

CLINICAL REVIEW

Procalcitonin-guided antibiotic treatment of respiratory tract infections in a primary care setting: are we there yet?

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Abstract

Clinical signs of infection do not allow for correct identification of bacterial and viral aetiology in acute respiratory infections. A valid tool to assist the clinician in identifying patients who will benefit from antibiotic therapy, as well as patients with a potentially serious infection, could greatly improve patient care and limit excessive antibiotic prescriptions. Procalcitonin is a new marker of suspected bacterial infection that has shown promise in guiding antibiotic therapy in acute respiratory tract infections in hospitals without compromising patient safety. Procalcitonin concentrations in primary care are low and can be used primarily to rule out serious infection. However, procalcitonin measurement should not be used as the sole basis for clinical decisions; clinical skills are prerequisites for the correct use of this new tool in practice. At present there is no point-of-care test for procalcitonin with acceptable precision, severely hampering its application in primary care. This article reviews the physiology of procalcitonin, describes the assays available for its measurement, evaluates the present evidence from primary care on its use to identify correctly patients who are likely to benefit from antibiotic treatment and to rule out serious infections, and comments on further research to determine a future role for procalcitonin in primary care.

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Introduction

An urgent issue in modern healthcare services is the increasing level of antibiotic resistance in common pathogenic microorganisms. At present the development of antimicrobial drugs is at a historically low level,¹ so controlling the development of resistance by limiting excessive and inappropriate use of antibiotics is pivotal to the future treatment of bacterial infections in primary care as well as in hospitals. Any reduction in antibiotic consumption will have a relatively higher impact when done in a primary care setting where most antibiotic prescriptions are issued.^{2,3}

The decision on when to prescribe antibiotics for a respiratory tract infection (RTI) in primary care is challenging and is often based solely on clinical symptoms, which is known to be of low sensitivity and specificity^{4,5} and with a high degree of inter-observer variability.⁶ Prescription practices

for similar illnesses vary substantially between European countries,⁷ highlighting the need for evidence-based guidelines incorporating strategies to help reduce inappropriate antibiotic treatment.

Several attempts have been made to decrease the use of antibiotics in primary care; however, a Cochrane review⁸ found only a limited effect, with a multifaceted approach at most offering a decrease in antibiotic prescriptions of 10–15%. Guidelines for prudent antibiotic prescription are frequently issued but adherence to these in daily clinical practice is far from optimal.⁹

At present, methods for differentiating bacterial from viral causes of RTI – including clinical symptom scores and radiological investigations – have not proved to be valid.^{5,6,10} However, the potential for controlling antibiotic resistance and improving patient care by better diagnosis is obvious as

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50–75% of RTIs in primary care are of viral origin.^{2,11} Interest has recently been centred on biomarkers to determine the aetiology of RTIs and hence the need for antibiotic treatment.

Biomarkers of infection

As a consequence of the inherent uncertainty in clinical judgements, doctors try to optimise their performance by using diagnostic tools. Biomarkers such as white blood cell count, C-reactive protein (CRP), and procalcitonin have been introduced to assist the clinician in diagnosing and monitoring infection. They act as surrogate measures, mirroring the extent and severity of an infection. An ideal biomarker for use in infection should enable rapid determination of the cause of fever by accurately predicting the presence or absence of bacterial infection, thereby allowing for appropriate therapeutic responses without adding excessive work for the clinician or costs to society. A biomarker suitable for use in primary care must be a point-of-care test which effectively discriminates milder infections from serious infections that would benefit from antibiotic treatment, in order to minimise excessive antibiotic prescriptions and limit concomitant side-effects.¹² A feasible and valid test would be warranted by many GPs to increase the possibility of 'selling' decisions not to prescribe antibiotics to patients.¹³ However, as with other surrogate tests, no ideal biomarker exists because they are subject to measurement errors, inappropriate handling by investigators, and differences in physiological responses to various kinds of infectious agents.¹⁴

This review will focus on the use of procalcitonin in primary care as it has been demonstrated to be clinically useful in a range of different patient populations and has proved to be valid in assisting the clinician in identifying patients who do not need antibiotic treatment.^{15–17}

Physiology of procalcitonin

Procalcitonin is a prohormone of the calcium homeostasis hormone calcitonin.¹⁸ In non-infectious conditions it is produced in the neuroendocrine medullary C-cells of the thyroid gland. In normal subjects circulating procalcitonin concentrations are low (<0.05ng/mL),¹⁹ but bacterial infections selectively induce an increase in the concentration of procalcitonin because both endotoxins (lipopolysaccharides) from the bacterial cell wall and host responses to infection activate the production of procalcitonin, mainly in parenchymal tissues. This results in an accumulation of procalcitonin because, unlike neuroendocrine cells, parenchymal cells lack the ability to cleave procalcitonin into its mature form, calcitonin.²⁰ Of note, interferon-gamma from predominantly viral infections blocks the procalcitonin response in human cells.²¹ The increase in the procalcitonin concentration following stimulation is very large (up to >10,000 times)²² and fast. It can be detected in serum 2–6 hrs after stimulation of healthy individuals with

endotoxins from *E. coli*, maintaining a high level plateau for the next 24 hrs,²³ and can be detected for up to 7 days.¹⁸ The half-life is approximately 24 hrs, which is partly dependent on renal function.²⁴ Patients with verified bacterial infections have higher procalcitonin concentrations than those with non-bacterial (including viral) infections.^{25,26} This is also true for respiratory pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae* which produce high procalcitonin concentrations in infection,^{27,28} whereas the influenza virus exhibits lower procalcitonin concentrations.²⁹

The exact role of procalcitonin in inflammation and the host response is not yet fully understood and is the subject of rigorous research. In severe infections, serial measurements of procalcitonin in patients with sepsis can predict mortality³⁰ and administration of procalcitonin to hamsters with sepsis increased mortality.³¹

The high sensitivity and corresponding high negative predictive value for serious and presumed bacterial infection may allow the identification of patients who would benefit from antibiotic treatment of RTIs in primary care settings.^{14,32,33}

Procalcitonin assays currently available

Point-of-care tests

The Brahms PCT-Q® (Brahms Diagnostica, Hennigsdorf, Germany), a manual assay that applies a chromatographic semi-quantitative technique (cut-off <0.5ng/mL, 0.5–2.0ng/mL, 2.0–10ng/mL, >10ng/mL) providing results in 30 min, is the only existing point-of-care test. However, this assay performs poorly,³⁴ and semi-quantitative measurements limit the possibilities of interpreting a trend with consecutive measurements.

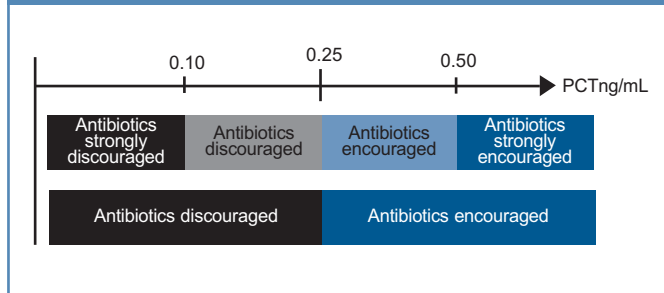
Laboratory-based tests

Quantitative procalcitonin assays are currently available only as laboratory tests. The Brahms PCT LIA® test (former LUMI) (Brahms Diagnostica) is an immunoluminometric assay which was used extensively until about 2003 but is still available. Results using 20µL plasma are available in approximately 1 hr. However, the target interval for localised infections (0.1–1.0ng/mL)³⁵ and the interassay variation of 9–82% in this range³⁰ limits its use in a primary care setting. The Brahms PCT KRYPTOR® test (Brahms Diagnostica) is a rapid and more sensitive laboratory-based assay, providing results in 20 min. The fully automated assay uses time-resolved amplified cryptate emission and has a functional sensitivity of 0.06ng/mL. Interassay variation is <8%.³⁶ Procalcitonin analysis has recently become available on other broadly used routine laboratory systems including VIDAS® (BioMérieux, Paris, France) and Elecsys® (Roche Diagnostics, Basel, Switzerland).

Cut-off ranges for procalcitonin-guided antibiotic therapy of RTIs

Suggested cut-off ranges for procalcitonin-guided antibiotic

Figure 1. Procalcitonin-based algorithms. Suggested cut-off levels for procalcitonin-guided antibiotic treatment of acute respiratory tract infections. Both algorithms have been used in primary care but were originally developed in emergency clinics. Burkhardt *et al.*³⁸ simplified the algorithm to be more feasible in primary care



strategies have been tested mainly in studies of lower RTIs in hospital emergency settings, and in two studies from primary care.³⁷ The application of these procalcitonin cut-off values in trials with >3,500 patients has not shown any changes in patient outcome or rate of complications when compared with the usual antibiotic guidelines, i.e. 'standard of care'.³⁷ In short, the standard cut-off ranges used in these trials (non-ICU settings) have resulted in the following recommendations: antibiotics are (i) strongly discouraged at procalcitonin concentrations <0.1ng/mL; (ii) discouraged with procalcitonin concentrations of 0.11–0.24ng/mL; (iii) encouraged when procalcitonin concentrations were 0.25–0.5ng/mL; and (iv) strongly encouraged with procalcitonin concentrations >0.5ng/mL. Recently, the following simple version has been suggested for primary care: antibiotics are discouraged at procalcitonin concentrations <0.24ng/mL and encouraged at procalcitonin concentrations ≥0.25ng/mL (Figure 1).³⁸

Assessment of new diagnostic markers against a 'gold standard' in RTIs

Traditionally, new diagnostic tools are tested against a 'gold standard' for identifying the specified condition. Despite the logic of this approach, the strategy is problematic as many clinical conditions do not have an acceptable 'gold standard', making assessment of new biomarkers difficult. In many cases the main motivation for introducing a new diagnostic tool is dissatisfaction with the alleged 'gold standard'. This is the situation in the field of inflammatory markers and bacterial infection. Diagnosis of bacterial RTI is often not sufficiently reproducible when done on clinical judgement alone.^{4,6} The 'gold standard' for bacterial pneumonia is often based on radiographic evaluations.³⁹ It is important to acknowledge the lack of accuracy of this 'gold standard' as since a bacterial aetiology is established in fewer than 30% of radiographic infiltrates from patients with community-acquired pneumonia (CAP), a viral cause is suspected in a minimum of 30% of

radiographic infiltrates, and the diagnosis of a pneumonic infiltrate is challenging, even for experienced radiologists.^{40,41} Microbiological evaluations are likewise controversial for a definite diagnosis as many patients are colonised with common respiratory pathogens. This is especially the case in chronic obstructive pulmonary disease (COPD).⁴²

Of note, a perfect biomarker (100% sensitivity and 100% specificity) for bacterial infection tested against the present diagnostic criteria in a primary care setting will probably perform far from perfectly as the 'gold standard' is not an entirely true picture of the pathophysiological processes taking place.

Apart from the issue of a true 'gold standard', the clinical setting is important since the performance of any test is affected by the disease prevalence in the target population. The positive predictive value is '*a priori*' lower in patients with a low probability of bacterial infection, e.g. in primary care as opposed to hospital settings.

A different approach from the above-mentioned³² – for example, the need for antibiotic treatment – is a patient-orientated concept. This concept bypasses the need for an alleged 'gold standard' and focuses on patient recovery and other measurable benefits or harms to the patient. Randomised controlled trials (RCTs) that measure the medical outcome of standard versus procalcitonin-guided antibiotic therapy may better estimate the utility of biomarkers in patients with RTIs. If the patient recovers without antibiotics at the same speed and with comparable rates of complications (hospitalisation, mortality, and number of re-infections), it may be concluded that the infection was of non-bacterial origin or so mild that the immune defence could clear the infection unassisted.⁴³

Box 1. Studies on use of procalcitonin in primary care: search strategy

Electronic searches were performed in PUBMED, EmBase, and Cochrane CENTRAL (latest January 2011). No limitations of age or study type were applied. Language limitations were not applied, but all relevant papers were in English. Combinations of the phrases 'procalcitonin', 'respiratory tract infections', 'community acquired pneumonia', 'general practice', and 'primary care' were used. Supplementary searches included reviewing reference lists of all available papers and review articles. Finally, we made personal contact with colleagues and collaborators working in the field to identify potentially relevant studies.

Study selection

Population: participants had to (i) present with symptoms clinically determined to be RTIs and (ii) be enrolled in a primary care setting.

Study aim: to assess the value of procalcitonin use, e.g. to determine the need of antibiotic treatment in RTIs using a reference (gold) standard or measures of patient recovery.

Table 1. Characteristics of procalcitonin studies in primary care

Type of study	Year	Author	Participants (n)	Illness	Follow up	Assay	Main outcome	Secondary outcomes	Remarks
Observational	2003	Korppi <i>et al.</i> ⁴⁴	Children (190)	CAP	-	PCT LIA	PCT lacked ability to predict the etiology of infiltrates on chest x-ray	PCT did not predict etiologies (serological testing)	PCT LIA insensitive. Problem of gold standard
Observational	2007	Holm <i>et al.</i> ²⁸	Adults (364)	CAP	-	Kryptor	PCT lacked ability to predict the etiology of infiltrates on chest x-ray	PCT did not predict etiology or adverse outcome	Problem of gold standard
Observational	2010	Burkhardt <i>et al.</i> ³⁸	Adults (702)	RTI	-	Kryptor	Characterisation of PCT levels in RTI	-	PCT values generally low
RCT	2008	Briel <i>et al.</i> ¹⁶	Adults (458)	RTI	14/28	Kryptor	No difference in days with restricted activities (8.7 vs 8.6)	72% decrease in ABx. No differences in adverse outcomes	Many diagnoses included that <i>a priori</i> did not need ABx
RCT	2010	Burkhardt <i>et al.</i> ³⁸	Adults (550)	RTI	14/28	Kryptor	No difference in days with restricted activities (9.00 vs 9.04)	42% decrease in ABx. No differences in adverse outcome.	Simplified PCT algorithm.

PCT = procalcitonin; CAP = community-acquired pneumonia; RCT = randomized controlled trial; RTI = respiratory tract infections (acute); ABx = antibiotic treatments

Procalcitonin in primary care: observational studies

Procalcitonin concentrations in suspected upper and lower RTIs including verified bacterial pneumonia have been assessed in three observational studies in primary care (see Box 1 and Table 1).

Korppi *et al.*⁴⁴ investigated the usefulness of procalcitonin to differentiate between viral and bacterial causes of radiologically-confirmed CAP in 190 Finnish children in a primary care setting. Procalcitonin was measured by the Brahms PCT LIA test® (today considered inappropriate – see above). Sixty percent of the procalcitonin measurements were below the functional assay sensitivity of 0.5ng/mL. No differences in procalcitonin concentrations were observed between patients admitted to hospital and those treated as outpatients, nor did procalcitonin indicate viral or bacterial aetiology.

Holm *et al.*²⁸ evaluated 364 Danish adults diagnosed with a lower RTI by their GP. Procalcitonin concentrations, measured with the Brahms PCT KRYPTOR® assay, were correlated with chest x-rays and microbial aetiology. Of the suspected cases of lower RTI, 13% had radiographically-verified CAP. In the group of patients with suspected pneumonia by the 'gold standard', 30% had normal procalcitonin concentrations (<0.06ng/mL). Of the patients without pneumonia only 1% had procalcitonin concentrations >0.25ng/mL, and all eight patients with procalcitonin concentrations >0.5ng/mL had radiographically-verified CAP, four of whom were subsequently identified with *S. pneumoniae* bacteraemia.

Burkhardt *et al.*³⁸ characterised procalcitonin concentrations

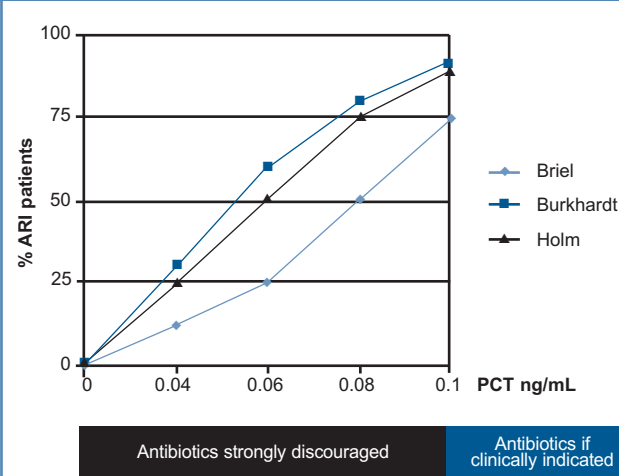
using the Brahms PCT KRYPTOR® assay in 702 adults with RTIs in primary care. Clinical diagnoses were predominantly lower RTIs, mainly acute bronchitis. The results confirmed that procalcitonin concentrations in patients with suspected RTI in primary care settings are low, with around 95% being <0.1ng/mL, which is considered to indicate a minimal risk of a bacterial aetiology with no benefit of antibiotic treatment (Figure 2).

Procalcitonin-guided antibiotic therapy in primary care: randomised trials

A procalcitonin-guided antibiotic strategy may have the potential to help in reducing antibiotic use in patients with suspected RTI in primary care. Two studies have compared standard care of RTIs with procalcitonin-guided antibiotic therapy in a randomised design,^{16,38} (see Box 1 and Table 1).

A multicentre RCT involving 53 primary care physicians and 458 adult patients with acute RTIs judged to be in need of antibiotic treatment was carried out in Switzerland by Briel *et al.*¹⁶ to assess the effect of procalcitonin-guided antibiotic treatment using the Brahms PCT Kryptor® assay. The study physicians were trained in acute RTI and management guidelines were issued to participants. The study was a non-inferiority trial with a pre-specified criterion of an increase of <1 day in restricted activities in the procalcitonin intervention group. For safety, an additional procalcitonin measurement was obtained after 6–24 hrs in the procalcitonin group if antibiotic treatment was initially withheld. The attending GP was allowed to overrule the procalcitonin algorithm if withholding

Figure 2 Percentage of patients with procalcitonin concentrations below certain limits in primary care settings. The figure is constructed using median and interquartile ranges in adults. Since only 10–25% of patients suspected of acute respiratory tract infection (ARI) had procalcitonin concentrations above 0.1ng/mL, it should be expected that 75–90% of patients attending their GP with ARI will not be prescribed antibiotics if a cut-off of 0.1ng/mL is applied. Procalcitonin should at present be used to stop/withhold antibiotics. At procalcitonin concentrations above the cut-off value, antibiotic treatment should rely on history and clinical examination. Inclusion criteria varied slightly between the three studies used; this may be the reason for the discrete difference in the procalcitonin concentrations in the populations



antibiotics was judged to be a safety risk for the patient. Cut-off values for procalcitonin-guided antibiotic treatment are shown in Figure 1. Both upper and lower RTIs were included on the basis of clinical judgement. Some 50% were lower RTIs, predominantly acute bronchitis. The adjusted increase in restricted activities at 14 days follow-up in the procalcitonin intervention group was 0.14 days (95% CI –0.53 to 0.81) (i.e. 3.6 hrs), confirming non-inferiority within the power limits of the trial. Furthermore, a decrease of 72% (95% CI 66% to 78%) in antibiotic prescription rates (25% vs. 97%) was demonstrated, with the most pronounced effect in acute bronchitis and upper RTIs. No differences in relapsing infections or complications were detected.

The results of the study by Briel *et al.*¹⁶ were confirmed and elaborated by Burkhardt *et al.*³⁸ who simplified the procalcitonin treatment algorithm by limiting the instructions to no antibiotic treatment with procalcitonin concentrations <0.25ng/mL and thus advising antibiotic treatment at procalcitonin concentrations >0.25ng/mL (Figure 2). Burkhardt *et al.*³⁸ also omitted the 24 hr re-evaluation of the procalcitonin concentration, thereby attempting to make the strategy more

feasible for use in a primary care setting. However, the option of clinicians to overrule the procalcitonin algorithm was maintained. No previous training of participating physicians in evidence-based medicine was done and patients were consecutively enrolled, thus providing a realistic primary care setting and minimising pre-selection. Patients primarily had upper RTIs (65%) and only three patients had pneumonia according to the attending physician. The main outcome – namely, days with restriction from an RTI at 14 days – was comparable between the groups (9.04 vs. 9.00). This was confirmed when adjusting for potential confounders. The procalcitonin-guided group had a 42% lower exposure to antibiotic therapy ($p < 0.0005$) and no differences were observed in the number of clinical reassessments performed or complications.

The evidence from the two RCTs of procalcitonin-guided antibiotic treatment of RTIs in primary care thus suggests that procalcitonin is potentially of clinical use in identifying patients who do not need antibiotic treatment, and introduction of this principle may facilitate a substantial reduction in antibiotic exposure.

Limitations of procalcitonin measurements

Procalcitonin measurement may produce false negative and false positive results.²² Not all micro-organisms produce similar increases in procalcitonin concentrations, and even viral causes may present with procalcitonin concentrations above 0.5ng/mL.⁴⁵ However, caution should be exercised in the interpretation of established viral infection since secondary bacterial infection may complicate the existing condition (e.g. influenza infection complicated by bacterial pneumonia). Awareness of patients with suspected mycoplasma infection is warranted as procalcitonin levels are generally low with this organism.²⁸ However, this is not a general feature of atypical pneumonias.³³ False negative values may also be of concern in localised states of infection (e.g. abscesses) and even in the early stages of systemic infections.³⁷

The cost of procalcitonin measurements is a key point in considering the potential of procalcitonin-guided antibiotic measurements in primary care. To be feasible in modern healthcare systems with tight budgets, the price of a procalcitonin-guided strategy and that of a more traditional approach should be at least comparable. Other issues to consider include ease of use, quality assurance, controls, shelf-life, storage of tests, and time taken to perform the test. However, information regarding these issues is lacking as no rapid point-of-care procalcitonin assay presently exists - which is an essential requirement before a procalcitonin-guided antibiotic treatment strategy for RTIs can be applied in primary care.

Conclusion and perspectives

Physicians and patients share a common goal of limiting the duration and intensity of RTIs and preventing complications from infections and drug therapy (i.e. side-effects). Apart from ensuring the best treatment and patient care, the GP plays an important role in preventing the emergence of bacterial resistance to antibiotics. Difficulties in reducing present prescribing practices may in part be due to doctors' fear of missing a potentially treatable RTI, especially a lower RTI.^{46,47} Clearly, a validated tool to predict benefit from antibiotic prescribing by assisting clinical assessment and differentiating mild from serious infection of presumed bacterial aetiology is highly warranted. To date, biomarkers seem to be powerful tools for reducing antibiotic prescriptions by ruling out serious infection.

The CRP test is more widely used because of the existing point-of-care tests and, at present, it is the best available tool to reduce antibiotic exposure in RTI, even though its potential has not been thoroughly validated. Two recent Dutch RCTs of CRP antibiotic guidance in patients with cough and RTIs found a 40% reduction in antibiotic prescriptions.^{48,49} However, the studies were not powered to detect a difference in patient recovery.

Procalcitonin-guided antibiotic treatment is a promising and increasingly validated tool for treating RTI in primary care. It has the possibility of reducing unnecessary antibiotic prescriptions (42–72%) with no differences in health impairment or risk of complications. The performance of procalcitonin and other markers of infection in confirming 'classical' but poorly defined diagnostic entities such as pneumonia or bronchitis is not convincing. However, this may not be of great importance if more interventional RCTs are undertaken to (1) increase the power of the results and confirm the safety of the strategy; (2) estimate better the net effect on antibiotic reduction; (3) investigate strategies that make procalcitonin-guided antibiotic treatment logistically feasible on a broader scale in primary care, e.g. by introducing point-of-care tests; and (4) access and compare the cost of a procalcitonin-guided strategy versus standard care.

Even taking into account the low degree of serious infections found in primary care,⁵⁰ the current evidence suggests that procalcitonin is a step towards tailored antibiotic treatment for patients with a high probability of a bacterial infection likely to benefit from antibiotic therapy, thus minimising unnecessary antibiotics for viral or other self-limiting diseases without compromising patient safety. Procalcitonin concentrations in primary care settings are low (Figure 2), indicating that it may be used as a negative predictor (e.g. to rule out the presence of a serious infection). Some studies suggest that procalcitonin concentrations at hospital admission can predict the severity and outcome of

CAP and specify that low procalcitonin concentrations may independently identify patients at low risk of death within clinical scoring systems (e.g. CRB-65, CURB-65, and Pneumonia Severity Index).^{51,52} A cut-off point of 0.1 ng/mL for antibiotic therapy would still result in 75–90% of patients with suspected RTI being excluded from antibiotic therapy (Figure 2) and no risk of increased mortality. At present, no repeat or safety procalcitonin testing is warranted on a routine basis. It is important to acknowledge that a low procalcitonin concentration does not mean 'no treatment' or 'no hospital admission', but indicates a low probability of benefit from antibacterial drugs. Procalcitonin can be used to withhold or stop antibiotic treatment (i.e. high negative predictive value), but there is still a place for the experienced and skilled clinician to decide when to start or escalate antibiotic treatment (at procalcitonin concentrations >0.1 ng/mL) based on clinical grounds in accordance with the setting and context of the patient.

Reports that antibiotic therapy of COPD⁵³ and CAP⁵⁴ can be shortened are of great interest, even though the question of an optimal duration of antibiotic therapy remains to be settled. A recent meta-analysis documented that the prescribing of any antibiotic in primary care increases the risk that bacteria develop antibiotic resistance in the individual (odds ratio 2.4), the impact lasting for more than one year.⁵⁵ It follows that, in order to combat the increasing incidence of antibiotic-resistant bacteria, we must seek to minimise the number of antibiotic courses initiated without jeopardising the safety of our patients.

However, before the widespread introduction of procalcitonin in primary care can be recommended, we need to have evidence from pragmatic trials, cost-effectiveness studies, verified cut-off values, and a 'head-to-head' trial with CRP. The introduction of a validated, cost-effective, present-best biomarker to predict benefit from antibiotic therapy may mark an important milestone in evidence-based medicine in primary care in the foreseeable future.

Handling editor

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Conflicts of interest

Rune Aabenhus: None declared

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Contributorship

Both authors contributed to the idea and analysed data. Rune Aabenhus wrote and edited the manuscript. Jens-Ulrik Stæhr Jensen edited the manuscript.

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COMMENTARY

Inflammatory markers are helpful when treating LRTI in primary care

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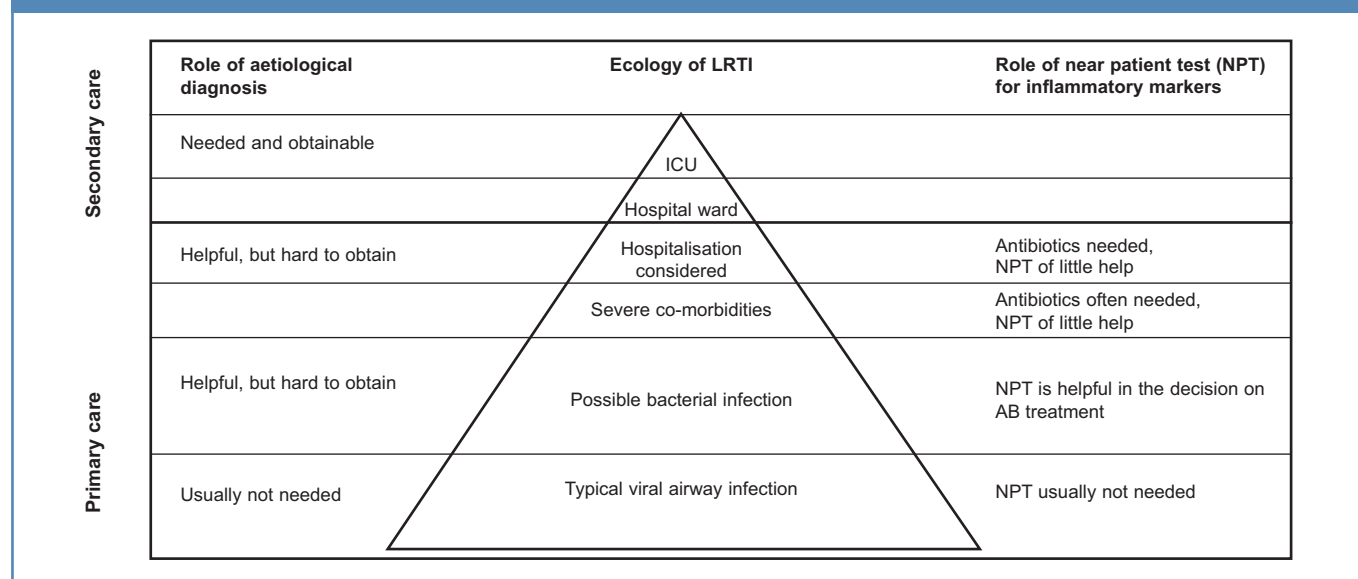
Antibiotic resistance is a growing problem, and unnecessary antibiotic use exposes people to the risk of adverse reactions, wastes money, and medicalises self-limiting conditions. Better targeting of antibiotics is therefore essential – especially in primary care, where most antibiotics are prescribed.

Inflammatory markers like C-reactive protein (CRP) and procalcitonin (PCT) do not adequately differentiate between bacterial and viral infection.¹ CRP is a better predictor of pneumonia than any symptom or sign.² The diagnostic value of PCT has been less studied in primary care, probably because a Near Patient Test (NPT) version is not yet available. However, it

seems to be a less sensitive marker of pneumonia than CRP.^{3,4} Nevertheless, as Aabenhus and Jensen point out in this comprehensive review,⁵ both the PCT and CRP tests have proved useful in guiding clinicians' prescribing decisions so as to achieve a reduction in unnecessary antibiotic use.^{5,6} A CRP NPT result can be obtained in under five minutes, and results are strongly weighted by GPs in Scandinavia when deciding on antibacterial treatment in patients with acute cough.⁷

Inflammatory markers are more useful as a guide when deciding on antibacterial treatment in primary care rather than in secondary care; in the former an aetiological diagnosis may be

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Figure 1. Incidence, severity, and the role of inflammatory markers and microbiological tests in decisions about antibacterial treatment for respiratory infections in primary and secondary care

less important than prediction of prognosis and treatment benefit. The pyramid in Figure 1 shows the different levels of incidence and severity of LRTI and the role of NPTs for inflammatory markers.

- The foundation layer at the bottom of the pyramid represents the great majority of patients with an acute cough. These have a high probability of respiratory viral infection. This broad syndromic diagnosis is usually obvious, due to the typical symptoms affecting both the upper (e.g. coryza) and lower respiratory tract (cough).
- The layer above represents patients who are moderately ill, but with a slightly increased risk of pneumonia and/or bacterial infection. As Aabenhus and Jensen point in this review,⁵ an inflammatory marker can be particularly helpful in ruling out a need for antibiotics in these patients – CRP probably more so than PCT as it is a better predictor of pneumonia.
- The next (third highest) layer represents patients with important co-morbidities, mainly those with severe COPD. The severity of their COPD and of the actual symptoms should probably overrule any information from tests for biomarker levels. However, a very high value of CRP or PCT will increase concern about pneumonia, and so clinicians will consider the need for hospital admission (and thus move up to the next layer in the diagram).
- Patients in the next layer up will receive little additional benefit if decisions about antibiotic treatment are made with the help of an inflammatory biomarker. These patients will almost certainly be treated with antibiotics, either at home or in hospital. Clinical and other laboratory findings such as blood pressure, respiratory rate, the mental alertness of the

patient, and age (all components of the CRB-65 score), will be more useful than biomarker test results in guiding antibiotic prescribing decisions.^{1,8} However, a decision to manage the patient in hospital rather than at home may be supported by high levels of CRP⁹ or PCT.¹

- Once in hospital, many more laboratory tests become available, and inflammatory markers can be used to monitor response to treatment. Regarding antibiotic choice, empirical treatment is usual, but with thorough and urgent efforts to obtain good specimens for detection of the aetiological agent. This is particularly important in intensive care units, where tracheal aspirates are often collected. In primary care, microbiological tests will usually be based on specimens from sputum or from the throat. Microbiological testing in primary care will be less useful because of the problems of getting a representative sample, the length of time for obtaining the result, and because the relationship between commensal and disease-causing organisms is often unclear. Improved diagnostics that are rapid enough for primary care is an important goal. Ideally, such tests should identify sensitivities to the relevant antibiotics, allowing the narrowest spectrum antimicrobial agent to be prescribed.

Managing LRTI in primary care with CRP can lead to reduced antibiotic prescribing, which can also be achieved by enhancing the communication skills of the GP.⁵ Improved consultation skills and CRP together have the greatest effect on safe reductions in antibiotic prescribing for LRTI without negatively impacting on recovery and satisfaction with care. Primary care clinicians and their patients point out that they would find a CRP NPT most useful in those cases where there is doubt in the minds of clinicians and/or patients about whether or not antibiotics

should be prescribed.^{10,11} Clinicians want the test to perform well, no doubt. The ability of NPTs to predict things like radiographic pneumonia is useful, but their ability to help reduce anxiety and gain an acceptance of non-antibiotic management may sometimes be even more important. Patients may sometimes be more willing to accept advice from a clinician that antibiotics are not necessary on this particular occasion if the advice is backed up by a test. If the test performs at least as well as clinical assessment alone, then the clinical decision should most often be confirmed, with the patient leaving the consulting room feeling they have been taken seriously, well managed and more accepting of non-antibiotic management.

Diagnostic performance should therefore not be the only consideration when evaluating biomarkers and other tests. Tests should not be parachuted into clinical care without careful consideration of their niche and of the complex surrounding clinical assessment and communication issues. And as the authors of this review point out,⁵ all-round excellence in consultation skills will ensure greatest added value from biomarkers and other tests in general practice.

Conflicts of interest

The authors declare that they have no conflicts of interest in relation to this article. All are doing research in related areas.

Contributorship

All authors contributed to the review of literature, formulation of content and drafting the manuscript.

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