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Journal club

Was the implementation strategy of the ProACT trial adequately proactive?

Commentary on:

Huang DT, *et al*. Procalcitonin-guided use of antibiotics for lower respiratory tract infection. *N Engl J Med* 2018; 379: 236–249.

Context

Rising antimicrobial resistance rates represent an alarming threat to public health, currently causing over 25000 and 23000 deaths per year in European Union and the USA, respectively [1, 2]. The significant global overuse of antibiotics amplifies the development of resistant bacterial strains [1, 2]. A recent national audit in the USA estimated that almost half of all antibiotic prescriptions were issued for respiratory tract infections (221 antibiotic prescriptions per 1000 population per year) and half of them were inappropriate [3]. Extensive campaigns have been carried out to promote antibiotic stewardship guidance in an attempt to limit the administration of unneeded antibiotics, but their impact has been modest [4, 5].

In this context, procalcitonin (PCT) has emerged as a promising biomarker to accurately guide antibiotic administration in respiratory tract and other infections [6, 7]. The safety and clinical effectiveness of PCT was assessed in a recent Cochrane systematic review that involved 26 randomised controlled trials (RCTs) evaluating 6708 patients with lower respiratory tract infections (LRTIs) and demonstrated that PCT guidance could decrease the mean antibiotic duration by 2.43 days, without significantly affecting mortality or treatment failure rates [6]. Another systematic review, involving eight RCTs and 1062 participants, focused on acute exacerbations of chronic obstructive pulmonary disease (COPD) and found that PCT guidance could reduce antibiotic prescription rates by 44%, without adversely affecting the clinical outcomes [7].

The ProACT study was a pragmatic trial aiming to evaluate the clinical effectiveness of PCT guidance at the point-of-care on antibiotic use for LRTIs in a real-life setting [8].

Methods

The ProACT study, a multicentre, pragmatic open-label RCT, evaluated a PCT antibiotic prescribing guideline *versus* usual care in the emergency departments of 14 hospitals across the USA. ProACT recruited adults presenting with suspected LRTI (COPD exacerbation, asthma exacerbation, acute bronchitis or community-acquired pneumonia) for whom there was clinical uncertainty regarding the need for antibiotic initiation. Participants were randomised in a 1:1 ratio to PCT-guided care *versus* usual care. In the intervention group, upon recruitment clinicians were provided with a PCT measurement and a PCT-based antibiotic prescribing guideline which strongly discouraged,

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The ProACT trial does not inform the evidence base regarding safety and clinical effectiveness of procalcitonin (PCT) as a biomarker to guide antibiotic administration for LRTIs, but reveals potential challenges in the introduction of PCT in real life. http://ow.ly/Enfr30n2TK6

discouraged, encouraged or strongly encouraged the administration of antibiotics for PCT levels of <0.1, 0.1–0.25, >0.25–0.5 or >0.5 μg·L^{-1}, respectively. In addition, for hospitalised patients PCT was also measured 6–24 h later, and on days 3, 5 and 7, while patients were receiving antibiotics. Aside from these measurements, clinicians maintained complete decision-making autonomy. In the control group, clinicians were unaware of the participants PCT levels and applied standard care.

The co-primary outcomes were total antibiotic exposure (in days) and adverse outcomes attributable to withholding antibiotics within a month from recruitment. Secondary outcomes captured further details on antibiotic administration patterns during the 1 month follow-up, healthcare resources use and quality of life.

To promote adherence to the PCT guidance, investigators employed implementation strategies routinely used in hospitals' quality improvement processes, which included the dissemination of the guidance through lectures, posters, reminders in the electronic health records and other promotional tools in the participating hospitals.

Main results

Among 1656 randomised participants, 39.3% had a final diagnosis of asthma exacerbation, 31.9% COPD exacerbation, 24.2% acute bronchitis and 19.9% community-acquired pneumonia. The baseline characteristics were similar between the study arms. Based on the PCT guidance, antibiotics would only be advisable for 8% of all participants, as 92% had PCT ≤0.25 μg·L^{-1} at presentation.

In ProACT, the interventions of PCT measurements and the associated guidance did not limit mean antibiotic exposure within a month from randomisation. Mean antibiotics duration was 4.2 days in the PCT group and 4.3 days in the control group (difference: –0.05 days, 95% CI: –0.6–0.5). Per protocol analysis yielded similar results (difference: –0.1 days, 95% CI: –0.7–0.6). Following patient randomisation at presentation in the emergency department, antibiotics were administered to 34.1% and 38% of participants in the PCT and control groups, respectively (difference: –4.6%, 99.86% CI: –12.2–3%). However, within a month from presentation 57% and 61.8% received antibiotics in each group (difference: –4.8%, 99.86% CI: –12.2–3%). In addition, there was a nonsignificant trend of a lower rate of adverse outcomes in the PCT group at 1-month follow-up (difference –1.5%, 95% CI: –4.6–1.7%).

Clinicians' adherence to the PCT guideline was very limited. Characteristically, in the PCT group among those with PCT levels <0.1, 0.1–0.25, 0.25–0.5 and >0.5 μg·L^{-1} at presentation antibiotics were administered to 30.3%, 28.6%, 74.1% and 77.1%, respectively. The corresponding percentages for the control group were 34.1%, 50.7%, 52.2% and 75.6%. Poor adherence was noted for both high and low PCT levels, suggesting that clinicians had very limited confidence in PCT results. The most commonly cited reasons for non-adherence were clinicians' belief that the patient had a bacterial infection or a COPD exacerbation requiring antibiotics. Interestingly, prescription occurring before the PCT result was available was another frequently cited reason for non-adherence.

Commentary

ProACT was a statistically negative trial and the investigators concluded that there may be fewer opportunities to change antibiotic decisions based on PCT compared with earlier trials, given the rise in antimicrobial resistance awareness and the improved antibiotic stewardship policies. Nevertheless, this is only the first of several levels of interpretation.

This study did not further inform the evidence base regarding the safety and clinical effectiveness of PCT as a biomarker to guide the administration of antibiotics in LRTIs. The main reason was the very low adherence to PCT guidance, which limits the interpretability of clinical outcomes. Hence, results from previous RCTs, which have demonstrated the clinical efficacy and safety of PCT in LRTIs, are more relevant. These include nine RCTs, involving 3429 patients with LRTIs, that succeeded in over 80% adherence to PCT guidance [6].

Instead, the main explanation seems to be that the implementation strategy employed was unsuccessful. Clinicians did not significantly change their clinical practice in response to PCT guidance. In the intervention group, 34% of the participants received antibiotics at presentation, while only 8% had PCT >0.25 μg·L^{-1}. The fact that one in four patients with raised PCT values at presentation did not receive antibiotics is also revealing. It would be crucial to evaluate the clinical outcome of those who did not receive antibiotics despite raised PCT levels, as an increased risk of adverse outcomes would suggest that PCT can more accurately guide antibiotic administration compared to clinical judgement. Unfortunately, these results were not presented.

The investigators presented a per-protocol sensitivity analysis for antibiotic exposure and adverse outcomes attributable to withholding antibiotics, showing similar results to the main analysis. However, this analysis is of limited value due to selection bias and does not adequately address the issue of low adherence to PCT guidance. More specifically, biomarker guidance is more likely to be followed in sicker patients with high PCT levels, who will require more antibiotics. Given that adherence to PCT guidance across different study centres ranged from 40% to 84%, it would have been more informative to present subgroup analyses of centres with higher adherence to PCT guidance.

Moreover, a nonsignificant 1.5% absolute reduction in adverse outcomes was reported. This was in agreement with previous studies. However, it remains unclear whether this reduction is linked to compliance with PCT guidance or not. Again, subgroup analyses of centres with higher adherence to PCT guidance would have been informative.

While the investigators tried to mimic implementation strategies normally used for the quality improvement of the care provided, there were important differences. Usually, such strategies are used to promote established interventions that are supported by clinical guidelines and are more acceptable to the clinicians. It is much more challenging to achieve adherence to an experimental intervention, especially if the body of relevant evidence from exploratory trials is lacking. Changing antibiotic prescription patterns is a particularly difficult task due to legal issues and habits of patients and clinicians. The lack of confidence and experience of physicians in the use of PCT may have been one of the most important factors leading to low adherence. Therefore, an important learning point from this study is that the timing of different trial designs is crucial. Previous trials evaluating PCT in LRTIs were more exploratory, open-label and achieved different levels of adherence to PCT guidance, up to 96.6%, mostly with positive safety and efficacy outcomes [6, 7]. However, the diverging levels of adherence to the PCT protocols have caused debate and have limited clinicians' confidence in the accuracy of PCT [6, 7, 9]. As a result, a well-designed and conducted double-blind effectiveness trial aiming to confirm the efficacy, safety and accuracy of PCT as a biomarker to guide antibiotic administration for LRTIs would have been a more informative next step. Positive results from such a trial would have empowered the implementation of PCT guidance.

It is integral for pragmatic or implementation trials to mimic real-life conditions and to capture all the breadth of real-life practice related to an intervention. Since the majority of LRTIs are routinely managed in primary care, the lack of primary care involvement was a notable limitation. While local general practitioners were informed of the ProACT trial and were provided with the last PCT measurement of discharged participants, they were not able to measure PCT. However, patients with LRTIs and persistent or recurrent symptoms or an unfulfilled expectation to receive antibiotics frequently re-present to their general practitioners [10]. In such cases, antibiotic prescription is frequently inevitable, if PCT guidance is not available. A previous low PCT result is of limited use, especially given the risk that patients with viral LRTIs may develop secondary bacterial infections [11]. Indeed, primary care visits emerged as a cause for increased antibiotic prescribing despite negative PCT results in ProACT.

Finally, it is worth discussing the study population of the ProACT study. Eligible participants were patients presenting with LRTIs, for whom there was diagnostic uncertainty regarding the need for antibiotics. It appears that less severe cases were selected, as only 8% of the participants had high PCT levels, which is a significantly lower proportion compared to previous trials. However, it has been demonstrated that PCT can also safely limit antibiotic administration among patients with symptoms that are considered more typical of a bacterial infection, such as sputum purulence (whose sensitivity is relatively limited). For example, among participants with severe (hospitalised) COPD exacerbations, who were included in a meta-analysis evaluating PCT guidance in COPD exacerbation, only 45.6% received antibiotics, without any safety signals [7]. By contrast, the European COPD audit reported that 61.4% of all hospitalised exacerbations were strictly fulfilling Global Initiative for Chronic Obstructive Lung Disease criteria for antibiotic administration [12].

Implications for research and practice

The ProACT study does not inform the evidence base regarding the safety and clinical effectiveness of PCT as a biomarker to guide the administration of antibiotics for LRTI. It reveals potential serious challenges in the introduction of PCT-guidance in real life, including a persistent lack of confidence in PCT results among clinicians, that could possibly be addressed by a well-designed and conducted double-blind trial, aiming to objectively evaluate the efficacy, safety and accuracy of PCT.

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Conflict of interest

A.G. Mathioudakis reports personal fees from Boehringer Ingelheim, and GlaxoSmithKline (consultancy for COPD research programmes), and grants from Boehringer Ingelheim (investigator-initiated grant for a RCT on COPD exacerbations), outside the submitted work. J. Vestbo reports personal fees from Chiesi Pharmaceuticals,

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