		182 (14.1)	228 (17.4)	0.76 (0.61 to 0.95)[c]
Total antibiotic exposure, median (IQR), d		5 (0 to 8)	9 (5 to 12)	−2.96 (−3.38 to −2.54)[b]
Patients treated in the intensive care unit	5	**(n = 287)**	**(n = 311)**	
Mortality, No. (%)		57 (19.9)	74 (23.8)	0.84 (0.54 to 1.31)
Treatment failure, No. (%)		57 (19.9)	74 (23.8)	0.84 (0.54 to 1.31)
Total antibiotic exposure, median (IQR), d		8 (5 to 15)	12 (8 to 18)	−3.21 (−4.32 to −2.10)[b]
Patients with community-acquired pneumonia	12	**(n = 999)**	**(n = 1028)**	
Mortality, No. (%)		92 (9.2)	111 (10.8)	0.89 (0.64 to 1.23)
Treatment failure, No. (%)		190 (19.0)	240 (23.4)	0.77 (0.62 to 0.96)[c]
Total antibiotic exposure, median (IQR), d		6 (4 to 10)	10 (8 to 14)	−3.98 (−4.44 to −3.52)[b]
Patients with exacerbation of COPD	6	**(n = 288)**	**(n = 296)**	
Mortality, No. (%)		9 (3.1)	8 (2.7)	1.15 (0.43 to 3.09)
Treatment failure, No. (%)		35 (13.7)	45 (15.2)	0.75 (0.46 to 1.22)
Total antibiotic exposure, median (IQR), d		0 (0 to 6)	7 (0 to 10)	−3.03 (−3.76 to −2.3)[b]

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NA, not available.
[a] Source: Schuetz P, Müller B, Christ-Crain M, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev*. 2012;9:CD007498.[4] doi:10.1002/14651858.CD007498.pub2
[b] $P < .01$.
[c] $P < .05$.

Evidence Profile

No. of randomized trials: 14

Study years: 2004-2011

No. of patients: 4211 with respiratory infections of varying severity, including upper respiratory tract infections, bronchitis, exacerbation of chronic obstructive pulmonary disease (COPD), community-acquired pneumonia (CAP), and ventilator-associated pneumonia

Men: 2282 (54%) **Women:** 1929 (46%)

Race/ethnicity: Unavailable

Age, mean (SD): 59.8 (19.2) years

Settings: Inpatient and outpatient, medical and surgical intensive care units (ICUs)

Countries: United States, Germany, Switzerland, France, Denmark, China

Comparison: Antibiotic therapy with vs without guidance from procalcitonin levels

Primary outcomes: (1) All-cause 30-day mortality and (2) treatment failure within 30 days defined as death, ICU admission, hospitalization, respiratory infection–specific complications, recurrent or worsening infection, and patients reporting any symptoms of ongoing respiratory tract infection at 30 days

Secondary outcome: Total antibiotic exposure at 30 days

gorithms for guiding antibiotic use.[3] These algorithms recommended antibiotic prescription only if procalcitonin levels are elevated and recommended antibiotic cessation when procalcitonin levels normalize. Yet the safety and efficacy of procalcitonin algorithms have not been conclusively demonstrated.

SUMMARY OF FINDINGS

There was no increase in all-cause mortality associated with procalcitonin testing for any clinical setting or any type of respiratory tract infection (TABLE). Treatment failure was lower for procalcitonin-guided patients treated in the emergency department (odds ratio [OR], 0.76 [95% CI, 0.61-0.95]) and in patients with CAP (OR, 0.77 [95% CI, 0.62-0.96]). Patients for whom procalcitonin was used to guide antibiotic therapy had lower antibiotic exposure, which was mainly due to lower antibiotic prescription rates for exacerbation of COPD (48% vs 73%) and bronchitis (24% vs 66%). Patients with measurement of procalcitonin also had shorter antibiotic courses in the emergency department (median, 7 days [IQR, 4-10] vs 10 days [IQR, 7-13]), in the ICU (median, 8 days [IQR, 5-15] vs 12 days [IQR, 8-18]), and with a diagnosis of CAP (median, 7 days [IQR, 5-10] vs 10 days [IQR, 8-14]).

COMMENT

Among 14 trials and 4211 patients with respiratory tract infections, measurement of procalcitonin to guide antibiotic therapy was not associated with increased mortality or treatment failure.[4] Results suggest that using procalcitonin to guide antibiotic therapy is associated with fewer antibiotic prescriptions in primary care settings and in patients with less severe infections, and with shorter courses of antibiotics for patients evaluated in the emergency department or the critical care setting. The lower risk of treatment failure associated with procalcitonin testing may in part relate to lower antibiotic exposure, but this needs furthers exploration.

Limitations

The randomized trials were not blinded in regard to allocation and outcome assessment. Adherence to procalcitonin algorithms was variable and lower in the critical care setting (between 47% and 81%). Included trials were mostly conducted in Europe (78%). Two trials were conducted in China and one multinational trial was conducted in the United States. Immunosuppressed patients, children, and patients with nonrespiratory infections were not included.

Comparison of Findings With Current Guidelines

There are currently no practice guidelines in the United States regarding measurement of procalcitonin to guide antibiotic therapy. The 2011 European Respiratory Society guidelines recommended using procalcitonin to guide antibiotic treatment duration in CAP, even in severe cases.[5] The 2012 international Surviving Sepsis Campaign guidelines emphasize procalcitonin for stopping antibiotics.

Areas in Need of Future Study

Further studies are needed to determine the safety of procalcitonin algorithms in critical care settings and for guiding treatment of nonrespiratory infections. Future trials should evaluate the cost-effectiveness of procalcitonin algorithms by considering country-specific costs of procalcitonin measurements and potential savings and health benefits by reducing antibiotic prescription rates.[6,7]

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Drs Schuetz and Mueller received support for research from BRAHMS/Thermofisher and bioMérieux and for speaking engagements. Dr Briel received research support from BRAHMS/Thermofisher.

REFERNCES

1. Mizgerd JP. Acute lower respiratory tract infection. *N Engl J Med*. 2008;358(7):716-727.
2. Becker KL, Nylén ES, White JC, Müller B, Snider RH Jr. Clinical review 167: Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors. *J Clin Endocrinol Metab*. 2004;89(4):1512-1525.
3. Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. *Arch Intern Med*. 2011;171(15):1322-1331.
4. Schuetz P, Müller B, Christ-Crain M, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev*. 2012;9:CD007498.
5. Woodhead M, Blasi F, Ewig S, et al; Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections: full version. *Clin Microbiol Infect*. 2011;17(suppl 6):E1-E59.
6. Heyland DK, Johnson AP, Reynolds SC, Muscedere J. Procalcitonin for reduced antibiotic exposure in the critical care setting: a systematic review and an economic evaluation. *Crit Care Med*. 2011;39(7):1792-1799.
7. Müller F, Christ-Crain M, Bregenzer T, et al; ProHOSP Study Group. Procalcitonin levels predict bacteremia in patients with community-acquired pneumonia: a prospective cohort trial. *Chest*. 2010;138(1):121-129.