Point of Care Testing for C-Reactive Protein in Acute Cough Presentations:

Feasibility, Efficacy, Benefits and Limitations

Acute cough is one of the most common illnesses in the UK with an estimated 48 million cases per annum (Morice, McGarvey, Pavord, 2006). The majority of these presentations are thought to be of viral aetiology and self-limiting in nature (Woodhead et al, 2011), yet Meropol, Localio and Metlay (2013) report antibiotic prescription rates of approximately 65% in the UK. Clincians' decision-making process can be influenced by both patient expectations and difficulty in differentiating between viral and bacterial aetiologies by clinical examination alone. Despite warnings about antimicrobial resistance (AMR) from the World Health Organisation (WHO, 2011) clinicians in the UK continue to have high prescription rates for acute cough presentations in comparison to other developed health care systems (Cooke et al, 2015; Smith et al, 2014; Hawker et al, 2014). This article will consider the feasibility, efficacy, benefits and limitations of using point of care testing (POCT) of C-reactive protein (CRP) within primary care in the United Kingdom to help inform management of acute cough.

Introduction

Paramedics are being employed increasingly in diverse clinical areas. One such area is primary care, where General Practitioner (GP) surgeries employing paramedics to undertake urgent work and, in some cases, consult with patients in non-urgent appointments (Primary Care Workforce Comission 2014). The Primary Care Workforce Comission (2014) identifies that paramedics may have a key role to play, as part of a multidisciplinary team, in improving the delivery of primary care in GP surgeries. Ball (2005) highlighted that specialist paramedics were employed in minor injury units, intermediate care teams and in out-of-hours GP services delivering urgent, unscheduled care. It seems that this area of paramedic practice is growing rapidly and, as such, many paramedics now need to be aware of common illnesses among the population to tailor their repsonses to a changing healthcare system.

Acute cough is one of the most common illnesses in the UK with an estimated 48 million cases per annum (Morice, McGarvey, Pavord, 2006). It is defined as a cough lasting no longer than three weeks and is one of the most common reasons to seek medical advice in primary care (Morice, McGarvey, Pavord, 2006). Whilst the majority of acute cough presentations are benign and self-limiting, viral and bacterial infections of the respiratory tract have the potential to develop into more serious conditions such as Community Acquired Pneumonia (CAP). The majority of CAP patients can be safely managed in the community however a significant proportion will require more intensive treatment and mortality rates are estimated to be as high

as 7% (Cilloniz et al, 2011). In recent years there has been a notable trend to admit elderly patients to hospital who are diagnosed with CAP therefore early identification of the disease is considered important for targeted management in the community (Woodhead et al, 2011). This presents a challenge for clinicians who have to differentiate between benign self-limiting respiratory illness and more complex bacterial infection within a primary care setting.

Whilst the precise aetiology is unknown it is believed that the majority of acute coughs are initially caused by viral nasopharyngitis, otherwise known as the common cold (Woodhead et al, 2011). In a healthy adult this condition is considered to be a benign and self-limiting virus therefore requiring minimal healthcare intervention at first presentation. In vitro studies have shown, however, that the initial viral infection creates favourable conditions for bacterial growth, making secondary bacterial infection more likely (Peltola and McCullers, 2004). The relationship between viral and bacterial respiratory tract infections (RTIs) is further emphasised by Cilloniz et al (2011) who identified 29% of pneumonias were of mixed viral and bacterial aetiology. It is therefore reasonable to assume that RTIs with mixed aetiology will present with a combination of viral and bacterial symptoms, making clinical diagnosis, and therefore targeted management, more problematic. This theory is well supported in the literature. Wipf et al (1999) and Metlay Kapoor and Fine (1997) both highlight the difficulty clinicians have in accurately diagnosing chest complaints with clinical signs and history alone. Additionally Hopstaken et al (2005) and Huijskens et al (2014) conclude in microbiological studies that there is significant overlap of symptoms for both viral and bacterial presentations of LRTI. From these studies we can surmise that clinicians' ability to differentiate between bacterial LRTI, viral LRTI and bronchitis using clinical assessment and history taking alone is insufficient to accurately formulate a targeted management plan. This conclusion is supported in a recent comprehensive review commissioned by the European Respiratory Society (ERS) and The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) (Woodhead et al, 2011).

Acute Cough and Antibiotics

Since 1964, anti-microbial resistance has been identified as one of the major threats to modern medicine prompting national governments and scientific communities to design strategies to combat AMR. In 2013 the UK Department of Health released a five year plan which identifies optimising prescribing practice as one of their main seven points of action (Department of Health, 2013). These sentiments are echoed at a continental and global level by the European Commission (EC, 2011) and World Health Organisation (WHO, 2011) highlighting the global threat posed by AMR. Additionally the Genomics to Combat Resistance against Antibiotics in Community Acquired Pneumonia (GRACE) has been specifically commissioned to focus on the management of patients with suspected lower respiratory tract infection (LRTI). Whilst the ambiguity of symptoms associated with acute cough presentations are considered a major factor in the over prescription of antibiotics (Woodhead et al,

2011), rising expectations of the patient has also been cited in the literature to contribute significantly. Coenen et al (2006) reports that GPs felt it was less appropriate to not prescribe antibiotics if the patient had requested it and McNulty et al (2013) demonstrated that 97% of patients who requested antibiotics from their GP received a prescription for their complaint. Additionally 23% of these prescriptions were prescribed without any further discussion about their illness with the doctor. While these are isolated studies, they raise questions about the current management strategies utilised by GPs when faced with demanding patients. Evidence suggests that patients are not well enough informed to make appropriate decisions regarding antibiotic prescriptions for acute cough symptoms (Cals et al, 2007; Coenen et al, 2013). It is therefore essential to implement a more robust decision making strategy for primary care clinicians around in management of patients presenting with acute cough.

CRP Testing as a Solution?

The problematic diagnosis of pneumonia, increasing concern over AMR and high incidence of side effects associated with antibiotics, has prompted research into how modern health care systems can safely reduce antibiotic prescriptions for acute cough presentations. One of the methods being considered in the UK is the use of POCT for detecting raised C-reactive protein (CRP) in the patients blood. CRP is an acute phase reactant protein synthesised by the liver. It is produced in response to inflammation, infection or trauma as part of the immunological response (Riodan and McWilliam, 2009). Levels of CRP in blood serum begin to increase 4-6 hours after the initial insult or infection and peak after 36-50 hours (Riodan and McWilliam, 2009). The technology to provide POCT for CRP is a relatively new development in primary care and has been shown to be equally as accurate as laboratory analysis by microbiologists (Seamark, Backhouse and Powell, 2003; Kotani et al, 2014).

CRP testing has been used in hospital settings for the last fifty years to monitor patients with acute infections and their response to treatment (Cooke et al, 2015). Its successful utilisation in primary care for acute cough presentations will essentially depend on the test's sensitivity and specificity in the diagnosis of CAP. Falk and Fahey (2009) conducted a comprehensive diagnostic accuracy systematic review of CRP in relation to CAP for patients both assessed in the community and emergency departments. They concluded that CRP measurements alone were insufficient to rule out CAP in a primary care setting, although they do concede that if the patient displays symptoms relating to CAP then CRP may have some diagnostic value. This is further qualified by Vugt et al (2013) who demonstrated patients with a CRP of under 20mg/L had a 3% chance of having radiographically confirmed pneumonia in primary care. This subgroup of patients were more likely to be on long term steroids which is known to reduce CRP readings (Vugt, 2013). In terms of ruling in CAP with CRP, Falk and Fahey (2009) report their findings were less clear in their meta-analysis. Many of the studies that met the inclusion criteria were deemed to have

heterogenous data and therefore require further research prior to making any robust conclusions. Individual studies such as Almirall et al (2004), Bafadhel et al (2011), Muller et al (2007) and Espana et al (2012) do however demonstrate high sensitivities and specificities in diagnosing CAP patients presenting to emergency departments with varying cut off CRP levels. Guidelines published by both the GRACE consortium and the National Institute for Clinical Excellence (NICE) indicate that they concur with these conclusions, specifying that CRP of over 100 mg/L implies a high probability of CAP (Little et al, 2013; NICE, 2014). Despite these promising studies and acceptance by large institutions, it is of note that the majority of evidence for ruling in CAP has been conducted in a hospital setting. It may be presumed that patients presenting to emergency departments will have more severe symptoms than patients presenting in primary care increasing the overall probability of having CAP. This is highlighted by Vugt et al (2013) in one of the only studies to be conducted in primary care, who demonstrated that only 35 % of patients with CRP of over 100mg/L were later radiographically confirmed to have pneumonia. Further research is therefore needed in patients presenting in primary care to assess the validity of POCT CRP for ruling in CAP.

POCT for CRP has already been introduced into primary health care systems in the Netherlands and Nordic countries to aid clinicians in their decision making in relation to acute cough symptoms (Cooke et al, 2015). The majority of the research from these health care systems has focussed on how effective CRP tests are at reducing antibiotic prescriptions in primary care. In a relatively large cluster randomised control trial (RCT) in the Netherlands the use of CRP POCT was shown to reduce antibiotic prescriptions by 22% (Cals et al, 2009a). This study excluded patients seen at home or in nursing homes which resulted in a sample with a lower mean age than would normally have been expected. Whilst this subgroup of patients at home are more likely to be prescribed antibiotics due to their age and co-morbidities, the study still demonstrated a significant reduction of prescriptions for those attending the surgery. Little et al (2013) conducted a multinational study across several countries in Europe, including Great Britain, on behalf of the GRACE consortium. They were able to demonstrate a 15% reduction in antibiotic prescriptions after CRP POCT measurements were introduced into primary care. Further studies were included in a large meta-analysis by Huang et al (2013) showing a mean reduction of 18.9% in antibiotic prescriptions for patients assessed with CRP measurements. Whilst this is by far the largest meta-analysis conducted to date, the review has received criticism for several methodological flaws and therefore may not be sufficiently valid to draw any robust conclusions (Aabenhus, Cals and Jenson, 2014). Additionally the majority of the studies were conducted in European health care systems where it may be assumed that there would be cultural and educational differences to the United Kingdom that would affect antibiotic prescribing. It is important to note however that no significant adverse events, increase in mortality or admissions were reported in any of the trials, indicating that the use of CRP POCTs and reduction in antibiotic prescriptions may be safe in primary care. Conversely Engel et al (2011) questions

whether the evidence in primary care is valid enough to draw this conclusion, with several of the studies being methodologically flawed.

Clinicians' perspectives

Whilst these studies show a significant reduction in antibiotic prescriptions clinicians have voiced concern about several aspects of CRP testing in primary care. Wood et al (2011) conducted a multi-country qualitative study to gather clinician and patient views in regards to POCT for CRP. The primary concerns for clinicians included questionable accuracy of tests and over reliance on CRP results, thereby detracting from the clinician's clinical skills. Clincians were concerned about some of the limitaitons identified in the literature. CRP is known to increase during an infection, it also rises in response to inflammation and trauma, causing false positive results. Chronic diseases like crohns disease, osteoarthritis and rheumatoid arthritis are common examples where CRP is likely to be chronically raised, making interpretation of CRP results more problematic (Pepys and Hirschfields, 2003). Additionally CRP levels within the blood do not peak until 36-50 hours which could result in false negative results on initial presentation. False negative results are more of a concern as bacterial infection could be dismissed by the clinician on the basis of the CRP result, only for a bacterial infection to develop without any antibiotic cover. Despite these shortfalls clinicians working in primary care with POCT for CRP held positive views about using CRP to guide clinical decision making (Wood et al, 2011). This was further reported by Anthierens et al (2014) and Cals et al (2009b) where clinicians felt that the CRP test decreased clinical uncertainty and supported non-prescribing decisions.

Patients' Perspectives

Patients were equally as positive when asked about the inclusion of POCT for CRP in primary care. Wood et al (2011) reports that patients felt the test gave the clinician a better chance of accurate diagnosis and therefore a more accurate management plan. These sentiments were echoed by Jones et al (2013) where clinicians described enhanced relationships with the patients and a more inclusive decision making process. Findings from Cals et al (2013) suggest that enhanced patient understanding and stronger patient-clinician relationships as a result of POCT for CRP may contribute to a reduction in follow up visits post LRTI. The authors concede that this trend is not statistically significant however it stands to reason that patients will gain a better understanding of their own illness in the context of their CRP result. Historically antibiotics would have been prescribed in the majority of acute cough presentations (Meropol, Localio and Metlay, 2013) thereby justifying the action of requesting a consultation. If however they had a negative CRP on their last consultation, they may perceive the need to seek professional advice less of a priority until their symptoms felt worse than the previous episode. Further research is needed to confirm whether or not CRP testing is influential in patient behaviour in this manner, and whether this may inadvertently increase the risk of patients not seeking medical advice when it is more appropriate to do so.

Financial Feasibility

In a climate of economic uncertainty and budget cuts to healthcare systems around the world (John & Price, 2013) the cost effectiveness of POCT for CRP must also be considered. In a costing statement NICE estimates the total initial spend on equipment for GP surgeries in England to be £3.8m. Each subsequent test would cost £13.50 when staff time, reagents and calibration are taken into consideration (NICE, 2014). Hunter (2015) investigated the potential cost effectiveness of CRP POCT in the UK by analysing data collected by Cals et al (2013), Huang et al (2013) and Little et al (2013). The cost of prescriptions, adverse events, training costs and quality-adjusted life years (QALYs) were all considered over a three year period. Whilst the data from these studies has primarily been acquired from European health care systems and therefore may not be directly applicable to UK prescription practices, Hunter (2015) concludes that CRP POCT would be cost effective within the NHS. In the study the initial costs of CRP testing were outweighed by reduction in prescriptions, reduction in attendances and increased QALY outcomes. The author concedes that the increase in QALY outcomes post intervention were largely based on a reduction of follow up attendances for acute cough over a three year period in Cals et al (2013). This reduction could have been caused by patients perceiving that they would not receive any antibiotics due to the new CRP procedure, therefore they may have chosen not to attend despite having cough symptoms. If this was the case it would have reduced their QALY scores thereby affecting the outcome of the study. Additionally the study uses data from Huang et al (2013) for analysis which as discussed in a previous paragraph has been criticised for its data collection techniques in the literature (Aabenhus, Cals and Jenson, 2014).

A second cost analysis was conducted in Norway and Sweden on behalf of the GRACE consortium, again utilising parameters such as QALYs, cost of testing, and cost of prescriptions for analysis (Oppong et al, 2013). The authors concluded that using CRP POCTs significantly raised the overall costs of managing patients with LRTI however this was deemed acceptable based on an increase in QALYs. The original data used in this study was sourced from Butler et al (2009) of which the primary outcome measure was related to prescribing trends across Europe and not primarily concerned with CRP testing. The practices from Norway and Sweden had already established the use of CRP POCT in primary care and only displayed a reduction in prescriptions of 5% between the CRP test group and the no CRP test group. Studies based in countries that had previously not had CRP testing have demonstrated a much larger reduction of 15%-22% of prescriptions (Little et al, 2013; Cals et al 2009a) which is likely to result in greater cost savings. One aspect that appears to have been overlooked by both of these economic evaluations is the potential reduction in radiological imaging which was demonstrated in a Russian study. Andreeva and Melbye (2014) reported a reduction of referral for chest x-ray of 20% in patients assessed with CRP POCT in primary care, with no adverse outcomes reported. This has significant implications for reducing unnecessary

radiological exposure, reduced transportation costs to secondary care centres and the cost of the imaging itself. The studies also concede that it is difficult to quantify the economic value of reducing prescriptions in relation to AMR. In theory reducing AMR will have significant implications for cost savings. Targeted therapy and early detection of disease is likely to result in reduced admissions, less repeat antibiotic prescriptions and fewer investigations.

Conclusion

In conclusion the use of CRP POCT within the primary care environment in the UK remains controversial. The accuracy of CRP for ruling in or ruling out CAP in primary care is not well defined at present, although hospital based studies would suggest that it may be of value in the presence of other clinical signs. The delay of CRP reaching its peak levels and false positive or false negative results are further limitations of the test in primary care. Despite these limitations, current evidence suggests that CRP testing can significantly reduce prescriptions for acute cough presentations within primary care. These results were achieved with few reported adverse events which would indicate CRP POCT is relatively safe to implement. The majority of the research was primarily conducted in European healthcare systems therefore prospective randomised control trials are required in the UK to draw any definitive conclusions. Clinician and patient perceptions of the intervention were primarily positive and indicate that it could strengthen the clinician-patient relationship. This could have further implications on how often patients choose to seek professional advice for acute cough symptoms although further research is needed to confirm this. Whether the use of CRP POCT is cost effective is also debated in the literature. The studies included in this article did not attempt to quantify the economic benefits of reducing the incidence of AMR and overlooked the benefit of reduction in imaging in their analysis. Taking these factors into account it is likely that CRP POCT will be cost effective in primary care, although data acquired from a UK based study would be beneficial for analysis.

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