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Biomarker-guided antibiotic use in primary care in resource-constrained environments



Because of antimicrobial resistance, the global overuse of antibiotics is now a threat to one of the most effective and mortality-lowering interventions in modern medicine.¹ One of the most important challenges is to substantially lower the use of antibiotics when these drugs are not needed. The fear of missing a severe case of pneumonia can incite health-care providers to ignore the fact that, in many non-severe cases of respiratory tract infections, antibiotic treatment will probably not markedly alter the outcome for the individual patient.² Reduction of antibiotic use will require reliable and broadly applicable segregation of non-bacterial infection and trivial bacterial infections from serious bacterial infections.

In *The Lancet Global Health*, Nga Do and colleagues³ report the results of a large (more than 2000 participants) randomised controlled trial of a point-of-care antibiotic strategy guided by C-reactive protein concentrations compared with usual best practice in primary care patients with non-severe acute respiratory tract infection in Vietnam. The results demonstrate that a point-of-care C-reactive protein intervention can reduce antibiotic prescribing in this setting, albeit with only a moderate reduction in absolute risk (adjusted 12.5%; intervention 64.4% vs control 77.9%). Importantly, there were no apparent differences in serious adverse effects or delayed patient recovery.

Do and colleagues should be congratulated on completing this ambitious, large-scale trial to assess a point-of-care biomarker-guided antibiotic strategy in a resource-constrained environment. The results expand the current evidence base by showing that such a stewardship approach is applicable in low-income and middle-income countries. Furthermore, Do and colleagues performed a very sensitive sample size calculation to prove the trial robust for subgroup analysis in children. The effect size was similar to adults.

The results support the findings from randomised trials in Europe, summarised in a 2014 Cochrane review,⁴ which found C-reactive protein effective in reducing antibiotic use with no apparent risk to patient safety. So, why was the effect of the current approach only moderate? Some limitations to the study should be

mentioned. First, the cut-off applied in the current study (10 mg/L in children younger than 6 years, 20 mg/L in all other patients) is low, allowing for antibiotic use in many low-risk patients and patients without bacterial infection. Second, overruling of the algorithm was very common; in fact, 88% of all C-reactive protein measurements were below 20 mg/L and thus the potential to reduce antibiotic use seems much higher than the actual numbers in the current study. In order to improve the effect size we should start looking at ways to optimise use of this tool.

Undoubtedly, part of this optimisation comes down to issues of public health and cultural habits among both patients and physicians. Physicians should be trained to adhere to the algorithm to a much larger extent. Improved education and associated increased adherence to the algorithm could lead to further reductions in antibiotic use, as can be read from the large degree of heterogeneity detected ($I^2=84%$) corresponding to differences in effect size among sites, which is a specific concern and limitation of the current study. Previous studies have shown that education in communicative skills works well together with point-of-care C-reactive protein testing.^{5,6} It has also been shown that doctors that do not understand a specific strategy well use it poorly.⁷

Arguably, many of these patients should not have a C-reactive protein test done in the first place. Only non-severe infections were included, thus increasing the risk of spectrum bias. Biomarker tests should ideally be used to rule out a high risk of severe infection when the provider is uncertain if antibiotic prescribing is likely to be beneficial, and to negotiate a perceived strong patient demand for an antibiotic prescription.

Future trials in settings like the current should consider increasing the cutoff for no antibiotic therapy. If the patient is in no acute distress, with a C-reactive protein level below 50 mg/L, a serious bacterial infection is rarely present. Alternatively, all cases of acute respiratory tract infections that do not need urgent admission to hospital could be included.^{4,5,8}

However, reduction of antimicrobial resistance cannot be achieved merely by the introduction of a

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single test. Access to education, the promotion of a change of behavioural norms, vaccination coverage, and other preventive measures must work in concert to preserve antibiotic efficacy. Regulatory authorities need to consider the vast self-purchase of antibiotics (eg, in Vietnam around 90% of prescriptions are self-purchased)⁹ and legislate to prevent this bypass of proper medical control of over-the-counter sales.

Implementation of antibiotic stewardship strategies often awaits proof of cost-effectiveness.¹⁰ This convention must be challenged: we are facing a problem of a magnitude that urges us to implement effective strategies even if they are marginally more expensive. The rise in antimicrobial resistance suggests that short-term savings of the current strategy could be vastly outweighed by future costs for hospital treatment of otherwise trivial infections with highly resistant infectious pathogens.¹¹

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We declare no competing interests.

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