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Key points

- Procalcitonin has been widely investigated as a biomarker of bacterial infection to aid diagnosis and decisions to start or stop antibiotics in a range of conditions, including in diseases of the lower respiratory tract.
- Meta-analysis suggests that the use of procalcitonin to guide antibiotic therapy in acute respiratory tract infections can reduce duration of antibiotic therapy and hospital admission without adversely affecting outcomes – however, there was significant heterogeneity in methodology and population in the included studies, and more recent studies have failed to show such significant benefits.
- The use of procalcitonin to guide stopping or shortening antibiotic therapy in sepsis/septic shock is suggested in the international guidelines for the management of sepsis (2016), but this is a “weak” recommendation, with a low quality of evidence recognised. Major international guidelines do not support a role for procalcitonin in the management of acute exacerbations of COPD, bronchiectasis, interstitial lung disease or pleural infection.
- Regardless of situation, decisions on initiating, altering, or discontinuing antimicrobial therapy should never be made solely on the basis of changes in any biomarker – while biomarkers such as procalcitonin may provide supportive information, they should only be used alongside regular and robust clinical assessment.

Educational aims

- To understand the principles of using procalcitonin to guide decisions regarding antibiotic use (procalcitonin-guided antibiotic therapy).
- To review important research studies into the use of procalcitonin as a biomarker of bacterial infection across the spectrum of diseases of the lower respiratory tract.
- To understand the current international guidelines regarding procalcitonin use in disease of the lower respiratory tract.

Review

Procalcitonin in respiratory disease: use as a biomarker for diagnosis and guiding antibiotic therapy

Procalcitonin (PCT) is a peptide measurable in serum which becomes elevated in response to bacterial infection. Multiple trials have explored the safety and efficacy of using PCT as a biomarker to guide decisions about starting or stopping antibiotic therapy in a wide variety of situations, and PCT assays have recently been approved by the Federal Drug Administration (FDA) in the US for use in both sepsis and respiratory tract infections. While there have been a number of promising results particularly in acute respiratory tract infections and intensive care unit settings, problems including adherence to protocol, cost of the assay and improved antimicrobial stewardship more generally, have limited more widespread adoption.

This educational article summarises the evidence for the use of procalcitonin as a biomarker of bacterial infection across the spectrum of respiratory disease and reviews how the use of procalcitonin-guided antibiotic therapy is reflected in current major international guidelines.

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Background

Procalcitonin (PCT) is a 116-amino acid polypeptide produced in health states by the medullary C-glands of the thyroid. It is a pro-hormone, and is metabolised to produce the 32-amino acid hormone calcitonin which has a role in calcium homeostasis *via* its actions on osteoclasts in bone [1]. In health, PCT is virtually undetectable, but in the 1990s, a series of studies identified that circulating serum levels of PCT are highly elevated in sepsis [2]. This in itself would not be particularly novel: nonspecific markers of inflammation, including acute phase proteins such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and elevated white cell count and differential are well established and widely used in clinical practice

to aid diagnosis and management of infection. However, these acute phase reactants rise indiscriminately in response to any inflammation – that includes bacterial infection, but also severe burns, pancreatitis, viral infection and autoimmune processes. They are therefore of limited specificity in determining the presence or absence of bacterial infection, and guiding subsequent decisions about antibiotic therapy.

In sepsis, PCT has been found to be released from the liver [3] and peripheral blood mononuclear cells [4] (the rise in response to sepsis is also seen in post-thyroidectomy patients [5], indicating extra-thyroid production of PCT in the inflammatory response). Levels of PCT have been shown to rise in response to both endotoxin injection in healthy human volunteers [6] and in response to cytokine

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Procalcitonin has been widely investigated as a biomarker of bacterial infection to aid diagnosis and decisions to start or stop antibiotics in a range of conditions, including in diseases of the lower respiratory tract <http://bit.ly/2ZgDwNO>



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administration (tumour necrosis factor (TNF)- α and interleukin (IL)-6) *in vivo* and *in vitro* [4]. Levels are detectably elevated at 3–6 h after the initial insult, and subsequently fall with a half-life of about 1 day. Although temporally linked with the immunological response to bacteria, the exact role of PCT as a mediator of the inflammatory response remains incompletely understood.

A landmark paper published in 1993 investigated PCT levels in sepsis and other inflammatory conditions in a paediatric population [2]. In this study, PCT levels were shown to be highly elevated in sepsis, but within (or just above) the normal range in viral infections or bacterial colonisation without infection. PCT levels fell in response to antibiotic therapy. This led to the hypothesis that PCT could be used as a biomarker of bacterial infection, distinguishing it from both non-bacterial causes of inflammation and noninvasive colonisation. Since then, multiple further studies have investigated PCT as a biomarker of bacterial infection, with multiple studies finding it to behave as an acute-phase reactant with a higher sensitivity and specificity for bacterial infection than conventional laboratory tests [2, 7–9]. It has been investigated across a wide range of infective conditions, including sepsis [10], upper and lower respiratory tract infections (LRTIs) [11], bacterial meningitis [12] and surgical site infections [13]. A meta-analysis of 12 studies comparing the diagnostic accuracy for bacterial infection of PCT compared to CRP in hospital in-patients found PCT was more sensitive (88% *versus* 75%) and specific (81% *versus* 67%) than CRP for differentiating bacterial from noninfective causes of inflammation [9].

Procalcitonin-guided antibiotic therapy

In principle, a biomarker sensitive and specific for bacterial infection could be used to guide decisions regarding antibiotic therapy, with an elevated result supporting a decision to start treatment and a fall indicating successful resolution of the infection and that antibiotic therapy could be safely discontinued. Unnecessary use of antibiotics is recognised to be a widespread problem: in a study of antibiotic prescriptions in primary care in the US, 30% of antibiotic prescriptions were deemed to be unnecessary, rising to 50% for acute respiratory conditions [14]. There are numerous concerns with inappropriate use of antibiotics, including development of antimicrobial resistance, *Clostridium difficile*-associated colitis and financial cost, and a sufficiently sensitive, specific and feasible marker would have the potential to dramatically improve antibiotic stewardship. This has led to the concept of procalcitonin-guided antibiotic therapy (PGAT), which is based on observations that serum PCT rises in response to acute bacterial infection, and falls with successful resolution [15].

The exact methods by which PCT is used to guide antibiotic therapy varies in different studies, but the principles remain the same. Rather than completing a defined length of antibiotic treatment, advice is given to discontinue antibiotic therapy when procalcitonin falls by a pre-determined amount (typically a 50–80% decrease [16]) or below a certain threshold level (typically <0.25 – $0.5 \mu\text{g}\cdot\text{L}^{-1}$). The aim of this is to reduce the duration of antibiotics needed, leading to reduced development of antimicrobial resistance, shorter inpatient stays and reduced financial cost. Initially, many of these studies were undertaken in the intensive care setting [17], but the use of PCT as a marker for diagnosing bacterial infection and guiding antibiotic therapy has since spread to a variety of conditions in both the inpatient and outpatient settings.

In June 2016, the US Food and Drug Administration (FDA) approved the use of the Elecsys BRAHMS commercial procalcitonin assay (Roche) for the purpose of guiding antibiotic therapy in the context of sepsis. The FDA-approved indications for use of PCT assays were expanded in February 2017 when the VIDAS BRAHMS Procalcitonin assay (bioMérieux) received FDA approval for use in guiding decisions to start or stop antibiotic therapy in LRTIs (including community-acquired pneumonia and acute exacerbations of chronic obstructive pulmonary disease (COPD)), as well as sepsis.

Procalcitonin in respiratory disease

Disorders of the lower respiratory tract present in a limited number of ways, with the symptoms of cough, dyspnoea, chest pain and pyrexia having a wide differential diagnosis. For example, worsening dyspnoea and cough in a patient with COPD may be due to bacterial infection driving an exacerbation, but could also be due to viral infection, noninfective airway inflammation or disease progression. A biomarker that could accurately and reliably distinguish bacterial infection from other conditions would therefore be of benefit in the initial and ongoing management of these patients. This has led to a myriad of studies investigating PCT and PGAT in a variety of respiratory conditions.

In the following sections, we consider common conditions of the lower respiratory tract in turn, and provide an overview of the current evidence for PCT as a biomarker for diagnosis and in guiding management decisions regarding antibiotic therapy. With a vast number of studies and meta-analyses published for many of these conditions, a full systematic analysis is beyond the scope of a single article; we instead focus on key randomised control trials or meta-analyses where available, or outline the best available evidence if no interventional trials have been conducted. We also

identify areas of novel development and review how the use of PCT to guide antibiotic therapy is reflected in current major international guidelines for respiratory disease.

Pneumonia and acute lower respiratory tract infections

Pneumonia is the leading infective cause of mortality worldwide and a common reason for presentation to primary and emergency care. In a recent active population-based surveillance study of community-acquired pneumonia requiring hospitalisation (adults only) in the US, no pathogen was detected in the majority of cases (62%) [18], despite extensive microbiological investigation. Viral infections including metapneumovirus and influenza can cause pneumonia, and may need specific therapies rather than antibiotics, and noninfective pathologies such as malignancy and congestive heart failure can also mimic the symptoms of pneumonia. There has therefore been significant interest in PCT as a marker for both diagnosis and guiding subsequent antibiotic therapy, with numerous trials conducted. This significant body of literature can be challenging to interpret, due to heterogeneity in population (*e.g.* community-acquired pneumonia, both upper and lower acute respiratory tract infections, and even infective exacerbations of COPD), clinical settings (primary care, emergency departments, inpatients or intensive care units), and difference in methodology. This section therefore focuses on early evidence, large-scale trials and meta-analyses.

Early evidence suggested that PCT could be a useful biomarker in guiding the initiation and use of antibiotics for pneumonia. CHRIST-CRAIN *et al.* [19] conducted a randomised controlled trial in patients with suspected community-acquired pneumonia presenting to the emergency department ($n=302$). 151 patients had their treatment guided by a PCT-based algorithm (PCT $<0.1 \mu\text{g}\cdot\text{L}^{-1}$ strongly discouraged, PCT $<0.25 \mu\text{g}\cdot\text{L}^{-1}$ discouraged, PCT $>0.25 \mu\text{g}\cdot\text{L}^{-1}$ encouraged, PCT $>0.5 \mu\text{g}\cdot\text{L}^{-1}$ strongly encouraged), while 151 received standard care. Procalcitonin guidance reduced total antibiotic exposure and the duration of antibiotic therapy (5 days *versus* 12 days).

BRIEL *et al.* [20] conducted a randomised multi-centre trial in primary care involving 458 patients who in the treating physician's opinion required antibiotics. These patients were then randomised to either PCT-guided therapy (antibiotics strongly discouraged if PCT $\leq 0.1 \mu\text{g}\cdot\text{L}^{-1}$ or encouraged if $>0.25 \mu\text{g}\cdot\text{L}^{-1}$) or a standard approach. In the PGAT group overall antibiotic prescription rate was 72% lower and on average, duration of therapy was also 1 day shorter. Adverse events were identical for both groups.

These findings suggest that, in combination with guidelines, PCT-guided therapy could reduce the use of antibiotics to treat acute respiratory tract infections in the community and emergency departments, without compromising patient care.

Many of these randomised control trials have been included in a large patient-level meta-analysis of the use of PCT to guide antibiotic therapy in respiratory tract infections [21], published in early 2018. This meta-analysis included 26 trials from 12 countries, across a range of conditions, including community-acquired pneumonia, hospital-acquired pneumonia, ventilator-associated pneumonia, exacerbations of COPD and bronchitis. Overall, this meta-analysis found that the use of PGAT in patients with acute respiratory infections reduces antibiotic exposure and side-effects, and improves survival. PGAT was associated with a 2.4-day reduction in antibiotic exposure (5.7 *versus* 8.1 days, 95% CI -2.71 to -2.15 , $p<0.001$) and lower risk of antibiotic-related side-effects (16.3% *versus* 22.1%, adjusted OR 0.68, 95% CI 0.57 to 0.82, $p<0.001$). There was also lower mortality in the PGAT arm (adjusted OR 0.83, 95% CI 0.70 to 0.99, $p=0.037$).

A subgroup analysis for community-acquired pneumonia identified 1442 patients who received PGAT and 1468 controls. Within this subgroup analysis, there were lower rates of treatment failure, length of hospital stay and rates of antibiotic-related side-effects in the PGAT group compared to standard therapy. The authors of this meta-analysis acknowledge the significant heterogeneity in the included studies, including population and condition studied, variable adherence to the PGAT protocol, and the use of different procalcitonin cut-off values. However, they concluded that PGAT effectively reduced antibiotic exposure and antibiotic side-effects while improving mortality, with the effect sustained across all clinical settings. We would recommend this detailed meta-analysis for readers interested in understanding more about studies investigating PGAT in the context of acute respiratory infections.

Despite the positive conclusion, more recent large scale trials have failed to replicate these findings in community-acquired pneumonia/LRTI. HUANG *et al.* [22] randomised 1656 patients who presented to the emergency department with suspected LRTIs, and whom clinicians were uncertain whether to treat with antibiotics, to either receive antibiotics based on PCT level or usual care. In the PCT group clinicians were given initial (and serial if the patient was admitted) PCT levels and an antibiotic-use guideline according to PCT values. This trial showed no significant difference in the use of antibiotics between the two groups (antibiotic days were 4.2 *versus* 4.3 days, $p=0.87$).

Despite the positive findings of the meta-analysis, the precise role of PGAT in managing LRTIs in a standard population remains undetermined. We discuss how PCT use is advised in national

guidelines later in this article. A sensible approach would be PCT used only alongside thorough clinical assessment, with a low level prompting clinicians to look for alternative causes of respiratory symptoms rather than definitively exclude bacterial infection.

Acute exacerbations of COPD

Due to diagnostic difficulty in distinguishing virally triggered acute exacerbations of COPD (AECOPD) from those driven by bacterial infection, there is the potential for unnecessary use of antibiotics in this group of patients. A reliable marker of bacterial infection would have the potential to determine patients in whom antibiotics would be beneficial, and guide their duration of use. Here we highlight key studies investigating the use of PCT for decisions to start and discontinue antibiotics in patients presenting with AECOPD.

Early evidence for PCT-guided therapy came from a randomised control trial by *Stolz et al.* [23], of antibiotics given according to serum PCT *versus* antibiotics given at the discretion of the clinician. This study of 208 AECOPD inpatients showed that PGAT reduced antibiotic prescription and exposure compared to standard therapy, with no difference in clinical outcomes (including subsequent exacerbation and rehospitalisation rates) between the groups.

Multiple similar studies have since been undertaken, and a meta-analysis of PCT-based protocols to guide antibiotic use *versus* standard care in AECOPD [24] was published in late 2017, including 1062 patients over 8 trials. This meta-analysis found that PCT-based protocols reduced antibiotic use, without negatively affecting clinical outcomes as measured by treatment failure, length of hospital stay, recurrence rates and mortality. However, the authors recognised the limitations of the current body of evidence; identifying a small overall study size and low event rates. Furthermore, methodological issues with clinicians disregarding the PGAT protocol when deciding on antibiotics were also common; an issue common to many randomised clinical trials of PGAT.

Point-of-care testing to obtain rapid PCT results with the aim of facilitating immediate decision making has also been studied. An open-label randomised control trial compared PCT-guided therapy using point-of-care testing (n=62) or antibiotics as per local guidelines (n=58) [25]. Patients in the PCT guided arm received antibiotics for a shorter duration (3.5 days *versus* 8.5 days) without any increase in adverse outcomes, suggesting that in future this could be used to reduce unnecessary antibiotic prescriptions.

However, as is frequently the case with clinical trials of PCT as a biomarker, the evidence remains conflicting. A 2010 study [26] analysed data from a placebo-controlled trial of doxycycline in addition

to systemic corticosteroids in AECOPD. It found that even in patients with a low PCT level ($<0.1 \mu\text{g}\cdot\text{L}^{-1}$), clinical outcomes were improved with doxycycline.

Many of the studies of PCT-guided antibiotic therapy in AECOPD suggest that it can reduce antibiotic exposure without compromising clinical outcomes. However, other findings such as the beneficial effect of antibiotics reported even when PCT was low, and the fact that there is no consensus on the PCT cut-off value that represents a bacterial AECOPD, means we are not yet at a stage where PCT testing can be recommended routinely for the management of AECOPD.

Pleural infections

Distinguishing a “simple” parapneumonic effusion from a “complex” effusion or empyema requiring pleural drainage requires an invasive procedure to obtain a sample of fluid [27]. Confirmed pleural infection is typically treated with a prolonged course of antibiotics, guided by clinical, biochemical and radiological response. This is therefore an area where a biomarkers with the ability to distinguish pleural infection from noninfected effusions and to guide subsequent antibiotic therapy duration would be of potential benefit. To date, we have been unable to find any studies investigating PGAT in pleural infection. However, a number of studies have investigated the value of serum PCT in differentiating pleural infection from noninfectious causes of pleural effusion.

In one such study, retrospective samples from confirmed infectious and noninfectious exudative pleural effusions were case-matched by severity of systemic inflammation, as measured by CRP [28]. Serum PCT was found to be significantly higher in the pleural infection group compared to controls with noninfectious pleural effusions, even when systemic inflammation as measured by serum CRP levels were matched ($0.58 \mu\text{g}\cdot\text{L}^{-1}$ *versus* $0.34 \mu\text{g}\cdot\text{L}^{-1}$, $p=0.003$). Furthermore, when talc pleurodesis (which induces intense aseptic inflammation) was performed, CRP levels became highly raised (360% over baseline), but there was only a minimal response in PCT. This study suggests that PCT offers enhanced ability to discriminate between infectious and noninfectious causes of pleural effusion beyond that of nonspecific markers of inflammation such as CRP.

More recently, a meta-analysis of 14 studies involving a total of 1320 subjects (463 patients with pleural infection and 857 controls) [29] looked at both serum and pleural PCT in the diagnosis of parapneumonic pleural infection. Again, serum levels of PCT were found to be significantly higher in patients with parapneumonic pleural effusion compared to malignant, tuberculous or transudative effusions, and serum PCT was found to be a more sensitive and specific marker than pleural PCT (sensitivity 0.78 *versus* 0.62, specificity 0.74 *versus*

0.71). However, this study did not discriminate “simple” parapneumonic effusion from “complex” effusions that require drainage [27]. Any rise in PCT could plausibly be attributed to the pneumonia alone, and therefore this meta-analysis does not provide evidence for the use of PCT to distinguish between pneumonia with associated simple parapneumonic effusion and true pleural infection.

Although the above studies present some evidence for serum PCT to discriminate pleural infection from other causes of pleural effusion, it is limited, and there is no recommendation for the use of PCT in the diagnosis or management of pleural infection in current guidelines [27].

Bronchiectasis

Bronchiectasis is a chronic lung disease characterised by fixed dilated bronchi leading to impaired sputum clearance and a predisposition to chronic or recurrent LRTIs. Patients present with chronic cough and recurrent infective exacerbations, recognised by increased volume and purulence of sputum. Given the risk of resistant organisms, exacerbations may require admission for intravenous antibiotics [30], with associated high healthcare costs and impact on patients. An infective exacerbation is typically diagnosed clinically on subjective and objective findings; however, distinguishing an acute infection from a baseline of chronic productive cough can be challenging. A serum biomarker that were able to accurately predict an acute infective exacerbation requiring antibiotic therapy would therefore be of putative benefit in the management of these patients.

The only study we were able to find investigating PCT in bronchiectasis was an observational trial of 38 inpatients and 63 outpatients with established bronchiectasis [31], which compared PCT with symptom severity, antibiotic use and other inflammatory markers. In outpatients, PCT levels were generally low (mean concentration $0.030 \mu\text{g}\cdot\text{L}^{-1}$, standard deviation 0.041). However, levels were also low in those patients admitted for intravenous antibiotic therapy, with the majority having levels of $<0.1 \mu\text{g}\cdot\text{L}^{-1}$ (median $0.055 \mu\text{g}\cdot\text{L}^{-1}$), a level which in most other studies would be interpreted as no active bacterial infection. Furthermore, in patients admitted for intravenous antibiotics, there was no significant change in serum PCT between days 0, 5 and 10 of treatment. A proposed explanation for the lack of PCT rise was infection and inflammation in bronchiectasis being largely confined to the airway lumen, while PCT behaving as a measure of systemic infection. The authors concluded that PCT was unlikely to be able to guide treatment in an infective exacerbation of bronchiectasis, and there are no recommendations for the use of PCT in the recent European Respiratory Society (ERS) [32] or British Thoracic Society (BTS) [30] guidelines for the condition.

Interstitial lung disease

A deterioration in a previously stable patient with chronic fibrotic lung disease could be due to a variety of causes. Infection (both bacterial and viral), pulmonary embolism, biventricular cardiac failure, and disease progression [33] all need to be considered, and with the poor prognosis of idiopathic pulmonary fibrosis (IPF) the length of any hospital admission should be minimised. We identified one randomised controlled trial investigating PGAT in acute exacerbations of IPF [34]. In a single centre in China, 39 patients were randomised to the PGAT group and 39 received standard care. Fewer patients in the PGAT group received antibiotics, and those that did received a shorter course (8.7 versus 14.5 days, $p<0.001$), but data on length of stay was not reported. There was no significant difference in mortality between the two groups.

Investigations that improve diagnostic accuracy for causes of acute deterioration in chronic fibrotic lung diseases are urgently needed [35], and an accurate test for the presence of bacterial infection would not only allow more judicious use of antibiotics, but if negative could also prompt active investigation for other noninfectious causes. While the results of DING *et al.*'s study [34] are promising, a single-centre study with small numbers alone is insufficient to form the basis for recommendations for its use, and further studies are required in this condition.

Use of procalcitonin to guide antibiotic therapy in respiratory disease: current international guidelines

The 2016 Surviving Sepsis international guidelines for the management of sepsis and septic shock advised that PCT could be used to support shortening or discontinuing antibiotic therapy in sepsis and septic shock [36], acknowledging that this was a “weak recommendation” with a low-quality evidence base, and that biomarkers should never be used in isolation to make decisions on starting or withdrawing antibiotics. However, for the specific management of respiratory disease, the use of PCT to guide antibiotic use has, at the time of writing, not entered into the major international guidelines.

For pneumonia, the 2007 Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) consensus guidelines for community-acquired pneumonia [37] make no reference to PCT, whilst the IDSA/ATS 2016 guidelines for the management of adults with hospital-acquired and ventilator-associated pneumonia [38] advise that “For patients with suspected HAP/VAP, we

Self-evaluation questions

- Which of these statements regarding the physiology of procalcitonin is correct?
 - As it is produced by medullary c-glands of the thyroid, the rise in serum procalcitonin in response to sepsis does not occur in patients following total thyroidectomy.
 - Procalcitonin levels in serum fall with a half-life of 7 to 10 days.
 - Procalcitonin has been shown to rise in response to cytokine administration to otherwise healthy volunteers.
 - Procalcitonin cannot be measured by enzyme-linked immunosorbent assay (ELISA).
- Which of these procalcitonin values and subsequent advice are typical of those used in published trials of procalcitonin-guided antibiotic therapy in the setting of acute lower respiratory tract infections?
 - Serum PCT $>1.0 \mu\text{g}\cdot\text{L}^{-1}$ – Advise against starting antibiotics.
 - Serum PCT $>0.5 \mu\text{g}\cdot\text{L}^{-1}$ – Antibiotic use recommended.
 - Serum PCT $<0.1 \mu\text{g}\cdot\text{L}^{-1}$ – Antibiotic use strongly encouraged.
 - 10% decrease in serum PCT – Strongly encouraged to stop antibiotics.
- Which of these statements regarding the use of procalcitonin-guided antibiotic therapy as recommended by major international guidelines is correct?
 - Procalcitonin is recommended by the British Thoracic Society guidelines for pleural infection (2010) for guiding duration of antibiotic therapy in confirmed empyema.
 - Procalcitonin is recommended in the European Respiratory Society guidelines for adult bronchiectasis (2017) to decide whether to commence antibiotic therapy in suspected infective exacerbation of bronchiectasis.
 - Procalcitonin is recommended by the UK National Institute of Health and Care Excellence to decide whether to start antibiotics in suspected community acquired pneumonia.
 - Serial procalcitonin measurements to guide ongoing antibiotic therapy in ventilator acquired pneumonia in complex clinical situations is considered “good clinical practice” in the ERS/ESICM guidelines for hospital acquired/ventilator-associated pneumonia (2017).
 - None of the above.

recommend using clinical criteria alone, rather than using serum PCT plus clinical criteria, to decide whether or not to initiate antibiotic therapy”. The international ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired and ventilator-associated pneumonia are somewhat more supportive of PCT use [38]; although the routine measurement of serial PCT when anticipated duration of antibiotics is 7–8 days is not recommended, the panel did advise that the measurement of serial PCT in specific clinical circumstances (for example, highly resistant pathogens, severely immunocompromised patients, or initially inappropriate antibiotic therapy), with the aim of reducing antibiotic treatment duration “represents good practice”. In the UK, the National

Institute for Health and Care Excellence (NICE) has reviewed the evidence for PCT guiding antibiotic decisions in sepsis and other bacterial infections, including bacterial LRTIs. NICE’s 2015 summary [39] concluded that there was currently insufficient evidence to recommend its routine adoption in the National Health Service. However, the report did recognise the potential, and recommended further research into the use of PCT.

The 2017 ERS/ATS guidelines for the management of COPD exacerbations [40] makes no reference to PCT, only noting that “Identifying biomarkers of bacterial infection may allow the patient population that definitively requires antibiotic treatment to be more precisely selected”.

Neither the 2019 BTS guidelines [30] nor the 2017 ERS guidelines [32] for the management of adult bronchiectasis make any reference to the use of PCT in managing the condition. Similarly, the 2010 UK guidelines for the management of pleural infection makes no reference to its use [27].

Discussion

At present, there is insufficient evidence to support PGAT in the management of patients with suspected infection of the lower respiratory tract in routine clinical practice outside of an intensive care unit setting. Although many early studies have shown promising reductions in duration of antibiotic therapy or length of stay, these have not been replicated in recent large-scale trials [22]. Similarly, although PCT is FDA-approved in the US, its use is not recommended in the vast majority of international guidelines on respiratory disease [30, 37, 38].

There are various possible reasons for the differing outcomes of trials of PGAT. Firstly, there are differences in the PCT-guidance protocols used, including what cut-off PCT value should inform the decision to start or stop antibiotic therapy. Interventional trials have used a range of thresholds, with anything from above $0.25 \mu\text{g}\cdot\text{L}^{-1}$ to $1.0 \mu\text{g}\cdot\text{L}^{-1}$ being used as the cut-off for deciding to start antibiotics [21]. A threshold value of $0.25 \mu\text{g}\cdot\text{L}^{-1}$ is most widely used in primary or emergency care settings, with $0.5 \mu\text{g}\cdot\text{L}^{-1}$ more often used as a threshold in patients in intensive care.

Secondly, there is significant variation in how strictly the PCT-guided protocol was enforced upon treating clinicians at the bedside. In the 2018 meta-analysis [8], adherence to PCT-guided antibiotic policy varied from 44 to 100%. Limited adherence to the PCT guideline was recognised as an issue in the recent HUANG *et al.* study [22], which failed to show reduced antibiotic use with PCT. Lack of experience or confidence in the use of PCT levels by treating clinicians has been proposed as a reason for this limited adherence [41]. Clinicians must balance competing interests to deliver safe patient care; considering both antimicrobial

stewardship initiatives on the one hand and current sepsis guidelines [36] with a greater emphasis on initiating timely antimicrobial therapy on the other. This has important implications when considering introducing a PGAT protocol into routine clinical practice: if clinicians in a trial were reluctant to make decisions regarding antibiotic therapy on the results of a single blood test, doctors working in clinical settings are likely to have similar reservations, at least until familiarity and experience with the biomarker grows.

Thirdly, another, potential reason for the lack of efficacy of PGAT in more recent trials may be increasing awareness of the dangers of antimicrobial resistance, leading to improving antibiotic stewardship in routine clinical care. As awareness of the need for more diligent antibiotic prescribing becomes more widespread, the extent to which a biomarker can improve things beyond standard practice diminishes.

A further difficulty in implementing PGAT in clinical practice lies in the present lack of availability of quality assured PCT testing round the clock in many hospitals. The current market cost of performing PCT is relatively high at around GBP20–60 per test (depending upon the number of tests performed per day/week). From an international perspective, the majority of mortality and morbidities due to respiratory tract infections occur in resource-poor countries. Implementing an expensive test which costs more than the cost of total duration of antimicrobial therapy may be difficult for policy makers to justify.

Conclusions

So when, if at all, should respiratory physicians use PCT to guide decisions on antibiotic use? Based on current international guidelines, there are no recommendations for its use in managing acute exacerbations of chronic lung diseases, including COPD, idiopathic pulmonary fibrosis or bronchiectasis. Neither is its use recommended in the most recent American (ATS) or British (BTS) guidelines for simple community-acquired pneumonia, although it should be noted that these guidelines are several years old. One situation where PCT measurement is supported by international guidelines is in helping guide decisions about duration of antibiotic therapy in complex hospital-acquired or ventilator-associated pneumonia [38], where clinical assessment and routine bloods alone may be insufficient; we would recommend serial PCT monitoring in this context.

Based on the existing evidence and current guidelines, we feel PCT deserves a role as an additional objective tool for deciding duration of antibiotic therapy in complex respiratory infections when used alongside clinical assessment. The consensus of current evidence demonstrates the limitations of serum PCT when used in isolation to make these decisions. Most importantly, the results of these trials and guidelines emphasise the importance of robust clinical assessment in any unwell patient and meticulous adherence to principles of appropriate antibiotic prescribing in all situations – these are essential principles of good medical practice that no blood test should ever replace.

Suggested answers

1. c
2. b
3. d

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Conflict of interest

None declared.

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