Biomarkers to improve rational antibiotic use in low-resource settings

See Articles page e119

The high and continuous rise of antibiotic use in low-income primary-care settings have called for the use of point-of-care biomarker testing, such as testing of C-reactive protein (CRP), to enhance antimicrobial stewardship interventions. Detecting the minority of patients with serious bacterial infections is challenging for health workers, particularly because of the scarcity of adequate diagnostics. To date, the optimal strategy of using biomarkers to inform antibiotic prescription in such settings is unclear.

In this issue of *The Lancet Global Health*, Thomas Althaus and colleagues[1] report the results of an individually randomised controlled trial that assessed the effect of two different CRP thresholds (20 mg/L and 40 mg/L) on the proportion of antibiotic prescriptions, when compared with current practice, among 2410 febrile patients in primary care in Thailand and Myanmar. The study included both children older than 1 year and adults, and showed that CRP point-of-care testing at a threshold of 40 mg/L might reduce antibiotic prescribing compared with current practice in these settings, albeit with only a modest absolute risk reduction of 5% (intervention group 34% and control group 39%). No differences in clinical recovery and severe adverse events were observed, although the study was not powered for these clinical outcomes. Althaus and colleagues[1] are to be commended for completing such a large multicentre, multicountry trial with diversity in terms of rural and urban environments. Importantly, and contrary to previous studies that assessed CRP use in southeast Asia,[2] this trial included patients at risk of bacterial infections—ie, patients who would benefit from biomarker testing.

The trial conveys several key messages related to the integration of biomarkers into primary-care antibiotic-stewardship interventions in low-resource settings. First, the study underlines that biomarker validation studies should not be limited to analytical performance assessments but should rather also measure the effects on relevant patient outcomes in the context of future implementation.[3] Findings from diagnostic accuracy studies often do not correlate with clinical effect. This discrepancy is in part because, especially in paediatrics, adequate reference standards to define serious bacterial infections are often absent, which makes diagnostic accuracy studies challenging.

Furthermore, the absence of effect in the group with a low CRP cutoff (20 mg/L) again showed that using low-specificity biomarker cutoffs at the primary-care level results in antibiotic use in many low-risk patients, and does not reduce antibiotic prescription.[4] Among primary-care patients without clear clinical signs of severity, the prevalence of serious bacterial infections is low.[5] As a result, a higher biomarker threshold with adequate specificity should be used to rule-in bacterial infection.

In the study by Althaus and colleagues,[1] CRP was used as a screening test for bacterial infection in all patients. However, studies in high-income settings have shown that at-risk patient selection through the integration of biomarkers into clinical guidelines is preferable over screening approaches.[6,7] Testing only at-risk patients raises the pretest probability of disease sufficiently high, so that biomarker testing is useful. Restriction of testing to patients at risk based on clinical signs might not only result in greater effect of the point-of-care biomarker test, but might also avoid test wastage. For example, integration of biomarker testing into a clinical decision algorithm avoided testing of around 60% of febrile children in a 2017 clinical trial in Tanzania.[8] Such electronic decision algorithms are possible solutions in supporting minimally trained health workers in systematic clinical assessments and in the interpretation of test results in a given clinical and epidemiological context. Moreover, these algorithms could improve guideline adherence;[9] indeed, non-compliance appeared to be a major contributor to the only modest effect on antibiotic prescription in the study by Althaus and co-workers.[1] 86% of CRP measurements were below 40 mg/L; the potentially attainable reduction in antibiotic prescription would have thus been 25%. The lower observed effect might also be attributable to the trial design itself; because of individual rather

than cluster randomisation, providers had to switch prescription strategies in between each patient, which is challenging. Although individual randomisation might be suited for controlled, efficacy studies, it leads to contamination in effectiveness studies, especially when health-care workers receive little guidance. The observed effect is small also because systematic patient follow-up in itself might lower antibiotic prescription, because providers note that the majority of patients in primary care recover spontaneously from minor infections.

The results from this study again emphasise that effective interventions to reduce antibiotic use cannot rely on the introduction of a single diagnostic test.[4] In addition to clinical guidance, provider training, patient education, supervision, and policy strategies have an important role.[11] As Althaus and colleagues[1] note, the results show, despite all the limitations of the study, additional gains of CRP testing in reducing antibiotic prescription, without effects on clinical recovery. These findings support the use of biomarkers in targeting antibiotic prescription in low-resource settings. Future effectiveness studies should focus on assessing biomarker testing within overall antimicrobial stewardship interventions, including clinical guidance, training, and patient education.

Kristina Keitel
Swiss Tropical and Public Health Institute, 4051 Basel, Switzerland; and Department of Paediatric Emergency Medicine, 3010 Bern University Hospital, Bern, Switzerland
kristina.keitel@swisstph.ch

I declare no competing interests.

1 Althaus T, Greer RC, Swe MMM, et al. Effect of point-of-care C-reactive protein testing on antibiotic prescription in febrile patients attending primary care in Thailand and Myanmar: an open-label, randomised, controlled trial. *Lancet Glob Health* 2019; **7:** e119–31.
2 Do NTT, Ta NTD, Tran NTH, et al. Point-of-care C-reactive protein testing to reduce inappropriate use of antibiotics for non-severe acute respiratory infections in Vietnamese primary health care: a randomised controlled trial. *Lancet Glob Health* 2016; **4:** e633–41.
3 Drain PK, Hyle EP, Noubary F, et al. Diagnostic point-of-care tests in resource-limited settings. *Lancet Infect Dis* 2013; **14:** 239–49.
4 Aabenhus R, Jensen J-US. Biomarker-guided antibiotic use in primary care in resource-constrained environments. *Lancet Glob Health* 2016; **4:** e586–87.
5 D'Acremont V, Kilowoko M, Kyungu E, et al. Beyond malaria—causes of fever in outpatient Tanzanian children. *N Engl J Med* 2014; **370:** 809–17.
6 Verbakel JY, Lemiengre MB, De Burghgraeve T, et al. Should all acutely ill children in primary care be tested with point-of-care CRP: a cluster randomised trial. *BMC Med* 2016; **14:** 131.
7 van Vugt SF, Broekhuizen BD, Lammens C, et al. Use of serum C reactive protein and procalcitonin concentrations in addition to symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough: diagnostic study. *BMJ* 2013; **346:** f2450.
8 Keitel K, Kagoro F, Samaka J, et al. A novel electronic algorithm using host biomarker point-of-care tests for the management of febrile illnesses in Tanzanian children (e-POCT): a randomized, controlled non-inferiority trial. *PLoS Med* 2017; **14:** e1002411.
9 Keitel K, D'Acremont V. Electronic clinical decision algorithms for the integrated primary care management of febrile children in low-resource settings: review of existing tools. *Clin Microbiol Infect* 2018; **24:** 845–55.
10 Cals JWL, Butler CC, Hopstaken RM, Hood K, Dinant G-J. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. *BMJ* 2009; **338:** b1374.