Newer Bio-Markers (Procalcitonin - PCT, Neutrophil Gelatinase Associated Lipocalcin- NGAL, N-Terminal Pro-Brain Natriuretic Peptide – NT- Probnp) : A Review

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Citation

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Abstract

Procalcitonin (PCT) as a biomarker is increasingly being used in current clinical scenario to indicate the presence/absence of sepsis, assessing the severity of sepsis (prognostication) and in differentiating infectious/non-infectious causes. It has been conclusively proved to differentiate bacterial from viral and fungal infection. We in this article discuss the biochemistry of PCT, its usefulness in various clinical settings, recent recommendations with regards to the use of PCT in guiding antibiotic therapy and comparison of PCT with various other markers of sepsis like CRP.

Another newer biomarker which has been extensively studied is NGAL (Neutrophil Gelatinase Associated Lipocalcin) in the early diagnosis of AKI. NGAL has been used for prediction of clinical outcomes such as dialysis requirement. NGAL has been proved better than serum creatinine which is a delayed and unreliable indicator of AKI. We in this article discuss the importance of NGAL in several common clinical scenarios like in cardiac surgeries (adult and pediatric), renal/liver transplantation & critical care settings.

Cardiac myocytes produce a variety of natriuretic peptides in response to cardiac wall stress that is left ventricular dysfunction or chronic heart failure or low ejection fraction. Recent studies have suggested that Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP), are superior to ANP (Atrial Natriuretic Peptide) and N-terminal pro-atrial natriuretic peptide (NT-proANP) in the detection of left ventricular dysfunction. We in this article discuss the clinical implications of NT-proBNP.

PROCALCITONIN

BIOCHEMISTRY :

Procalcitonin (PCT) is a 116 amino acid, 13 kDa protein, encoded by the CALC-1 gene on the short arm of chromosome 11. It is produced in the C-cells of the thyroid gland as a prohormone of calcitonin. Structurally, the PCT peptide comprises of 3 parts. Situated in the centre of the peptide is calcitonin; at the aminoterminal end is aminoprocalcitonin and at the carboxyterminal end is calcitonin carboxyterminal peptide-1 (CCP-1)1.

ROLE OF PCT IN SEPSIS :

The role of PCT in the host inflammatory response remains a mystery which has yet to be clarified. Pro-inflammatory effects of PCT include2 :

1. PCT may induce cell death by decreasing calcium availability.

2. PCT may influence bone remodeling during sepsis.

3. PCT may act as a secondary mediator in the inflammatory cascade.

4. Higher PCT values augur poor outcome. PCT doesn't by itself initiate the response but it may augment or amplify the inflammatory response3.

Anti-inflammatory role of PCT has also been described. Studies suggest that PCT significantly reduces the effects of the pro-inflammatory mediators, TNF-alpha and interferon gamma. PCT may reduce iNOS (inducible nitric oxide synthetase enzyme) thereby decreasing NO production, thus ameliorating the circulatory failure of sepsis.

PCT Vs CRP (C reactive protein)4 :

	PCT	CRP
Secretion starts	</= 4hrs of stimulus	4-6hrs after stimulus
Secretion peaks	8hrs of stimulus	>/= 36hrs after stimulus
Secretion decreases	Once the infection is under control.	Stays elevated for many days post trauma, inflammation and surgery even without any infection.
Ease of performing the test	Easy to perform	Very easy to perform
Results available	Within 2hrs	Automated
Cost of the assay	$10/test	$5/test

It has been suggested that PCT is an accurate marker of bacterial infection and it reliably and conclusively differentiates bacterial from viral infections and infectious causes from non infectious cause of sepsis5.

RECOMMENDATIONS FOR STARTING/STOPPING ANTIBIOTICS (PRORATA trial)6,7 :

Recommendation on initiation/starting of antibiotics		Recommendation on continuing/stopping antibiotics	
Procalcitonin level	Use of antibiotic	Procalcitonin level	Use of antibiotic
< 0.25 ug/l	Antibiotics strongly discouraged.	< 0.25 ug/l	Antibiotics strongly discouraged.
0.25-0.5 ug/l	Antibiotics usage discouraged.	0.25-0.5 ug/l or > 80% decrease from peak level	Antibiotics usage discouraged.
0.5- 1 ug/l	Antibiotics usage encouraged.	0.5- 1 ug/l or < 80% decrease from peak level	Antibiotics usage encouraged.
>/= 1 ug/l	Antibiotics strongly encouraged.	>/= 1 ug/l or increase from peak level	Antibiotics strongly encouraged.

ROLE OF PCT IN DIAGNOSING SEPSIS IN CRITICAL CARE SETTING :

Serum PCT can be used as 'an adjunctive diagnostic tool for discriminating infection as the cause for fever or sepsis' in the evaluation of new fever in critically ill adults.

Factors that suggest discontinuation of antibiotic therapy:

1. Available cultures negative. 2. No clear source of infection. 3. Repeat low PCT value. 4. Clinical judgement . Such an approach is likely to avoid upto 3–4 days of broad-spectrum antibiotic therapy/patient.

In a meta-analysis of 25 studies, done by Uzzan et al, the sensitivity of PCT and CRP ranged from 42% to 100% and 35% to 100% respectively and the specificity ranged from 48% to 100% and 18% to 84%. The Q* value (a measure of performance that is less affected by study heterogeneity) was significantly higher for PCT than CRP: 0.78 versus 0.71, P value of 0.028. Results of this meta-analysis clearly depict the superiority of PCT over CRP.

ROLE OF PCT IN DIAGNOSIS AND MANAGEMENT OF VAP IN ICU :

Ventilator Associated Pneumonia poses a great diagnostic challenge to all intensivists because of absence of gold standard tests, difficulty in differentiating colonizers from pathogenic organisms. This usually leads to either under-diagnosis or over-diagnosis of VAP, both of which are detrimental to patients on mechanical ventilation. VAP is most commonly caused by bacteria and so the use of PCT is being considered as a diagnostic aid.

In a study done by Tsangaris et al9 who compared the diagnostic ability of PCT with CRP and WBC in 27 patients in ICU who developed proven infection (bacteraemia, respiratory or abdominal) with 23 patients without infection. The AUROC for PCT was 0.85 (95% CI 0.71–0.93), for CRP it was 0.65 (95% CI 0.46–0.78) and for WBC it was 0.68 (95% CI 0.49–0.81). The sensitivity and specificity for a PCT cut-off of 1.0 ng/mL were 70% and 91% respectively.

There is a strong recommendation from some observers about sequential measurement of PCT in identifying healthcare-associated infection. PCT measured twice or thrice weekly and on the day infection is suspected for the first time is being considered sufficient and clinically useful10.

Serial measurement of PCT in such a way appears to reduce antibiotic usage in patients who deteriorate for non-infection reasons. But on the other hand, it also adds to critical care costs. The cost-effectiveness of such an approach needs to be evaluated for any recommendation to be made in this regard.

USEFULNESS OF SERUM PROCALCITONIN IN VARIOUS SCENARIO :

Mean levels of PCT in various infections are : Control value (0.1ng/ml), pneumonia (0.5ng/ml), viral meningitis (0.7ng/ml)11, urinary tract infection (0.8ng/ml)12, local infection (1.0ng/ml), sepsis (10ng/ml)13, pyelonephritis (10ng/ml)12, septic shock(50ng/ml), malaria (55ng/ml)14 and bacterial meningitis (60ng/ml)15.

It has been suggested that, viral infections and localised infections (pneumonia, UTI, abscess) do not cause rise in PCT levels of > 1ng/ml. Also parasitic infections like malaria cause significant rise in PCT levels.Greater elevations in PCT are observed in Gram-positive than Gram-negative meningitis15. This might be of relevance in the neurosurgical critical care unit, where patients are at risk of nosocomial meningitis.

In surgical cases like in acute pancreatitis, elevated levels of serum PCT suggested infected pancreatic necrosis, thereby differentiating this from sterile pancreatic necrosis (a very common clinical dilemma)16.

Other uses of serum PCT assay include :

1. Solid tumours (as a marker of bacteraemia)17

2. Liver transplantation (to distinguish between infection and rejection)18

3. Haemodialysis (to identify infective complications)19 and

4. Burns patients (to diagnose superinfection).20

5. Post-chemotherapy febrile neutropenic patient.

Harbarth et al21 in there study found that the median PCT concentrations were :

0.6 (range 0 - 5.3) ng/mL in SIRS (systemic inflammatory response syndrome),

3.5 (range 0.4 - 6.7) ng/mL in sepsis,

6.2 (range 2.2 - 85) ng/mL in severe sepsis and

21.3 (range 1.2 - 654) ng/mL in septic shock.

The authors also noted that a slow decrease or no decrease in PCT levels 48 hr after admission was correlated with a poor outcome. In those who died, the serum PCT level never fell below 1.1 ng/mL.

Neutrophil Gelatinase Associated Lipocalcin (NGAL) :

BIOCHEMISTRY :

Human NGAL consists of a single disulphide-bridged polypeptide chain of 178 amino-acid residues. It has a molecular mass of 22 kDa22. Glycosylation increases its apparent molecular mass to 25 kDa. In neutrophils and urine it occurs as a monomer, with a small percentage of dimer and trimer and NGAL also occurs as a complex with human neutrophil type IV collagenase, also called gelatinase B or matrix metalloproteinase-9 (MMP-9).

NGAL & ACUTE KIDNEY INJURY (AKI) :

PATHOPHYSIOLOGY :

NGAL is expressed at low concentrations in normal kidney, trachea, lungs, stomach, and colon. NGAL expression is induced by injured epithelia of lung, colon and kidney. Increased NGAL accumulates within two distinct pools, namely a systemic and a renal pool23,24.

Factors causing increased NGAL in AKI include :

1. AKI results in increased NGAL mRNA expression in distant organs (liver and spleen) which is mostly released into systemic circulation.

2. NGAL is a known acute phase reactant and may be released from neutrophils, macrophages, and other immune cells.

3. Decrease in glomerular filtration rate (GFR) decreases the clearance of NGAL, further leading to its accumulation in the systemic pool.

4. Rapid upregulation of NGAL mRNA in the thick ascending limb of Henle's loop and the collecting ducts occurs in AKI. This results in excessive synthesis of NGAL protein in the distal nephron (the renal pool) and secretion into the urine where it comprises the major fraction of urinary NGAL25,26,.

DISADVANTAGES WITH SERUM CREATININE AS AN INDICATOR OF AKI :

Serum creatinine is a delayed and unreliable indicator of AKI for a variety of reasons23,24 :

1. Several non-renal factors such as age, gender , muscle mass, muscle metabolism, medications, hydration status, nutrition status and tubular secretion influence level of serum creatinine.

2. > 50% of renal function must be lost before serum creatinine rises.

3. Serum creatinine concentrations do not reflect the true decrease in GFR in the acute setting. As for a new equilibrium to be achieved several hours to days must elapse.

4. An increase in serum creatinine represents a late indication of a functional change in GFR.

NGAL AND PREDICTION OF AKI IN VARIOUS SETTINGS:

NGAL & ELECTIVE CARDIAC SURGERIES :

AKI is a serious complication after Cardio Pulmonary Bypass (CPB). Lack of reliable early biomarkers in AKI has crippled our ability to initiate timely therapy.

The ability to predict which patients will develop AKI after CPB is also very important to the clinician as it will not only enable early initiation of interventions to prevent AKI but also change the poor outcome in such situation..

Studies on elective pediatric cardiac surgery, where NGAL measurement was done by ELISA revealed a 10-fold or more increase in the urine and plasma NGAL within 2–6 h of the surgery in those patients who later developed AKI27,28.

Both urine and plasma NGAL were excellent independent predictors of AKI in pediatric patients, with an area under the receiver-operating characteristic curve (AUC-ROC) of >0.9 for the 2–6 h urine and plasma NGAL 29,30,.

For adults, the AUC-ROC ranged from 0.61 to 0.96 the 2–6 h urine and plasma NGAL measurements which is fairly low 31.

Various confounding factors like older age groups, pre-existing kidney disease, prolonged bypass times, chronic illness and diabetes are likely reasons for poor performance in adults31.

NGAL & ELECTIVE CARDIAC CATHETERISATION :

In pediatric elective cardiac catheterization patients with contrast administration, both urine and plasma NGAL predicted contrast induced nephropathy (defined as a 50% increase in serum creatinine from baseline) within 2 h after contrast administration with an AUC-ROC of 0.91–0.9232.

In adults undergoing cardiac catheterization and concomitantly administered with contrast, an early rise in both urine (4 h) and plasma (2 h) NGAL was documented suggesting NGAL as an early biomarker of contrast nephropathy33.

NGAL & CRITICAL CARE SETTING :

In adult ICU patients, elevated plasma NGAL concentrations on admission had an outstanding co-relation with development of AKI in the next 2 days, with AUC-ROC ranges of 0.78–0.92.34.

Urine and plasma NGAL measurements in paediatric ICU patients, had a very strong association with AKI. They predicted AKI about 2 days before the rise in serum creatinine, with high sensitivity and AUC-ROC of 0.68–0.78.35.

In the critical care setting, an elevated plasma NGAL level can warn the clinicians and trigger immediate interventions like avoiding the use of additional nephrotoxic drugs, optimize hydration and improve renal perfusion thereby preventing any further injury.

NGAL & RENAL TRANSPLANTATION :

In kidney transplantation, biopsies of kidneys obtained 1 h after vascular anastomosis revealed a significant correlation between NGAL and the subsequent development of delayed graft function36.

In larger multicentre cohort, where urine NGAL was measured within 6 h of kidney transplantation predicted subsequent delayed graft function with an AUC-ROC of 0.8137.

NGAL & CHRONIC KIDNEY DISEASE(CKD) :

There is an emerging literature suggesting that urine NGAL is also a marker of CKD and its severity. In this population, urine NGAL levels are elevated and significantly correlated with serum creatinine, GFR and proteinuria.38

Urine NGAL has also been shown to represent an early biomarker for the degree of chronic injury in patients with IgA nephropathy, lupus nephritis and urinary tract infections.

Urine NGAL levels in these situations are significantly blunted compared with that typically measured in AKI.

Plasma NGAL	Urinary NGAL
Advantages :	Advantages :
1. Powerful early biomarker.	1. Non invasive
2. Risk stratification with elevated levels possible.	2. Reduced number of interfering proteins
	3. Self-testing kits
Disadvantages :	Disadvantages
1. Invasive.	1. Lack of samples in severe oliguric patients
2. Many confounding factors leading to low performance in adults.	2. Changes in concentration can occur as a result of hydration/ diuretics

LIMITATIONS OF NGAL AS AKI BIOMARKER :

Several studies have shown age as an effective modifier of performance of NGAL as a biomarker of AKI. Other factors

that have shown to have an impact on plasma NGAL levels include CKD, chronic hypertension, systemic infections, inflammatory conditions, anaemia, hypoxia and malignancies.

FUTURE BIOMARKERS OF AKI :

Other AKI biomarkers being studied include interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), cystatin C and liver-type fatty acid binding protein (L-FABP). The availability of a variety of validated AKI biomarkers like in case of acute MI can revolutionize and personalize renal care in patients.

NT –PROBNP (N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE)

Cardiac myocytes produce endocrine hormones like ANP, BNP and their N-terminal pro-hormones namely NT-proANP and NT-proBNP. Left ventricular dysfunction causes stress on cardiac wall thereby leading to elevated levels of these hormones41.

ANP Vs BNP42 :

Characteristic	ANP	BNP
Localization within heart	Atrial	Atrial and ventricular
Atrial storage pool	Large	Small
Basal cardiac secretion	++	+
Relative increase in heart failure	+	+++
Gene transcription response to stretch	Slow	Rapid

Recent studies have suggested that BNP and NT-proBNP may be superior to ANP and NT-proANP in the detection of left ventricular dysfunction. Probable reasons are:

1. Storage pool of ANP is very large. So, any acute change in atrial stretch causes change in the circulating peptide levels which are more rapid for the ANP than for BNP related peptides. 2. Chronic myocyte stretch as in chronic heart failure causes an upregulation more of BNP related peptides than for the ANP related peptides.

The biological effects of BNP include diuresis, vasodilatation, inhibition of renin and aldosterone production and of cardiac and vascular myocyte growth. Biological effects, if any of NT-pro BNP are currently unknown43.

The concentrations of NT-proBNP increase with increasing age. The reason for the age related increase in NT-proBNP is unknown but this finding is important to consider when defining cut off values for NT-proBNP44

Bay et al, in there study on the diagnostic value of NT-proBNP (cut off - 357pmol/l), for the detection of a left ventricular ejection fraction of < 40%had the following results.

NT-proBNP levels have a inverse relationship with LVEF. The diagnostic value of NT-proBNP was high in patients with LVEF of < 40% with an area under the ROC curve of 0.8955.

The diagnostic value of NT-proBNP in patients with LVEF < 30% is even higher with an area under the ROC curve of 0.8945,46.

They found that the median value of NT-proBNP was significantly higher in patients with an LVEF of < 40% than in patients with a normal LVEF (> 50%) and patients with an LVEF of between 40–50%. They concluded that, NT-proBNP levels appears to have a prognostic significance in the patients who have an elevated NT-proBNP at the time of admission.

In a study done by Dao et al, suggested BNP concentrations seem to fall after treatment with loop diuretics and ACE inhibitors. They said this probably reflected a reduction in left ventricular filling pressure. But still the relation between LVEF and concentrations of NT-proBNP was preserved and they concluded that the diagnostic value of a single NT-proBNP measurement in estimating LVEF was good47.

Alternatives to assessment of LVEF are 2D-echocardiography and radionucleotide ventriculography. Option of 2D-echo is limited, as not always a cardiologist and the portable echo machine is available. Also very few institutes can boast of having facilities like of radionucleotide ventriculography as primary diagnostic screening tools for assessing LVEF.

CONCLUSION

PCT levels are being increasingly used by the clinicians to diagnose sepsis, prognosticate the outcome and guide antibiotic therapy. Measurement of serial levels of PCT is of greater significance in managing patients of sepsis than a single value. In conclusion, the utility of serum

procalcitonin as a diagnostic test of sepsis is still under evaluation and PCT levels along with clinical judgement and decision making appear to be the best available guide for clinicians in the management of sepsis.

NGAL is a novel AKI biomarker and has been conclusively proved better than serum creatinine, which is a delayed and unreliable indicator of AKI. An early measurement of raised levels of plasma and urinary NGAL indicate kidney damage. This can sound a warning bell to the clinicians and they can avoid the use of nephrotoxic drugs (NSAID's, antibiotics etc), can take measures to optimize hydration and improve renal perfusion to prevent further injury.

A single measurement of NT-proBNP at the time of admission to hospital can provide important information about LVEF, thereby providing clinicians with an opportunity to prognosticate the patient.

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