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Technology Assessment Unit of the McGill University Health Centre (MUHC)

Use of serum procalcitonin levels in treatment decisions for adult patients in the intensive care unit

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by

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PRINCIPAL MESSAGES

Serum procalcitonin (PCT) level is a biomarker for the presence and persistence of infection, and has been used to guide decisions around the initiation of, continuation of, and termination of antibiotic treatment.

Measurement of single or serial PCT levels as a part of a treatment algorithm do not appear to be useful in determining when to start or escalate antibiotics, and its use is not recommended.

There is evidence that measurement of serial PCT levels as part of a treatment algorithm results in reduction in duration of antibiotic administration, but no difference in measures of clinical outcome, including mortality. It is recommended that this evidence be re-reviewed when the results of three ongoing RCTs become available.

LIST OF ABBREVIATIONS

ARR	Absolute risk reduction
CADTH	Canadian Agency for Drugs and Technologies in Health
CAP	Community-acquired pneumonia
CI	Confidence interval
DARE	Database of Abstracts of Reviews of Effects
EMBASE	Excerpta Medica Database
ER	Emergency room
HAP	Hospital acquired pneumonia
ICU	Intensive care unit
INAHTA	International Network of Agencies for Health Technology Assessment
LOS	Length of stay
MUHC	McGill University Health Centre
OR	Odds ratio
PCT	Procalcitonin
Q*	The point along a symmetrical SROC curve at which sensitivity equals specificity
RCT	Randomized controlled trial
RR	Risk ratio
SAP II	New Simplified Acute Physiology Score
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential Organ Failure Assessment score
SROC	Summary receiver operating characteristic
TAU	Technology Assessment Unit, MUHC
VAP	Ventilator-acquired pneumonia
WMD	Weighted mean difference

EXECUTIVE SUMMARY

Background

Serum procalcitonin (PCT) level is a biomarker for the presence and persistence of infection, and has been used to guide decisions around the initiation of, continuation of, and termination of antibiotic treatment. The Technology Assessment Unit (TAU) was asked by Dr. Peter Goldberg (Director of Adult ICU, Royal Victoria Hospital) to evaluate the use of PCT in the diagnosis of infection and/or sepsis and in antibiotic treatment decision-making for patients with infection/sepsis in the ICU.

Method

We conducted systematic searches of EMBASE (Ovid), PubMed, the Cochrane Collaboration, DARE, INAHTA, CADTH and ISI Web of Science for systematic reviews of diagnostic and clinical studies of the use of PCT in ICU patients with infection.

Results: Literature review

Diagnostic performance of a single procalcitonin measurement

We retrieved 3 systematic reviews and diagnostic meta-analyses of the use of PCT for the diagnosis of infection/sepsis, carried out in critically ill patients/patients in ICU, as well as several meta-analyses of seriously ill patients in other settings (eg, bacteremia in ER patients, infection in neutropenic or burn patients). Included diagnostic studies were heterogeneous in terms of patient population and reference standard, and meta-analysis results varied according to study selection and methods of analysis. The calculated areas under the SROC curve for critically ill patients ranged from 0.78 – 0.85. The calculated diagnostic OR was 7.79 (95%CI 5.86, 10.35) in one meta-analysis of patients with sepsis and 15.7 (95%CI 9.1-27.1) in a second. The first result indicated poor performance, whereas the authors of the second paper considered the test performed well.

Procalcitonin in the decision to initiate antibiotics in ICU patients with infection

Two RCTs and one systematic review reported on the clinical use of PCT measurements in the decision to start antibiotics. In one RCT, the use of a single PCT measurement was compared with standard management. The authors found no difference between the two groups for number of treated patients or antibiotic treatment duration. The second, which used serial PCT levels in the initiation and escalation of antibiotics, found increased antibiotic use and poorer clinical performance in the PCT-guided group.

Procalcitonin in the decision to terminate antibiotics in ICU patients with infection

Five recent systematic reviews assessed the safety and efficacy of using PCT-guided treatment algorithms in the decision to terminate antibiotics in ICU patients with sepsis/infection. Four of these meta-analyses drew from the same pool of 6 RCTs. Results of the meta-analyses were generally consistent: they concluded that use of PCT results in reduction in measures of antibiotic duration, but no difference in measures of clinical outcome, including mortality, ICU- or hospital length of stay. All articles commented on the heterogeneity and small number of trials analysed. Quality was generally assessed as low to moderate, since trials were unblinded as to intervention group. The maximum available number of patients was 1010, 621 of which came from a single trial. The power of the individual trials to detect modest worsening of clinical outcomes is limited. Three large trials of PCT-guided algorithms are ongoing, so updated information will be forthcoming.

Costs

Two analyses assessed the cost impact of using PCT-guided algorithms that reduced duration on antibiotics. In addition, one study compared duration of ICU stay. Both studies showed a favourable impact driven by antibiotic cost, but the variables in the model were limited, given the lack of observed difference in clinical outcomes. Assuming 300 cases of sepsis, and an estimated 3-5 tests per patient, the cost to the MUHC of the test alone would be $9 000 to $22 500.

Conclusions

- Single PCT levels are only moderately sensitive and accurate in the diagnosis of infection, using infection confirmed by culture as a comparator. Such a test would not have the sensitivity required to inform a decision to withhold antibiotic therapy in a critically ill patient.
- Measurement of single or serial PCT levels as a part of a treatment algorithm do not appear to be useful in determining when to start or escalate antibiotics, although only a limited number of studies have tested it.
- Measurement of serial PCT levels as part of a treatment algorithm may have some usefulness in determining when to discontinue antibiotics. Studies have not compared PCT algorithms to best practice intended to reduce antibiotic use, and studies to date have not been large enough to detect small differences in clinical outcomes, especially mortality. Three large studies are ongoing.

Recommendations

- The use of single PCT measurements in the detection of infection in ICU patients or to guide in the decision to initiate or escalate antibiotics is not recommended.

- The available evidence does not support routine use of PCT-guided algorithms in the decision to terminate antibiotics. We recommend the question be reviewed when the results of three large ongoing studies become available.

SOMMAIRE

Contexte

Le dosage sérique de la procalcitonine (PCT) est un biomarqueur reflétant la présence et la ténacité d'une infection et a été utilisé comme guide pour l'initiation, la poursuite et l'arrêt de l'antiobiothérapie. L'Unité d'évaluation des technologies (ETS) fut sollicitée par le Docteur Peter Goldberg (directeur de l'unité des soins intensifs pour adultes de l'Hôpital Royal Victoria) pour évaluer l'utilisation de la PCT dans le diagnostic d'infection et/ou de septicémie et dans la prise de décision pour une antibiothérapie chez les patients présentant une infection/septicémie à l'unité des soins intensifs.

Méthodologie

Nous vons mené des recherches systématiques dans les bases de données EMBASE (Ovid), PubMed, la Collaboration Cochrane, DARE, INAHTA, ACMTS et "ISI Web of Science" en regard de revues systématiques de diagnostics et d'études cliniques traitant de l'utilisation de la PCT chez les patients infectés à l'unité des soins intensifs.

Résultats. Revue de la littérature

Performance diagnostic d'un dosage unique de procalcitonineNous avons retenu 3 revues systématiques et de méta-analyses diagnostiques traitant de l'utilisation de la PCT dans le diagnostic d'infection/septicémie menées chez les patients gravement malades ou admis à l'unité des soins intensifs, de même que plusieurs méta-analyses en regard de patients très malades dans d'autres contextes (par exemple, bactériémie chez les patients admis à l'urgence, infection chez les patients neutropéniques ou brûlés). Les études diagnostiques retenues étaient hétérogènes quant à la population des malades et aux références standards et les résultats des méta-analyses variaient selon le type d'étude et des méthodes d'analyse. Les surfaces sous la courbe SROC ("Summary Receiver Operating Characteristic") pour les patients gravement malades s'échelonnaient de 0,78 à 0,85. La valeur de OR diagnostique calculée était de 7,79 (95% CI 5,86 - 10,35) dans une méta-analyse portant chez les patients septiques, et de 15,7 (95% CI 9,1 - 27,1) dans une deuxième étude. Le premier résultat reflétait une faible performance tandis que les auteurs de la seconde publication estimaient que le test était concluant.

La procalcitonine dans la prise de décision pour initier une antibiothérapie chez les patients infectés admis à l'unité des soins intensifs.

Deux études randomisées et une revue systématique portaient sur l'utilisation clinique du dosage de la PCT dans la prise de décision pour démarrer une antibiothérapie. Dans la première étude randomisée, l'utilisation d'un seul dosage de la PCT était comparée au management standard. Les auteurs ne trouvèrent aucune différence entre les deux

groupes quant au nombre de patients traités ou de la durée de l'antibiothérapie. Dans la seconde étude où l'on utilisait des valeurs consécutives de la PCT pour décider du démarrage et de l'intensification de l'antibiothérapie, une augmentation de l'utilisation des antibiotiques fut rapportée ainsi qu'une performance clinique plus faible dans le groupe de la PCT.

La procalcitonine dans la prise de décision pour interrompre une antibiothérapie chez les patients infectés admis à l'unité des soins intensifs.

Cinq revues systématiques publiées récemment ont évalué l'innocuité et l'efficacité de l'utilisation d'algorithmes de traitement basés sur le dosage de la PCT pour décider d'interrompre une antibiothérapie chez les patients infectés/septiques admis à l'unité des soins intensifs. Quatre de ces méta-analyses étaient issues des mêmes six études randomisées. Les résultats de ces méta-analyses étaient généralement cohérents: ils concluaient que l'utilisation des dosages de la PCT se traduisait par une diminution de la durée des antibiothérapies mais qu'il n'y avait pas de différence au niveau des résultats cliniques, incluant la mortalité et le séjour à l'unité des soins intensifs ou hospitalier. Tous ces articles soulignaient l'hétérogénéité et le faible nombre des études analysées. Puisque ces études étaient ouvertes, leurs qualité était généralement évaluée de faible à modérée. Le nombre maximal de patients était de 1010, où 621 patients provenaient d'une seule étude. La puissance des études individuelles est alors limitée pour identifier une détérioration modeste des résultats cliniques. Trois études importantes portant sur des algorithmes basés sur le dosage de la PCT sont actuellement en cours de sorte qu'une mise à jour de l'information sera bientôt disponible.

Coûts

Deux analyses ont évalué l'impact budgétaire de l'utilisation des algorithmes basés sur le dosage de la PCT pouvant réduire la durée des antibiothérapies. Une première étude estima des économies variant de 193 $ à 470 $, selon le coût de l'antibiotique utilisé. La seconde étude, qui considérait la diminution de l'utilisation des antibiotiques, le séjour à l'unité des soins intensifs et le séjour hospitalier, calcula des économies moyennes de €886.4 par patient admis à l'unité des soins intensifs. En supposant que 300 cas de septicémie nécessitent 3-5 tests par patient, l'impact budgétaire pour le CUSM serait de 9 000 $ à 22 500 $ pour les tests, uniquement.

Conclusion

- Des dosages individuels de la PCT sont modérément sensibles et précis pour émettre un diagnostic d'infection, par comparaison à une analyse de culture. Un tel test n'aurait pas la sensibilité requise pour supporter la décision de ne pas initier une antibiothérapie chez un patient gravement malade.

- La mesure de dosages individuels ou sériés de la PCT faisant partie d'un algorithme de traitement ne semble pas utile pour déterminer le moment de démarrer ou d'intensifier une antibiothérapie, même si un nombre restreint d'études l'ont considéré.
- La mesure de dosages sériés de la PCT faisant partie d'un algorithme de traitement peut avoir une certaine utilité pour déterminer le moment d'interrompre une antibiothérapie. Les études n'ont pas comparé les algorithmes de traitement basés sur les dosages de la PCT aux meilleures pratiques visant la réduction de l'utilisation des antibiotiques; à ce jour, les études disponibles ne sont pas suffisamment importantes pour déceler les faibles différences au niveau des résultats cliniques et tout particulièrement, de la mortalité. Par contre, trois études importantes sont actuellement en cours.

Recommandations

- **L'utilisation de dosages individuels de la PCT dans la détection de l'infection chez les patients admis à l'unité des soins intensifs ou pour la prise de décision d'initier ou d'intensifier une antibiothérapie, n'est pas recommandée.**
- **Les preuves disponibles ne supportent pas l'utilisation courante des algorithmes basés sur la PCT dans la prise de décision pour interrompre une antibiothérapie. Nous recommandons que ce questionnement soit revu lorsque les résultats des trois études actuellement en cours seront disponibles.**

Use of serum procalcitonin levels in treatment decisions for adult patients in the ICU

1. BACKGROUND

Procalcitonin (PCT), a polypeptide precursor to the hormone calcitonin, is known to be up-regulated from its normal low serum concentration in response to bacterial endotoxin or mediators of bacterial infection (as well as in patients with pancreatitis, recent trauma or surgery, and some viral infections)[1,2]. Measurement of serum PCT has been investigated as a biomarker for the presence and persistence of infection, in order to guide decisions around the initiation of, continuation of, and termination of antibiotic treatment[1,3]. Delayed initiation of antibiotics in patients with sepsis contributes to increased mortality[4], and inappropriately prolonged use of antibiotics increases the risk of adverse events, including *Clostridium difficile* infection, and the development of antibiotic resistance[5].

The Technology Assessment Unit (TAU) received a request from Dr. Goldberg (Director of Adult ICU, Royal Victoria Hospital) to evaluate the use of procalcitonin in the diagnosis of sepsis and in treatment decision-making for ICU patients with infection including sepsis (microbial invasion of normally sterile regions of the body[6]).

2. OBJECTIVE(S)

- **To assess the available evidence for the use of PCT in the diagnosis of infections including sepsis in critically ill patients**
- **To assess the available evidence for the use of PCT in antibiotic initiation for patients in the ICU**
- **To assess the available evidence for the use of PCT in determining the length of antibiotic treatment in patients in the ICU**

3. METHODS

3.1. Literature search and quality assessment

We conducted systematic searches of the following databases for systematic reviews, health technology assessments, and diagnostic studies or RCTs which addressed (1) clinical practice incorporating PCT measurements in ICU patients with infections and (2) sensitivity and specificity of PCT in the diagnosis of infection/sepsis in ICU patients.

- The Cochrane Collaboration (to end of 2011)
- The Centre for Reviews and Dissemination (CRD), University of York
- International Network of Agencies for Health Technology Assessment (INAHTA)
- Canadian Agency for Drugs and Technologies in Health (CADTH and CADTH confederated search)
- EMBASE/Ovid (includes Medline, 1996-2012 Week 3)
- PubMed (to 2012 Week 3)
- ISI Web of Science (for abstracts)

Searches all used “procalcitonin”, both as a keyword and, where available, mapped to a subject heading. Searches for diagnostic studies used offered filters (PubMed clinical filters) combined with searches for text-words commonly used in the title and abstracts of diagnostic studies (“sensitivity”, “specificity”, etc). In clinical searches “antibiotic” or “antimicrobial” (as text words and assigned to keywords, and with and without wildcards) were used to narrow the searches to studies of antibiotic therapy. Where the number of hits in EMBASE or PubMed suggested additional narrowing was needed, “procalcitonin” was combined with “guided” or “algorithm”. In addition, results from searches of “procalcitonin” combined with “antibiotic” or “antimicrobial” were filtered using the PubMed clinical queries filter for systematic reviews and RCTs. The last date of search was January 25, 2012.

To retrieve ongoing trials, three large clinical trial registries (ClinicalTrials.gov, the ISRCTN Register of Clinical Trials, and the WHO Clinical trials registry) were searched using “procalcitonin” as a text word, and the results manually reviewed.

Citation lists from retrieved reviews, studies and commentaries were also reviewed for additional references. Quality of reviews was assessed using the AMSTAR checklist[7].

4. RESULTS

4.1. Procalcitonin for the diagnosis of sepsis/infection

4.1.1. Systematic reviews and meta-analyses of diagnostic studies

We identified three systematic reviews with meta-analysis[8-10] that considered the diagnostic accuracy of a single PCT measurement in the diagnosis of either infection in patients in ICU[8,9] and/or patients with the systemic inflammatory response syndrome[10] (SIRS). Additional reviews of the use of single PCT measurements in critically ill patients included both adults and children[11], burn patients[12], and selected studies on neutropenic patients[13]. Jones et al[14] reviewed the use of PCT in the diagnosis of bacteremia in patients in the emergency department.

For the diagnosis of infection in patients with SIRS, Ning et al[10] calculated the area under the SROC curve of 0.85, sensitivity 76% (95%CI 73%, 76%) and specificity 80% (95%CI 77%, 83%; see Appendix 1 for further explanation of measures of diagnostic test reliability). Their systematic review included 11 Chinese-language articles (of 20 total) not included in the other systematic reviews. They concluded that "serum measurements of PCT may be valuable in differentiating between [n]on-infectious SIRS sepsis and infectious SIRS, the latter including sepsis".

For the diagnosis of sepsis in critically ill patients, Uzzan et al[9] calculated a pooled diagnostic OR of 15.7 (95%CI 9.1-27.1), a maximum joint sensitivity and specificity (Q*) of 0.78 (95%CI 0.71, 0.84), and concluded PCT was a good diagnostic marker (see Appendix 1 for further explanation of measures of diagnostic test reliability). From a search of PubMed only (to October 2004) they identified 25 studies for inclusion, using the in-study definition of sepsis which included sepsis, severe sepsis, and septic shock. Studies that involved children, non-ICU patients, and patients with immunosuppression were excluded. All studies used the earlier, less sensitive LUMITest assay (Brahms Diagnostica GmbH, Berlin, Germany), with a functional detection limit of 0.3 ng/mL. Sensitivities for individual studies ranged from 42-100% and specificities from 48-100%, with optimal cutoff values as determined from the ROC curves from 0.6-5 ng/mL.

For the diagnosis of sepsis in critically ill patients in the ICU, Tang et al[8] reported an overall AUC of 0.78 (95%CI 0.73, 0.83) and Q* of 0.71 (95%CI 0.67, 0.76), and in a subgroup of 14 studies defined as Sackett stage I, calculated a diagnostic OR of 7.79 (5.86, 10.35), AUC 0.79, Q* 0.73. They concluded that PCT "cannot reliably differentiate sepsis from other non-infectious causes". From a search of Medline, EMBASE, and Current Contents (to November 2005), they identified 18 studies for inclusion, requiring that studies report sepsis according to the ACCP/SCCMCC criteria with confirmation by culture. They excluded studies with non-critically ill patients, or which concerned a subset (eg, burns or immunosuppressed). They detected publication bias, and in a sensitivity analysis that corrected for the underrepresentation of smaller studies, found that the test performed even more poorly.

According to the quality items of the AMSTAR scale[15], Uzzan et al conducted a more limited literature search, and did not assess quality. Tang et al did not specify an a priori design (although such a design was implied). Both sets of authors declared lack of conflict of interest within the reviewing/writing team. Neither assessed sponsorship of individual studies or potential for conflict of interest.

4.2. Procalcitonin in the decision to initiate (or increase) antibiotics in ICU patients with infection

One systematic review[2] retrieved 2 studies[16,17] that included algorithms that used PCT measurements to recommend for or against initiating antibiotics in ICU patients, and concluded that PCT guidance was “relatively ineffective” in reducing rates of antibiotic prescription[2]. After the search date of the systematic review, results were reported for a large RCT which used PCT in an antibiotic-escalation strategy[18].

Both initiation studies used a single measurement of PCT and recommended antibiotics be started if PCT>0.5 µg/L (strong recommendation if PCT>1.0 µg/L), and be withheld if PCT<0.5 µg/L (strong recommendation if PCT<0.25 µg/ml). In a study of 529 patients at 5 centres, randomized to either a PCT-guided approach or a standard approach, Layios et al[17] found no difference in the number of treated patients (88% versus 87%) or antibiotic days between patients assigned to PCT-guided treatment or control treatment. The area under the ROC curve for PCT-level compared with confirmed infections was 0.67. In Bouadma et al[16], 630 patients (9 were later excluded) were randomized to either PCT-guided treatment or standard care. Among 307 patients randomized to PCT-guided treatment, 65 (10.3%) received antibiotics although their PCT was <0.5 µg/L, and 4 did not, although their PCT was >0.5 µg/L. The authors did not summarize the proportion of patients receiving antibiotics, and their algorithm incorporated criteria for both initiation and discontinuation, so one cannot isolate the clinical outcomes for the decision around initiation alone.

In Jensen et al[18], 1200 critically ill ICU patients were randomized to receive either standard of care or standard of care augmented by PCT guided drug-escalation and intensified investigations. Allocation was blinded, although interventions were not. At baseline, an alert level was PCT≥1.0 µg/L, and after baseline, PCT≥1.0 µg/L with <10% decrease from the previous day. Patients in the PCT group with an alert level PCT received initial or escalated antibiotics according to individual site protocols, cultures, and acute diagnostic imaging (investigator-determined). At 28 days, 190/604 (31.5%) of patients randomized to the PCT group had died compared to 191/596 (32%) patients in the control arm, an absolute risk reduction of 0.6% (95%CI -4.7, 5.9%). The median length of antibiotic treatment was greater in the PCT group (6 days versus 4 days), although the time to appropriate administration of antibiotics did not differ, except for those with bacteremia. Median length of stay in the ICU increased by one day and rate of mechanical ventilation increased by 4.9% (95%CI 3.0, 6.7%).

4.3. Procalcitonin in the decision to terminate antibiotics in ICU patients with infection

4.3.1. Systematic reviews and meta-analyses

Five recent systematic reviews[2,19-22], four of which included a meta-analysis[19-22] assessed the safety and efficacy of using PCT-guided treatment algorithms in the decision to terminate antibiotics in ICU patients with infection[2,19,20] or sepsis[21,22]. Each of the four included 5 or 6 RCTs of a pool of 6 (Table 1). In addition, one Cochrane SR/MA (Pugh et al, 2010[23]) examined studies of PCT-guided treatment algorithms as a subset of a larger review of short versus long course antibiotics in patients with ventilator-associated pneumonia (VAP), and another review examined the efficacy and safety of de-escalation strategies in sepsis/septic shock[24]. For this latter review, no eligible studies were retrieved. Two systematic reviews/meta-analyses examined the use of PCT-guided therapy in the general hospitalized population[25,26], but are not discussed here. We searched for RCTs published in the last 4 years that might have post-dated the systematic reviews, but did not find any additional published trials.

Table 1 Studies included in systematic reviews/meta-analyses of the use of procalcitonin-guided discontinuation of antibiotic therapy in ICU patients

Reference	Indication	Included trials
Agarwal, 2011[2]	Adult, ICU, any infection	Bouadma 2010; Hochreiter 2009; Layios 2009 (abstract, initiation only); Schroeder 2009; Stolz 2009; Nombre 2008
Heyland, 2011[19]	Adult, ICU, any infection	Bouadma 2010; Hochreiter 2009; Schroeder 2009; Stolz 2009; Nobre 2008
Schuetz, 2011[20]	Adult, ICU, any infection	Bouadma 2010; Hochreiter 2009; Schroeder 2009; Stolz 2009; Nobre 2008; Svoboda 2007
Wilke, 2011[22]	Adult ICU, sepsis	Bouadma 2010; Hochreiter 2009; Schroeder 2009; Stolz 2009; Nobre 2008; Svoboda 2007
Kopterides, 2010[21]	Adult, ICU, any infection	Bouadma 2010; Hochreiter 2009; Schroeder 2009; Stolz 2009; Nobre 2008; Svoboda 2007
Pugh, 2011[23]	Adult, ICU, HAP, VAP	Bouadma 2010; Stolz 2009; Pontet 2007 (abstract)

In the least heterogenous but smallest meta-analysis (3 studies involving 308 patients) Pugh et al[23] found that for patients with VAP, treatment with a PCT-guided algorithm reduced the weighted mean duration of antibiotics by -3.20 days (95%CI -4.45, -1.95), but was not associated with a difference in 28-day mortality (OR 0.66 [95%CI 0.39, 1.16]), hospital mortality, length of stay in either the ICU or hospital, or reinfection. However, the confidence intervals were broad.

Schuetz et al[20], Kopterides et al[21], and Wilke et al[22] drew from the same pool of 6 studies. Schuetz et al[20] decided that the antibiotic outcomes were too heterogenous to pool, and found no difference in 28-day mortality (RR 0.89 [95%CI 0.66, 1.20], by the Peto method) or hospital mortality, between patients treated according to a PCT-guided algorithm, and those treated according to standard care. Kopterides et al[21] found reduced weighted mean difference (WMD) of total antibiotic duration (-4.19 days [95%CI -4.98, -3.39], 3 studies) and duration of antibiotic for first infection (-2.14 days [95%CI -2.48, -1.80], 5 studies), and no difference in 28-day mortality (OR 0.93 [95%CI 0.69, 1.26]), hospital mortality, ICU- or hospital length of stay. The set of studies was statistically heterogeneous, with a reported I^2 of 71.5%. As part of a cost analysis, Wilke et al[22] calculated a WMD in antibiotic duration of -4.0, and of ICU duration of -1.8 days.

Heyland et al included 5 of the 6 trials, and produced similar results: reduction in total antibiotic duration (WMD -2.14 days [95%CI -2.51, -1.78], 4 studies), and no difference in 28-day mortality (RR 0.98 [95%CI 0.75, 1.29], 5 studies, fixed effects), ICU- or hospital length of stay.

The quality of the reviews was generally good, although Wilke et al[22] did not provide enough detail for assessment. Three reviews[19-21] limited their article types to published articles or abstracts and did not search grey literature. All but one review[20] reported that the number of studies retrieved was too small for assessment of publication bias. All reviewers commented on the heterogeneity and small number of trials analysed. Individual RCT quality was generally assessed as low to moderate, since trials were unblinded as to intervention group.

4.3.2. Description of included trials

As noted by the authors of all the systematic reviews, the clinical trials retrieved were heterogeneous in indication, setting, patient severity, PCT-guided treatment algorithm (summarized in Table 2), control treatment algorithm, and recorded outcomes (especially measures of antibiotic exposure). The study by Layios et al[17] concerned antibiotic initiation and was considered previously. Details of the other studies are given in end-of-text Table 4. Three studies recruited postoperative patients with infections or severe sepsis[27-29]; two studies involved patients with sepsis[16,30] (one of which had 10% post-operative patients); one was on patients with ventilator acquired pneumonia[31]. The largest study, Bouadma et al[16], which is discussed below, contributed almost two-thirds of the patients to any meta-analysis of ICU patients that included it; the next-largest study was a quarter its size. Despite the disparity in size, results across trials were consistent.

Table 2 Treatment-decision algorithms used in trials of procalcitonin in guiding length of antibiotic treatment in ICU patients

Review	Strong stop	Stop	Continue	Strong continue	Assay used
Bouadma, 2010[16]		<0.5 µg/L, or >80% ↓ from peak	(Start: >0.5-1 µg/L)	(Start: >1 µg/L)	Kryptor (LLD 0.06 ug/L)
Hochreiter, 2009[27]		≤1 µg/L, or >1 µg/L with ↓ to ≤25-35% of initial value over 3d			Brahms PCT LIA (normal <0.5 µg/L)
Schroeder, 2009[28]		≤1 µg/L, or >1 µg/L with ↓ to ≤25-35% of initial value over 3d			Brahms PCT LIA (normal <0.5 µg/L)
Stolz, 2009[31]	<0.25 µg/L at Day 3	0.25-0.5 µg/L, or ≥80% ↓ from BL to Day 3	≥0.5 µg/L or ↓ <80% from BL to Day 3	>1 µg/L at Day 3	Kryptor (LLD 0.06 µg/L)
Nobre, 2008[30]		<0.25 µg/L or >90% ↓ from peak (BL ≥1 µg/L) at Day 5; <0.1 µg/L (BL <1 µg/L) at Day 3.			Kryptor (LLD 0.06 µg/L)
Pontet, 2007		If <0.5 µg/L at Day 7	If ≥0.5 µg/L at Day 7		Brahms PCT LIA (normal <0.5 µg/L)

In Bouadma et al[16], 630 ICU patients with suspected bacterial infections were randomized to receive antibiotics according to a PCT-guided algorithm or according to standard care, with the objective of establishing the effectiveness of the algorithm in reducing antibiotic exposure. The algorithm incorporated both a single PCT measurement to inform antibiotic initiation and serial daily measurements with recommendations for discontinuation (see Table 2). The primary endpoints were 28-day and 60-day mortality (by a noninferiority design), and number of days without antibiotics by day 28 (superiority analysis). The noninferiority margin was 10%. Of the patients for whom the infection site was known, most had pneumonia (394/542 patients, 73%). Outcomes were available for 621 patients, 307 in the PCT group and 314 in the control group. At 28 days, mortality was 21.2% (65/307) in the PCT group and 20.4% (64/314) in the control group, an absolute difference of 0.8% (95%CI -4.6, 6.2), suggesting non-inferiority. This difference increased to 3.8% (95%CI -2.1, 9.7) at 60 days. Antibiotic exposure was reduced: at 28 days the PCT group had 14.3 days without antibiotic (SD 9.1) compared with 11.6 days (SD 8.2), an absolute difference of 2.7 days (95%CI 1.4, 4.1). The rate of physician-override of the algorithm was high: antibiotics were stopped for 39 patients (12.7% of those assigned to PCT) with PCT>0.5 µg/L, because treating physicians assessed the infection as clinically cured, and continued for 111 patients (35.6% of those assigned to PCT) with PCT<0.5 µg/L, who were either clinically unstable or had been discharged from the ICU.

4.3.3. Ongoing clinical trials

Searches for clinical trials in progress retrieved 7 ongoing studies of PCT-guided treatment in ICU patients with sepsis and/or infection (non-post-operative), and one that had been terminated due to slow recruitment. Target recruitment for ongoing studies ranged from 81 to 2246 patients. Details of the three largest relevant studies are given below, in order of expected date of completion and, coincidentally, descending order of size.

“Safety and efficacy of procalcitonin guided antibiotic therapy in adult intensive care units (SAPS)”[32], sponsored by UV University Medical Centre, Netherlands, is a randomized open-label trial of PCT-guided therapy versus standard therapy in ICU patients receiving antibiotics for no more than 24 hours (ClinicalTrials.gov identifier NCT01139489). If PCT decreases to certain prespecified levels (not stated in summary), antibiotics are to be discontinued. The primary outcomes are 28-day mortality and antibiotic use, measured as defined daily dosage and days of treatment. Secondary outcomes are length of ICU stay and costs. A planned total of 2246 patients were to be recruited at 11 centres, and the projected date of study completion (ie, data collection) was July 2011.

“Procalcitonin to shorten antibiotics duration in ICU patients (ProShort)”[33], sponsored by the National Taiwan University Hospital, is a randomized open-label trial of PCT-guided therapy versus standardized therapy in patients with symptoms of severe infection (in or admitted to the ICU) confirmed by laboratory or diagnostic imaging and initial PCT>0.5 µg/L (ClinicalTrials.gov identifier NCT00832039). Serum PCT is measured on Days, 5, 7, and 9; the levels used for decision-making are given. The primary outcomes are 28-day mortality, and average antibiotic duration. Secondary outcomes are proportion treated with antibiotic in each arm, severity scores, rates of re-infection, and 90-day mortality. The planned recruitment is 1700 patients at 8 centres and the projected date of study completion is June 2013.

“Placebo-controlled trial of sodium selenite and procalcitonin-guided antibiotic therapy in severe sepsis (SISPCT), sponsored by Kompetenenz Sepsis”[34] (ClinicalTrials.gov identifier NCT00832039). In a randomized 2x2 factorial design, adults with recent-onset (within the 24 hours) severe sepsis or septic shock are assigned to either sodium selenite or placebo as a double-blind therapy, and open-label PCT-guided or standard antibiotic therapy. PCT will be measured on Days 4, 7, 10, and 14, with per-protocol termination of antibiotics from Day 7 on if PCT ≤ 1.0 µg/L, or if PCT decreases by >50% between measurements. The primary outcome is 28-day all-cause mortality, and secondary outcomes include measures of disease severity by scale and need for intervention (ventilation, vasopressors, diagnostic procedures), measures of antibiotic dose, duration, cost, and effectiveness, and 90-day mortality. The planned recruitment is 1180 patients at 51 centres, and the projected date of study completion is April 2014.

5. COSTS

5.1. Published analyses of costs

Heyland et al[19] carried out a cost analysis based on their meta-analysis of 5 studies, which showed reduction in duration in antibiotics but no impact on mortality, length of ICU stay, or length of hospital stay. They calculated an average savings of $470.62CDN per case with a PCT guided strategy in a base cost minimization analysis, incorporating costs of acquisition and administration of antibiotics and the cost of the PCT test itself. With less expensive antibiotics, costs would increase by $193.64CDN in comparison with standard, non-PCT guided therapies.

Wilke et al[22] simulated costs for the use of PCT-guided treatment for patients with sepsis treated in a Diagnoses Related Groups (DRG) reimbursement system. They used data from 16 hospitals on diagnoses and procedures, and ICU and hospital length of stay, and calculated the impact of PCT-guided therapy from a meta-analysis which gave a WMD for duration of antibiotic treatment and ICU LOS (see Section 4.3.1). The threshold for treatment initiation was PCT ≥0.5 μg/L. PCT was measured daily and reassessed at Day 3: if the PCT level had increased ≥30% between Days 2 and 3, therapy was considered inadequate and the regimen was changed. Thereafter antibiotic therapy was continued until PCT ≤0.25 μg/L, at which point it was to be discontinued. The authors anticipated an average of 7 tests per patient, at an average of €25/test. They calculated average cost savings of €886.4 per ICU patient and €136.2 for non-ICU patients.

5.2. MUHC budget impact

According to Dr Goldberg, the MUHC ICU sees approximately 300 cases of severe sepsis/septic shock per year, although he could not estimate the number with suspected infection. With an estimated 3-5 tests used to monitor the condition of each patient, and an estimated total cost for each test of $10-$15 (including the kit, conduct and reporting, according to Dr Blank), the cost to the system of the test alone would be $9 000 to $22 500. This estimate does not take into account any difference in the cost of antibiotics or other hospital treatments.

6. DISCUSSION

We reviewed the use of PCT measurements in the diagnosis of infection and in antibiotic treatment decisions for patients in the ICU.

The reported metrics of single measurement PCT do not suggest it has the sensitivity needed for the diagnosis of sepsis, when used in isolation. To withhold antibiotic treatment in a patient near death with possible septic shock would require a test with near 100% sensitivity. The evidence cited in Section 4.3 does not suggest that PCT is such a test. It is therefore not surprising that nonadherence to/overriding of the algorithm was high in studies that reported adherence (Bouadma et al[16], 45.3%, Stolz et al[31], 16%, Nobre et al[30], 19%),

The PCT algorithms varied across studies, using thresholds of 0.25 µg/L to 1 µg/L, with or without changes from baseline of 80-90%. This variation may partially have been due to the movement from the less sensitive Brahms assay to the more sensitive Kryptor assay[21]. Within a study, a common algorithm with a common cut-off was used across indications, which may have allowed for inappropriate continuation of antibiotics in circumstances where PCT was elevated for other reasons[21,25,35]. Some studies also incorporated change from baseline into the criteria to mitigate that.

Control groups generally represented standard of care, reinforced in some cases by training, rather than alternatives shown to be specifically effective in reducing antibiotic exposure[21], such as continuing prospective reminders of current guidelines[36] Use of such alternatives might have narrowed or even removed the measured differences in antibiotic duration[36,37]. PCT guided algorithms incorporated a daily decision-point, which would have promoted the earlier discontinuation of antibiotics compared with standard care.

Different measures of antibiotic exposure were used across studies. Agarwal et al concluded that studies were too heterogeneous to meta-analyse[2], while Karopides et al reported outcomes according to their individual subsets, with broad confidence intervals. Mortality was consistently reported across studies, but Heyland et al[19] considered that they could not exclude an increase in mortality of up to 7%.

7. CONCLUSIONS

- **Single PCT levels are only moderately sensitive and accurate in the diagnosis of infection, using infection confirmed by culture as a comparator. Such a test would not have the sensitivity required to inform a decision to withhold antibiotic therapy in a critically ill patient.**

- **Measurement of single or serial PCT levels as a part of a treatment algorithm do not appear to be useful in determining when to start or escalate antibiotics, although only a limited number of studies have tested it.**
- **Measurement of serial PCT levels as part of a treatment algorithm may have some usefulness in determining when to discontinue antibiotics. Studies have not compared PCT algorithms to best practice intended to reduce antibiotic use, and studies to date have not been large enough to detect small differences in clinical outcomes, especially mortality. Three large studies are ongoing.**

8. RECOMMENDATIONS

- **The use of single PCT measurements in the detection of infection in ICU patients or to guide in the decision to initiate or escalate antibiotics is not recommended.**
- **The available evidence does not support routine use of PCT-guided algorithms in the decision to terminate antibiotics. We recommend the question be reviewed when the results of three large ongoing studies become available.**

TABLES

Table 3 Systematic reviews/diagnostic meta-analyses of procalcitonin measurement in the management of infection

Reference	Objective (Patients)	Contrast	No. studies (No. patients)	Meta-analytic results for selected outcomes (CI)
Gomez Silva, 2011[24]	De-escalation of antibiotic treatment in adults with sepsis/severe sepsis/ septic shock. (Adult critically ill patients).	Any de-escalation strategy including PCT-guided.	0	No studies selected.
Agarwal, 2011[2]	Safety and effectiveness of procalcitonin measurement in the guidance of duration of antibiotic us (Adults).	PCT-guided strategy versus standard care.	6 (1476)	No meta-analysis.
Heyland, 2011[19]	Evaluation of clinical and economic outcomes of PCT-guided antibiotic therapy. (Adult critically ill patients)	PCT-guided strategy versus standard care.	5 (947)	28-day mortality: RR 0.98 (0.75, 1.29) Total duration of antibiotics WMD -2.14 days (-2.51, -1.78) Hospital mortality RR 1.06 (0.86, 1.30) Hospital LOS WMD -1.86 days (-4.75, 1.04) ICU LOS WMD -1.50 days (-4.50, 1.05) Re-infection RR 1.26 (0.68, 2.35)
Pugh, 2011[23]	Short course versus long course antibiotics in hospital-acquired pneumonia in critically ill adults. (Adults in ICU)	PCT-guided strategy versus standard care (subset).	3 (308)	28-day mortality: OR 0.66 (95%CI 0.39, 1.16) Total duration of antibiotics WMD -3.20 days (-4.45, -1.95) Hospital mortality OR 0.63 (0.25, 1.58) Hospital LOS WMD -2.40 days (-6.40, 1.60) ICU LOS WMD -2.68 days (-6.01, 0.66) Recurrence OR 2.06 (0.74, 5.70)
Schuetz, 2011[20]	Summarize evidence from RCTs using PCT in respiratory infection and sepsis in clinical care. (Adults in ICU)	PCT-guided strategy versus standard care.	6 (1010)	28-day mortality OR 0.89 (0.66, 1.20)
Wilke, 2011[22]	Derive inputs for cost analysis of PCT in ICU patients with sepsis	PCT-guided strategy versus standard care	6	Total duration of antibiotics WMD -4 days ICU LOS -1.8 days

Reference	Objective (Patients)	Contrast	No. studies (No. patients)	Meta-analytic results for selected outcomes (CI)
Kopterides, 2010[21]	Effectiveness and safety of PCT-guided algorithms for septic patients in ICU (Adults with sepsis in ICU)	Treatment with and without PCT-guidance	6 (1010)	28-day mortality OR 0.93 (0.69, 1.26) Total duration of antibiotics WMD -4.19 days (-4.98, -3.39) Hospital mortality OR 0.86 (0.2, 1.44) Hospital LOS OR -0.49 days (-1.55, 0.57) ICU LOS -0.49 days (-1.55, 0.57) Re-infection OR 2.06 (0.74, 5.70)

Table 4 Summary of outcomes of RCTs of PCT-guided treatment in ICU patients with infection

Reference	Patients	N PCT/ N control	Population characteristics	Outcomes
Initiation				
Layios, 2009[17]	ICU patients with suspected infection. France, single centre.	268/261	Post-surgical: 40%.	ICU LOS PCT 8 days (IQR 4-18), control 7 days (IQR 4-16). Proportion treated: PCT 88%, control 87%.
Escalation				
Jensen, 2011[18]	ICU patients, signs of infection not required, in ICU<24h. Denmark, medical/surgical. Excluded: elevated bilirubin, triglycerides, at-risk from blood sampling.	604/598	Post-surgical: 40%. Clinical infection at baseline: 996/1200 (83%)	28-day mortality: PCT 190/604 (31.5%), control 191/596 (32%), ARR 0.6% (95%CI -4.7, 5.9%). ICU LOS PCT one day longer Length of ventilation, PCT +4.9% (95%CI 3.0, 6.7%).
Initiation and discontinuation				
Bouadma, 2010[16]	ICU patients with suspected bacterial infections. France, medical, surgical units. Excluded: neutropenia, need for prolonged antibiotics.	307/314	Post-surgical 66/621 (10.7%) Infections: Pneumonia 394/642 (72.7%), VAP 141/621 (22.7%)	28-day mortality: PCT 65/307 (21.2%), control 64/314 (20.4%). Abs diff 0.8% (-4.6, 6.2). 60-day mortality: PCT 92/307 (30.0%), control 82/314 (26.1%). Abs diff 3.8% (-2.1, 9.7). Antibiotic-free days at day 28: Abs diff 2.7 days (95%CI 1.4, 4.1).
Discontinuation				
Hochreiter, 2009[27]	Postop patients with infections. Germany, post-surgical. Excluded: immunosuppressed.	57/53	Post-surgical: 100% Infections: Pneumonia 33/110 (30%)	Length of antibiotic treatment: PCT 5.9 (SD 1.7) days, control 7.9 (SD 0.5). LOS ICU: PCT 15.5 (SD 12.5) days, control 17.7 (SD 10.1). SOFA score, leukocytes, biomarkers: no difference between groups over time.
Schroeder,	Postop with severe sepsis. Germany,	13/14	Post-surgical: 100%.	Length of antibiotic treatment: PCT 6.6 (SD

Reference	Patients	N PCT/ N control	Population characteristics	Outcomes
2009[20]	post-surgical. Excluded: prior antibiotics.		Infections: Pneumonia 8/27 (30%).	1.1) days, control 8.3 (SD 0.7). LOS ICU: PCT 16.4 (8.3) days, control 16.7 (5.6). Deaths: PCT 3/14, control 3/13.
Stolz, 2009[31]	Ventilator-acquired pneumonia. Switzerland. Excluded: prior antibiotics.	51/50	Post-surgical: 47/101 (46%). Pneumonia (VAP): 100%	Antibiotic-free days alive at day 28 (median): PCT 13 (2-21) days, control 9.5 (1.5-17) days. Overall length antibiotic treatment: PCT 15 (10-23) days, control 10 (6-16) days. 28-days mortality: PCT 12/51 (24%), control 8/50 (16%).
Nobre, 2008[30]	Sepsis. Switzerland, medical-surgical ICU. Excluded: prior antibiotics, need for prolonged antibiotics.	39/40	Pneumonia: 52/79 (65.8%)	Length of first antibiotic treatment (ITT): PCT 6 days (2-33 days), control 9.5 (3-34) days . Days alive without antibiotics: 15.3 (SD 8.9) days, 13 (SD 8.2) days. 28-day mortality: PCT 8/39 (20.5%), control 8/40 (20%)
Pontet, 2007[38]	VAP. Uruguay. Excluded: leukemia, immunosuppressed.	40/41	Pneumonia: 100%	Antibiotic duration: PCT 7.9 (SD 2.4) days, control 11.9 (SD 3.6) days. No difference crude mortality.
Svoboda, 2007[29]	Postop with septic shock. Excluded: chemical or burns trauma. Czech republic.	38/34	Post-surgical: 100%. Sepsis: 100%.	28-day mortality PCT 10/38 (26%) versus control 13/34 (38%) (not significant) LOS ICU PCT 16.1 (SD 6.9) days versus 19.4 (8.9) days

PCT algorithms for antibiotic discontinuation are shown in Table 2.

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Appendix 1 Definitions and interpretation of measures of diagnostic test performance

Measures typically reported in a single study setting

A **diagnostic test** generally measures response along a continuum, with a set value chosen as a cut-off point such that a response above the cut-off is positive, and response below a cut-off is negative (or vice versa).

Test properties can be described by several parameters including the following:

Test parameter	Definition
Sensitivity	Probability of testing positive in a patient who has the disease
Specificity	Probability of testing negative in a patient who does not have the disease
Positive predictive value	Probability that a patient who tests positive has the disease
Negative predictive value	Probability that a patient who tests negative does not have the disease
Accuracy	Proportion of cases correctly classified
Positive likelihood ratio (LHR+)	Ratio of true positive (sensitivity) to false positive (1-specificity)
Negative likelihood ratio (LHR-)	Ratio of true negative (specificity) to false negative (1-sensitivity)
Negative likelihood ratio (DOR)	Ratio of LHR+ to LHR-

The **receiver operating curve (ROC)** of a diagnostic test is a graphical display of the true positive rate (sensitivity) on the Y axis against the false positive rate (1-specificity) on the X axis across all possible cut-off values. Integration of the area under the ROC curve (**AUC**) gives an overall measure of test performance. The Q* value is the point where the sensitivity and specificity are equal. In a symmetrical ROC plot, this represents the point where the best test properties are achieved.

The table below gives a rough guide to the interpretation of these measures in terms of diagnostic usefulness, although they are debated (see, Reinhard et al, 2007[39], in response to Tang et al, 2007[26], on procalcitonin).

	Accuracy	LHR+	LHR-	AUC	DOR
Excellent	>90	>10	<0.1	>90	>100
Good	0.75-0.90	5-10	0.1-0.2	0.75-0.90	25-100
Poor	0.5-0.75	1-5	0.2-1	0.5-0.75	1-25
Of no value	0.5	1	1	0.5	1

Source: Ray et al, 2010[40]

Measures typically reported in a meta-analysis setting

Individual studies typically report a single sensitivity and specificity estimate at one cut-off value. Meta-analyses report **pooled sensitivity and specificity** values that account for between and within study variation. These values are typically accompanied by a prediction region. The **summary receiver operating curve**

(SROC) is a graphical presentation corresponding to the ROC but across individual studies rather than cut-off values.