Prospective evaluation of procalcitonin in sepsis in the Illawarra area of Australia: PEPSIA study

Kumar A Muthiah, Kanaka S Rachakonda, Michael J Davis, Edward G Simmons, Gary Schier and Fernando San Gil

ABSTRACT

Introduction: Procalcitonin (PCT) is a precursor of the hormone calcitonin and has been proposed as a marker of infection in critically ill patients. We evaluated the role of procalcitonin in the early detection of sepsis in an Australian intensive care–high dependency unit (ICU/HDU).

Methods: This prospective observational study enrolled 204 consecutive patients admitted to the ICU/HDU of Wollongong Hospital, NSW, over a 3-month period, October to December 2001. Of the 204, 172 (84%) were included in the final analysis. Patient demographic data, serum PCT levels and the vital signs required to score the criteria for systemic inflammatory response syndrome (SIRS) and sepsis were recorded daily until the patient left the ICU. Cultures were obtained when clinically indicated.

Results: PCT measurement appears a useful screening test for sepsis with a cut-off value > 0.85 ng/dL. At levels > 10 ng/dL, its diagnostic accuracy improves significantly. PCT level was able to discriminate between sepsis and non-sepsis, and between septic shock and non-septic shock. However, it failed to discriminate well between bacterial and non-bacterial SIRS with a 95% CI for area under the receiver operating characteristic curve of 0.59–0.76.

Conclusions: The use of PCT as a screening test (PCT > 0.85 ng/dL) in conjunction with traditional criteria is of value in the early diagnosis of bacterial sepsis in suspected cases in the ICU. PCT appears to be a reliable diagnostic test for bacterial sepsis at levels > 10 ng/dL.

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Sepsis is a leading cause of morbidity and mortality in the intensive care unit. The hospital mortality rate for severe sepsis ranges from 30% to 50%.[1] Important recent advances in treatment include the use of activated protein C and moderate doses of corticosteroids in septic shock, and goal-directed resuscitation during the first 6 hours after recognition of sepsis.[2] The key to initiating these treatments is accurate and early diagnosis of sepsis. While early risk stratification is possible in specific situations, such as in the emergency department using the Mortality in Emergency Department Sepsis (MEDS) score,[3] early diagnosis of sepsis still relies mostly on the skill of the clinician.

A simple, rapid and reliable biochemical marker of sepsis is therefore important to help accurately diagnose sepsis and allow early treatment. Lactate, C-reactive protein and interleukin-6 have all been advanced as possible markers, but their usefulness has been limited by problems with timeliness and diagnostic accuracy.[4]

Procalcitonin (PCT) is a prohormone protein complex of 116 amino acids that is the precursor of calcitonin (32 amino acids). Assicot et al first described elevations of serum PCT concentration in patients with bacterial sepsis in 1993.[5] Meisner performed most of the pioneering work on PCT. Generally, PCT levels are not elevated in viral infections, localised bacterial infections or autoimmune states. Levels are significantly elevated in bacterial and systemic fungal infections associated with systemic inflammatory response syndrome (SIRS). Levels in healthy individuals are less than 0.5 ng/dL.[6] After a specific bacterial insult, PCT levels start to rise in 2–3 hours, reach peak values in 14–16 hours, and remain elevated beyond 24 hours. The plasma half-life of PCT ranges from 25 to 35 hours and is not significantly altered by renal failure or continuous 24-hour haemodiafiltration[7-9] in the critically ill.

In this study, we investigated the role of PCT in the early detection and management of bacterial sepsis in an Australian setting. We studied baseline trends in PCT levels with antibiotic therapy in bacterial sepsis and profiled the utility of PCT as a marker in the diagnosis of bacterial sepsis in commonly encountered ICU conditions.

Methods

The study was a prospective observational study over 3 months from 1 October to 31 December 2001. It enrolled 204 consecutive patients admitted to the multidisciplinary intensive care/high dependency unit at Wollongong Hospital, New South Wales. This is a tertiary referral hospital and teaching facility affiliated with the University of New South Wales and the University of Wollongong, and is the main referral hospital for a population of over 400 000.

The study was approved by the Human Research Committee of the University of Wollongong. The need for written informed consent was waived by the committee as PCT testing was included in routine morning blood tests

and required no additional venepuncture. Patients and their representatives were provided with full written information about the study, and verbal consent was obtained from either the patients or their representatives.

Procalcitonin measurements

Serum PCT levels were measured daily for each patient in the ICU/HDU during the study period using the LUMItest PCT immunoluminometric assay (BRAHMS Diagnostica GmbH, Berlin, Germany). PCT testing was begun on every new patient admitted to the ICU/HDU from Day 1 of the study. All patients admitted before this date were excluded. Similarly, PCT testing ceased on the last day of the study, and all patients still present in the ICU/HDU after this time were excluded. Blood collection for PCT levels was performed once daily in the morning. Because of the long half-life of PCT, this was done irrespective of the time the patient was admitted. Blood samples were stored in a –70°C freezer, and PCT estimations were carried out in batches.

The database of samples and laboratory numbers was maintained jointly by the ICU data collector and laboratory scientist. To facilitate smooth transfer, the laboratory scientist maintained the database linking each patient study number to a separate laboratory number on a daily basis. The microbiologist and intensive care specialists were blinded to PCT results until follow-up data collection on discharges and deaths was completed.

Data collection and definitions

A total of 996 PCT measurements were recorded for final review. Patient demographic data were recorded along with daily PCT levels, and daily records of vital signs to score SIRS and sepsis criteria, Glasgow Coma Score, admission APACHE II scores, duration of antibiotic and inotrope therapy, and ventilation, ICU length of stay, and ICU and hospital mortality.

The definitions derived from the 1992 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference on sepsis[10] were applied to score the number and percentages of patients expected to have SIRS, sepsis or septic shock.

The number of patients admitted to the ICU/HDU with the admission clinical diagnosis of sepsis was recorded. This diagnosis was based on the presence of two or more of the four criteria for SIRS plus a strong suspicion of infection on the basis of a definable focus of infection or positive bacterial cultures consistent with the focus of infection.

Infections were diagnosed based on the following criteria:

- Pneumonia — presence of a pulmonary infiltrate on x-ray plus auscultation findings consistent with pneumonia, or symptoms such as dyspnoea, chest pain and cough.
- Aspiration pneumonia — pulmonary infiltrate plus a history of, or signs consistent with, aspiration.
- Bacteraemia — clinical evidence of infection and a positive blood culture.
- Urinary tract infection — dysuria, frequency, urgency and a positive urinalysis or urine culture.
- Ascending cholangitis — ultrasound evidence of choledocholithiasis plus right upper quadrant pain, fever and jaundice.
- Intra-abdominal infection — laparotomy or radiological evidence.
- Skin sepsis — wet gangrene, cellulitis or pus.
- Other sources of infection — confirmatory radiological evidence, such as abscess formation confirmed by computed tomography.

Bacterial cultures

Blood and body fluid were cultured when indicated as in routine clinical practice. Bacterial culture results were classified as significant, probably significant, possibly significant or not significant based on the microbiological validity of the isolate and the strength of the clinical context. Bacterial culture of any of the three grades of significance was defined as an episode where an organism was grown from an expected site or sites (eg, blood and catheter tip in the case of line sepsis) and was clinically perceived to be the relevant pathogen causing the septic episode.

Bacterial cultures were considered:

- significant when the organism was grown from a normally sterile site or was identified as one not normally present in that site;
- probably significant when the isolate was a recognised pathogen for the clinical condition but was also known to be part of the normal flora;
- possibly significant when the organism was not a classic pathogen at the site but could have been a pathogen, and was also known to be present in the normal flora; and
- not significant when only contaminants were grown.

The number of sites and times the organism was isolated and the strength of the clinical context added to the significance of the isolate. All microbiological data were scrutinised by a clinical microbiologist and the chief investigator. The criteria for SIRS, sepsis and septic shock were evaluated in conjunction with the clinical diagnosis of sepsis.

Statistical analysis

Data were presented in a Microsoft Excel database. Patients were classified into two groups according to PCT level: normal PCT (peak level ≤ 0.5 ng/dL) and raised PCT (peak level > 0.5 ng/dL).

Table 1. Characteristics of the 172 patients included in the analysis by procalcitonin (PCT) group

Variable	Normal PCT	Raised PCT*	P
No. of patients	94 (55%)	78 (45%)	
Mean age (years)	59	71	< 0.01
Male to female ratio	1.02	1.03	NS
Mean APACHE II score	13.59	19.83	< 0.001
Mean days of			
Antibiotics	1	5	< 0.001
Inotropes	0	3	< 0.001
Ventilation	0	5.25	< 0.001
ICU/HDU stay	3	8.25	< 0.001
ICU/HDU mortality	3%	13%	< 0.02
Hospital mortality	6%	22%	< 0.001

* Raised PCT defined as peak PCT level > 0.5 ng/dL. NS = not significant. APACHE = Acute Physiology and Chronic Health Evaluation.

Table 2. Procalcitonin (PCT) levels in selected disease states

Disease state	PCT (ng/dL) Mean ± SD	PCT (ng/dL) Median	No. of patients
Medical conditions without sepsis			
Acute severe asthma	0.67 ± 0.6	0.31	3
Acute exacerbation of chronic airway limitation	1.1 ± 1.5	0.41	8
Acute myocardial infarction	5.7 ± 8.7	1.22	3
Bleeding gut	0.61 ± 0.67	0.385	10
Drug overdose	0.18 ± 0.07	0.18	8
Medical conditions with sepsis			
Pneumonia, aspiration	11.81 ± 18	1.55	9
Pneumonia, community	7.21 ± 5.4	6.78	5
Sepsis, skin*	10.51	10.51	1
Sepsis, gastrointestinal tract	34.54 ± 23	30.355	6
Sepsis with neutropenia*	86.68	86.68	1
Sepsis, urological†	494	494	3
Bacterial meningitis*	16.32	16.32	1
Postoperative surgical cases			
Carotid endarterectomy	0.61 ± 1.6	0.16	15
General surgery	1.5 ± 2	0.61	5
Lower gastrointestinal surgery	4.24 ± 9	0.96	19
Neurosurgery	0.94 ± 2.6	0.2	13
Abdominal aortic aneurysm repair			
Elective	1.2 ± 1.6	0.405	6
Emergency	5.5 ± 5	3.51	7
Upper gastrointestinal surgery	4.11 ± 2.9	5.72	3
Urological surgery	4.3 ± 3.95	5.27	5

* One case. † Included one case of *Escherichia coli* sepsis.

The Mann–Whitney test was used to assess differences in outcomes between the normal and raised PCT groups. For categorical data, Pearson's χ^2 was used to determine whether there was a relationship between death in hospital and PCT (ie, raised versus normal) group. No adjustments were made for multiple comparisons. A P value < 0.05 was classed as significant.

Continuous variables that were normally distributed were analysed using a *t* test. The *t* test was also used to compare mean APACHE II scores between the raised and normal PCT groups. As admission PCT was not normally distributed, Spearman rank correlations were used to quantify the association between admission PCT and APACHE II scores.

Receiver operating characteristic (ROC) curves were created to determine the cut-off values for the accuracy of PCT as a screening and diagnostic test for sepsis. The area under the curve (AUC) indicates the accuracy of the test, with AUC > 0.7 indicating a "good" level of accuracy.

PCT was deemed to be a good screening test for sepsis at the cut-off value that provided high sensitivity and negative predictive value (NPV). Similarly, it was deemed to be a good diagnostic test for sepsis at the cut-off value that provided high specificity, positive predictive value (PPV) and NPV.

From available information on PCT, a cut-off value of 10.0 ng/dL seemed to serve as a good diagnostic test for sepsis.[6] However, Bell et al found a cut-off value of 15.75 ng/dL to provide a better diagnostic test.[11] Because of this, we analysed the performance of PCT at two cut-off values: 10.0 and 15.0 ng/dL.

Results

Of the 204 patients, 32 (16%) were excluded because of incomplete PCT follow-up data, leaving 172 (84%) in the analysis. Characteristics of the 172 patients are summarised in Table 1. Mean age of patients was higher in the raised PCT group than in the normal group ($P < 0.01$). The male to female ratio was almost identical in the two groups.

The mean ± SD admission APACHE II scores for the raised and normal groups were 19.83 ± 12.18, and 13.59 ± 7.22, respectively. The mean difference in APACHE II score between the groups was 6.25 ± 1.57 (95% CI, 3.15–9.35; $P < 0.001$). However, there was no association between APACHE II score and admission PCT values for the normal PCT group ($r = 0.14$, $P = 0.18$) or the raised PCT group ($r = 0.02$, $P = 0.84$).

The mean ± SD peak PCT level in the raised PCT group was 9.31 ± 15.3 ng/dL (after exclusion of a patient with a PCT level of 494.29 ng/dL). The percentage of patients with a clinical diagnosis of sepsis was higher in the raised PCT group (38%; 30/78) than in the normal PCT group (7%; 7/94).

Table 3. Cut-off values for serum procalcitonin (PCT) level in SIRS, sepsis and septic shock

Patient group	PCT cut-off (ng/dL)	Area under the curve (AUC)	95% CI for AUC
SIRS	0.27	0.67	0.59–0.76
Sepsis	0.85	0.84	0.77–0.91
Septic shock	0.70	0.84	0.76–0.92

SIRS = systemic inflammatory response syndrome.

Table 4. Ability of serum procalcitonin (PCT) level to discriminate bacterial from non-bacterial SIRS, sepsis from non-sepsis, and septic from non-septic shock

PCT cut-off (ng/dL)	Sensitivity	Specificity	PPV	NPV
Bacterial v non-bacterial SIRS				
0.27	68%	48%	80%	32%
10.0	12%	100%	100%	28%
15.0	8%	100%	100%	26%
Sepsis v non-sepsis				
0.85	81%	72%	44%	93%
10.0	35%	99%	87%	85%
15.0	35%	99%	87%	85%
Septic v non-septic shock				
0.70	91%	65%	29%	98%
10.0	39%	96%	60%	91%
15.0	30%	98%	70%	90%

PPV = positive predictive value. NPV = negative predictive value. SIRS = systemic inflammatory response syndrome.

In the raised PCT group, all the patients who fulfilled all four criteria for SIRS developed sepsis. The mean ± SD and median PCT values were 14.5 ± 20 ng/dL and 3.82 ng/dL in this subgroup, respectively. Of those who fulfilled two or three criteria for SIRS, 35% developed sepsis. The mean and median PCT values were 5.42 ± 8.18 ng/dL and 1.7 ng/dL in this subgroup, respectively.

Three-quarters of patients (76%; 130/172) enrolled in the analysis met two or more criteria for SIRS, and 29% (37/130) of these developed sepsis. As part of the usual ICU working policy, we collected blood and body fluids for culture only if clinically indicated. A bacterium was isolated in 48% (82/172) patients, but was considered significant in only 8% (13/172) patients and probably significant in another 2% (4/172). Patients with significant or probably significant isolates comprised 4% (4/94) of the normal PCT group and 17% (13/78) of the raised PCT group.

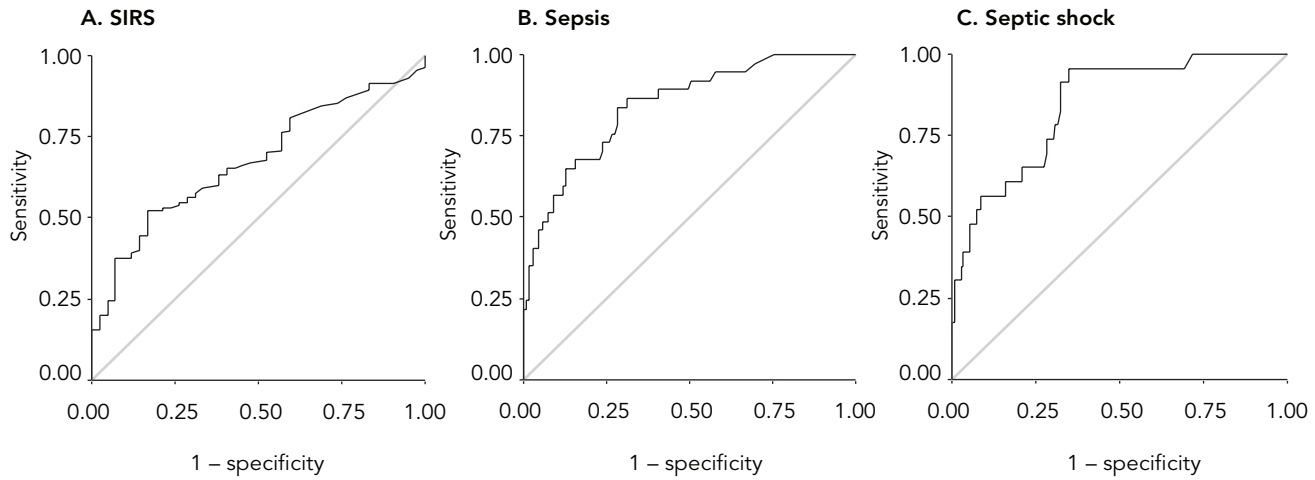
The overall incidence of sepsis in patients admitted to the ICU in the Illawarra area was 22% (37/172). Among the 37 patients with sepsis, 17 (46%) had significant or probably significant cultures, and another seven (19%) had possibly significant cultures. Twenty-three of the 37 patients (62%) were treated for septic shock during their ICU stay.

Procalcitonin and selected ICU disease states

The data on peak levels of PCT were examined in relation to selected disease states encountered during the study period. PCT levels in these disease states are shown in Table 2. Mean PCT levels were close to or greater than 10 ng/dL in most of the septic disease states.

Gram-negative sepsis was associated with higher PCT levels (mean, 43.0 ng/dL) than gram-positive sepsis (mean, 9.6 ng/dL).

Figure 1. Receiver operating curves for procalcitonin as a predictor of sepsis and related disorders*



*Diagonal segments are produced by ties.

Table 5. Statistics for differences in average antibiotic days, inotrope days, ventilation days and ICU days between the raised procalcitonin (PCT) and normal PCT groups

	Normal PCT group			Raised PCT group*			
	Median	Lower quartile	Upper quartile	Median	Lower quartile	Upper quartile	*P*
Duration (days)							
Antibiotics	1.0	0.0	1.0	2.5	0.0	5.0	< 0.001
Inotropes	0.0	0.0	0.0	0.0	0.0	3.0	< 0.001
Ventilation	0.0	0.0	0.0	1.0	0.0	5.25	< 0.001
ICU stay	2.0	1.0	3.0	3.0	1.0	8.25	< 0.001

* Raised PCT defined as peak PCT level > 0.5 ng/dL. PCT = serum procalcitonin level.

Procalcitonin in SIRS, sepsis and septic shock

As a marker, serum PCT level was unable to discriminate bacterial from non-bacterial SIRS, but it discriminated well between sepsis and non-sepsis, and between septic shock and non-septic shock (Table 3).

Serum PCT level poorly discriminated bacterial from non-bacterial SIRS, with an AUC value as low as 0.59 (Table 3, Table 4 and Figure 1A).

At a cut-off value of 0.85 ng/dL, PCT was shown to be a good screening test for sepsis (high sensitivity and NPV) (Table 4 and Figure 1B). At a cut-off value of 10.0 ng/dL, PCT performed well as a diagnostic test (high specificity, PPV and NPV). There was no appreciable difference in its performance as a diagnostic test at 15.0 ng/dL.

PCT followed a similar trend and was shown to be a good screening test for septic shock at a cut-off value of 0.70 ng/dL (Table 4 and Figure 1C). Again its diagnostic accuracy for septic shock improved at 10.0 ng/dL, with no appreciable difference in its performance at 15.0 ng/dL.

Raised versus normal procalcitonin groups

The differences between the raised and normal PCT groups for the duration of antibiotics, inotropes, ventilation and ICU stay was found to be significant ($P < 0.001$; Table 5). The patients in the upper quartile of the raised PCT subgroup had longer inotropic and ventilatory support and a longer ICU stay. The average duration of antibiotic use needed to return PCT to a normal level in this subgroup was 4.85 days.

Mortality rates

The ICU crude mortality rate was 7.6% (13/172), and the hospital crude mortality rate was 13.4% (23/172).

There were 13% (10/78) deaths in the ICU for the raised PCT group compared with 3% (3/94) deaths in the ICU for the normal PCT group ($\chi^2 = 5.66$; $P = 0.02$). A significant difference was seen in the number of deaths in the ICU between the raised and normal PCT groups.

There were 22% (17/78) deaths in hospital for the raised PCT group compared with 6% (6/94) deaths in hospital for the normal PCT group ($\chi^2 = 8.74$; $P < 0.001$). A significant difference was seen in the number of deaths in hospital between the raised and normal PCT groups.

The 48 patients in the raised PCT group who still had an elevated PCT level at the time of discharge from the ICU were followed up with regard to hospital mortality. Three died, none as a result of sepsis. PCT levels for these three patients before discharge from the ICU were 0.76 ng/dL, 1.24 ng/dL and 1.26 ng/dL, respectively.

Discussion

Our study is one of the largest prospective observational studies on PCT conducted to date in Australia. We found that a PCT level at or above a cut-off value of 0.85 ng/dL was a good screening test for sepsis, and a level at or above a cut off-value of 10.0 ng/dL was once again highly specific for sepsis.

Diagnostic accuracy did not improve when the cut-off value for PCT was raised to 15 ng/dL. The fact that PCT did not discriminate bacterial from non-bacterial SIRS indicates that SIRS should be considered as an early response to both bacterial and non-bacterial conditions producing a sepsis-like syndrome.

The number of SIRS criteria an individual fulfils has prognostic value in predicting the likelihood of sepsis in that individual. This was substantiated in the recent European multicentre SOAP (Sepsis Occurrence in Acutely ill Patients) study.[12] In our study, those who fulfilled all four criteria for SIRS (heart rate > 90 beats per minute, respiratory rate > 20 breaths per minute, temperature > 38° C or < 36° C, and white cell count $> 12.0 \times 10^9$ cells/L) developed sepsis, and some of these were subsequently treated for septic shock. This subgroup also had higher mean and median admission PCT levels than the subgroup who fulfilled two to three criteria for SIRS. Hence, examination of the number of SIRS criteria in conjunction with

admission PCT levels should enable us to predict more accurately those who are likely to develop sepsis.

As summarised in Table 1, patients in the raised PCT group had significantly higher APACHE II scores, longer duration of antibiotic and inotropic therapy, ventilation, and ICU length of stay, and higher mortality. PCT could therefore be a useful marker for severity of illness in future sepsis trials, particularly when these common ICU parameters are studied.

On average, with antibiotic therapy, it took 4.9 days for PCT levels to drop below 0.5 ng/dL in the group with raised PCT levels and full follow-up. Because of inadequate power, this needs to be verified prospectively in a multicentre study using daily SOFA scores and "septic workup" in every patient. Whether these data can help determine a safe duration of antibiotic therapy in critically ill patients remains a matter for future clinical investigation.

In our study, PCT levels were found to be elevated in patients admitted to the ICU with a range of medical and post-surgical conditions. However, the mean and median PCT level always remained below 10.0 ng/dL in all medical and postoperative surgical patients who lacked a clinical diagnosis of sepsis. In contrast, in every medical condition with a clinical diagnosis of sepsis, the mean and median PCT value remained close to, or above, 10.0 ng/dL. Hence, performing PCT measurements in an ICU setting appears to be more appropriate and valuable in patients with a clinical diagnosis of sepsis, rather than as a routine screening test.

Study limitations

Positive blood cultures remain the "gold standard" test for bacterial sepsis. A limitation of our study was that cultures were not undertaken routinely in every patient, but only when clinically indicated. Hence, we may have missed some patients with bacterial sepsis with normal PCT levels. Cost and lack of administrative resources prevented us studying PCT trends in the raised PCT group after discharge from the ICU to the general ward. As a result, we had full follow-up of PCT trends in only 39% of patients (30/78) with an elevated PCT level.

Conclusions

PCT measurements are indicated in patients with suspected bacterial sepsis producing SIRS.[13] PCT appears to be a good screening test at levels above 0.85 ng/dL when used in an appropriate clinical context. Levels greater than or equal to 10 ng/dL should prompt the clinician to look actively for a focus of sepsis in the critically ill patient.

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Author details

Kumar A Muthiah, Registrar, Intensive Care Unit[1]
Kanaka S Rachakonda, Intensive Care Specialist[1]
Michael J Davis, Intensive Care Specialist[1]
Edward G Simmons, Intensive Care Specialist[1]
Gary Schier, Director of Pathology[2]
Fernando San Gil, Laboratory Scientist[2]
1 Department of Critical Care, Wollongong Hospital, Wollongong, NSW.
2 Department of Pathology, Wollongong Hospital, Wollongong, NSW.
Correspondence: k_muthiah@hotmail.com

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