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Horizon scanning prioritising summary

Update Number 2

Brahms PCT Assays for the diagnosis of systemic bacterial infection

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UPDATE PRIORITISING SUMMARY

REGISTER ID: **0000069**

NAME OF TECHNOLOGY: **BRAHMS PCT ASSAYS**

PURPOSE AND TARGET GROUP: **DIAGNOSING AND CONTROLLING TREATMENT OF SYSTEMIC BACTERIAL INFECTION IN EMERGENCY AND INTENSIVE CARE PATIENTS**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☐	Experimental	☐	Established
☐	Investigational	☐	Established *but* changed indication or modification of technique
☒	Nearly established	☐	Should be taken out of use

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Switzerland	✓		
Australia		✓	

IMPACT SUMMARY:

Brahms introduced a new *in vitro* assay for the quantitative determination of procalcitonin (PCT) in blood serum and plasma. PCT is a 116 amino acid protein with a sequence identical to that of the prohormone calcitonin. Under normal metabolic conditions, hormonally active calcitonin is produced and secreted in the C-cells of the thyroid gland after specific intracellular proteolytic procession of the prohormone PCT. Intact PCT is found in the blood of patients with severe bacterial infections and sepsis (Brahms, 2004).

Indications for using the assay include differential diagnosis of bacterial vs viral infection, early diagnosis of systemic bacterial and fungal infections, and monitoring for sepsis and infectious disease in high-risk patients.

The PCT assay is available in 4 formats;
1) **BRAHMS PCT-Q** - a rapid format for quick semi-quantitative results (available in the U.S. for investigational or research use only)
2) **BRAHMS PCT LIA** - a luminometer based, semi-manual, full quantitative method
3) **BRAHMS PCT KRYPTOR** – an automated method run on the BRAHMS Kryptor instrument (there are 7 installed in Maternal Genetic Screening Units in Australia). The KRYPTOR PCT was launched in Europe in 2002.

4) **LIAISON BRAHMS PCT** – an automated method run on the Diasorin Liaison instrument (not in use in Australia).

The increase in PCT in response to severe *systemic* bacterial infections may provide high diagnostic specificity. Meisner (2002) reports results from previous studies indicating that the PCT assay is 100% sensitive at 1.5 ng/ml at correctly identifying septic shock, with a specificity of 72%. The PCT assay does not react to locally limited bacterial infections, viral infections, chronic inflammatory disorders or autoimmune processes, thus enabling diagnostic differentiation between these clinical symptoms. Importantly, an increase in PCT may be detectable early in the course of severe sepsis and septic shock. The analytical sensitivity of Brahms quantitative test methods ranges between 0.06 ng/ml for Kryptor PCT and 0.1 ng/ml for PCT LIA (Meisner 2002).

A cluster randomised controlled trial (level II evidence) conducted in Switzerland assessed the effect of PCT guided diagnosis on the treatment of 234 patients admitted to hospital with suspected lower respiratory tract infections. Patients assessed with the assistance of KRYPTOR PCT assays received significantly fewer antibiotics (49% reduction, $p < 0.0001$) than patients receiving standard care (Christ-Crain et al 2004).

In Australia Brahms supplies the PCT-Q and PCT LIA formats. The Brahms PCT LIA luminometer system is currently available commercially and is the most commonly used method in Australia. It is currently not required to be listed on the Australian Register of Therapeutic Goods as the product does not diagnose a communicable disease, is not a home-use device and is not made from material of human origin. The regulations governing the listing of goods on the TGA will, however, change as of next year and the assay will be listed. The PCT LIA assay is being used in public hospitals in New South Wales, Victoria and Western Australia in emergency care and intensive care units. The quantitative tests cost approx $12.00 – 15.00 and the semi-quantitative device cost approximately $22.00.

In 2001-2 in Australia there were 12,688 public hospital and 2,261 private hospital separations for principal diagnosis codes A20-A49. Septicaemia is included in this range of diagnoses. This is an under-estimate of those who would actually receive the test as those found to have viral or local bacterial infections are not included. The total mortality from septicaemia in 1996 was 280 deaths in males and 315 in females (3.1 and 3.4 per 100,000).

FEBRUARY 2004 RECOMMENDATION:

Based on the limited information currently available on the Brahms quantitative tests and the small proportion of people likely to benefit from their application (through earlier or more appropriate treatment), it is therefore recommended that this technology be monitored.

FEBRUARY 2004 SOURCES OF FURTHER INFORMATION:

Brahms. PCT-Molecule and Kinetics. Brahms PCT [Internet] Brahms Aktiengesellchaft, Hennigsdorf, Germany. Availabe at : http:www.procalcitonin.com [Accessed March 11, 2004].

Christ-Crain, M., Jaccard-Stolz, D. et al (2004). 'Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial', *Lancet*, 363 (9409), 600-607.

Meisner, M. (2002). 'Pathobiochemistry and clinical use of procalcitonin', *Clin Chim Acta*, 323 (1-2), 17-29.

SEARCH CRITERIA TO BE USED:

Amino Acid Sequence
Calcitonin/analysis/ biosynthesis/genetics/ metabolism
Inflammation/physiopathology
Molecular Sequence Data
Protein Precursors/analysis/ biosynthesis/genetics/ metabolism
Protein Processing, Post-Translational
Sepsis/physiopathology
Sequence Homology, Amino Acid

JANUARY 2007 – UPDATE - EFFECTIVENESS AND SAFETY ISSUES

A meta analysis of randomised studies (level I diagnostic evidence), including a diverse range patient groups and ages, evaluated the accuracy of utilising procalcitonin (PCT) and C reactive protein (CRP) levels for the diagnosis of bacterial infection compared to diagnosis of bacterial infection by culture (Simon et al 2004). This analysis included 12 studies, which evaluated PCT and CRP as markers for the diagnosis of bacterial infections in hospitalised patients. Patients included in the meta-analysis included 46 neonates, 638 children and 702 adults, with half of the patients in intensive care units. It was reported that that PCT levels measured by the Brahms assay were a more accurate diagnostic marker for bacterial infection than CRP levels. This applied when differentiating bacterial infection from non-infective causes of inflammation and viral infection.

PCT diagnosis was more sensitive (88% [95% CI 80%, 93%] vs. 75% [95% CI 62%, 84%] $p<0.05$) and more specific (81% [95% CI 67%, 90%] vs. 67% [95% CI 56%, 77%] $p<0.05$) than CRP for differentiating bacterial from non-infective causes of inflammation. The sensitivity for differentiating bacterial from viral infections was also higher for the PCT marker (92% [95% CI 86%, 95%] vs. 86% [95% CI 65%, 95%] $p<0.05$). The specificity of the two markers were similar with PCT 73% [95% CI 42%, 91%] and CRP 70% [95% CI 19%, 96%, $p<0.05$].

In addition the authors discuss the difference in the timing of secretion of the markers. PCT secretion begins within 4 hours after stimulation and peaks at 8 hours, compared to 4-6 hours for CRP, which peaks only after 36 hours (Simon et al 2004). Therefore the use of PCT as a biomarker of infection may provide a more timely diagnosis and may be more clinically useful.

A study (level I diagnostic evidence) of 302 patients with community-acquired pneumonia admitted to a hospital emergency department assessed PCT guidance for the initiation and duration of antibiotic therapy (Christ-Crain et al 2006). The control group patients (n=151) received antibiotics according to usual practice. Patients allocated to the PCT group received antibiotic therapy by classification into four groups of PCT levels. In this study the duration of antibiotic courses was reduced from a median of 12 to 5 days in patients in the PCT group. The total rate of antibiotic exposure decreased in patients with PCT guidance (relative risk 0.52, [95% CI 0.48, 0.55] $p<0.001$).

OTHER ISSUES

A study is currently underway which aims to evaluate the use of PCT in guiding antibiotic therapy in general practice patients (Briel et al 2005). This is the first study (level I diagnostic evidence) of PCT that aims to evaluate potential reductions in antibiotic usage for acute respiratory tract infections (ARTI) in primary care (Briel et al 2005). The study aims to compare PCT-guided antibiotic therapy to a standard approach based on evidence-based guidelines for approximately 600 patients with ARTI.

The primary endpoint is days when normal activity was restricted by ARTI within 14 days after randomisation. At the time of preparing this update results from this trial were not available.

A study (Christ-Cain et al 2006) included in this update was part-funded by Brahms whilst an author of another study (Briel et al 2004) declared previous renumeration from Brahms.

At the time of preparing this update a PUBMED search for new studies of the PCT identified few randomised controlled studies and numerous studies of lower level evidence for the use of the Brahms PCT assay in different patient groups and hospital settings.

JANUARY 2007 – CONCLUSION:

Early recognition of bacterial infections in clinical practice is important for both guiding treatment and reducing misuse of antibiotics.

HEALTHPACT ACTION:

From the new high-level evidence the Brahms assay appears to be effective for PCT determination of bacterial infection. Point-of-care testing and the associated benefits in quick and accurate identification of patients in need of antibiotic therapy would be a valuable tool to guide therapy, especially in rural areas. Given the body of evidence it is likely that the company will apply fro public funding via the MSAC process. T Therefore HealthPACT has recommended that further assessment of this technology is no longer warranted.

JANUARY 2007 - SOURCES OF FURTHER INFORMATION:

Briel, M., Christ-Crain, M. et al (2005). 'Procalcitonin-guided antibiotic use versus a standard approach for acute respiratory tract infections in primary care: study protocol for a randomised controlled trial and baseline characteristics of participating general practitioners [ISRCTN73182671]', BMC Fam Pract, 6, 34.

Christ-Crain, M., Stolz, D. et al (2006). 'Procalcitonin Guidance of Antibiotic Therapy in Community-acquired Pneumonia: A Randomized Trial', Am J Respir Crit Care Med, 174 (1), 84-93.

Simon, L., Gauvin, F. et al (2004). 'Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis', Clin Infect Dis, 39 (2), 206-217.

LIST OF STUDIES INCLUDED

Level I diagnostic	3