Urinary Neutrophil Gelatinase Associated Lipocalin (NGAL) as an Early Marker of Acute Kidney Injury in Septic Patients

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Abstract

Sepsis: is a leading cause of mortality all over the world. NGAL belongs to the Lipocalin superfamily of more 20 structurally related secreted proteins that are thought to transport a variety of ligands within a barreled calyx.

The study included 30 patients with sepsis not associated with AKI and 50 septic patients with AKI for estimation of the predictive role of NGAL in AKI.

NGAL is shown to be a valid biomarker, being better positive than negative in prediction of AKI among septic group.

- Key words: NGAL – AKI - Sepsis

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I dedicate this study to my ;

Mother,

Father,

Sister,

Brothers,

and my lovely kids.

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List of Abbreviations

ACCP	American College of Chest Physicians
ACE	Angiotensin Converting Enzyme
ADA	American Diabetes Assoociation
ADMA	Asymmetric Dimethyarginine
ADQI	Acute Dialysis Kidney Initiative
AGE	Advanced Glycemic End-products
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
ALI	Acute Lung Injury
ARBS	Angiotensin Receptor Blocker
ARDS	Adult Respiratory Distress Syndrome
ARF	Acute Renal Failure
ATS	American Thoracic Society
AUC	Area Under Curve
C1	Complement Fragment 1
CAPD	Continuous Ambulatory Peritoneal Dialysis
CCPD	Continuous cyclic Peritoneal Dialysis
CD	Cluster of Differentiation
cGMP	Cyclic Glycosyl Monophosphate
CKD	Chronic kidney disease
CRH	Corticotropin Releasing Hormone
CRP	C-Reactive Protein
CVAHD	Continous VenoArterial Haemodialysis
CVC	Central Venous Catheter
CVD	Cardiovascular disease
CVP	Central Venous Pressure
CVVHD	Continous VenoVenous Haemodialysis
DDAH	Dimethylarginine Dimethylaminohydrolase
DN	Diabetic Nephropathy
ELISA	Enzyme Linked Immunosorbent Assay
ESICM	European Society of Internal Care Medicine
ESRD	End stage renal disease
FiO2	Fraction of Inspired Oxygen
FPG	Fasting plasma glucose
GFR	Glomerular filtration rate
HCT	Haematocrit
ICAM	IntraCellular Adhesion Molecule

ICU	Intensive Care Unit
IHD	Intermittent Haemodialysis
IL	Interleukin
INF-alpha	Interferon-alpha
IPD	Intermittent Peritoneal Dialysis
KDIGO	Kidney Disease Improving Global Disease Outcome
MA	Microalbuminuria
MAP	Mean Arterial Pressure
MDL	Myeloid DAP12 associated Lectin
MDRD	Modification of Diet in Renal Disease
MODS	Multiple Organ Dysfunction Syndrome
NGAL	Neutrophil Gelatinase Associated Lipocalin
NKF	National kidney foundation
NO	Nitric oxide
NOD	NucleotideOligomerization Domain
PAMPs	Pathogen Associated Molecular Patterns
PCWP	Pulmonary Capillary Wedge Pressure
PMNs	Polymorphnuclear Leucocytes
pNGAL	Plasma Gelatinase Associated Lipocalin
PO2	Oxygen saturation tension
PPR	Pattern Recognition Receptor
PRA	PreRenal Azotemia
RIFLE	Risk Injury Failure loss Endstage
RIG	Retinoic acid Inducible Gene
ROC	Reciever Operating Characteristics
RRT	Renal replacement therapy
SCCM	Society of Critical Care Medicine
Scr	Serum creatinine
ScvO2	Central venous oxyhaemoglobin saturation
SIRS	Systemic Inflammatory Response Syndrome
SIS	Surgcal Infection Society
SLED	Sustained Low Efficiency Dialysis
SNP	Single Nucleotide Polymorphism
SPKT	Simultaneous transplantation of pancreas and kidney
TLR	Toll Like Receptor
TREM	Triggering Receptor Expressed on Myeloid cell
UAE	Urinary Albumin Excretion
UKPDS	U.K. Prospective Diabetes Study
uNGAL	Urinary Neutrophil Gelatinase Associated Lipocalin
USRDS	United States Renal Data System
VCAM	Vascular Cell Adhesion Molecule

Introduction

In current clinical practice, AKI is typically diagnosed by measuring serum creatinine. Unfortunately, creatinine is an unreliable indicator of AKI **(Bellomo et al., 2004).** Serum creatinine varies with age, sex, muscle bulk, metabolism, drugs and hydration status. It will not change until more than 50% of kidney function has already been lost **(Prasad et al., 2007).** Hence identification of a novel AKI biomarker has been designated as a top priority by the American Society of Nephrology **(American Society of Nephrology, 2005).**

NGAL belongs to the Lipocalin superfamily of more than 20 structurally related secreted proteins that are thought to transport a variety of ligands within a barreled calyx. Human NGAL was originally identified as a 25-KD protein covalently bound to gelatinase from human neutrophil secondary granule protein **(Flower et al., 2000).**

Neutrophil gelatinase-associated lipocalin (NGAL) is a rapidly emerging biomarker for early detection of acute kidney injury (AKI). Seemingly NGAL levels in both plasma and urine can be used to detect AKI days before creatinine, at least when the time of insult to the kidneys is known **(Bachorzewska et al., 2007).**

Released by neutrophils upon activation, NGAL is also a marker of bacterial infection and systemic inflammation **(Mori et al., 2005).** As AKI often is associated with sepsis **(Bagshaw et al., 2007)** this might hamper the predictive properties of plasma NGAL as a biomarker of AKI, at least in the general intensive care unit (ICU)

setting. Whether sepsis affects the specificity of urinary NGAL as an early AKI marker is still unclear.

Few studies have investigated the predictive properties of NGAL as an AKI marker in a general ICU population. In a study by **(Cruz et al., 2010)** plasma NGAL was a good predictor of AKI. The Cruz study considers many factors that might confound the predictive properties of plasma NGAL. Still, sepsis incidence was almost twice as high in AKI versus non-AKI patients **(Cruz et al., 2010).** Similar studies on pediatric ICU patients have shown urinary NGAL to be a good predictor of AKI **(Zappitelli et al., 2007)**. Again, in these pediatric studies AKI and sepsis coincided to a great extent.

Aim of the work

This study will be conducted to:

- Asses the effect of sepsis on urinary NGAL levels.

- Study the effect of AKI on urinary NGAL levels.

- Examine the diagnostic utility of NGAL as an early marker of AKI in patients diagnosed with sepsis. This may allow early intervention to avoid developing AKI.

Chapter 1

Sepsis

INTRODUCTION

Sepsis is a clinical syndrome that complicates severe infection. It is characterized by the cardinal signs of inflammation (vasodilation, leukocyte accumulation, increased microvascular permeability) occurring in tissues that are remote from the infection. Systemic inflammatory response syndrome (SIRS) is an identical clinical syndrome that complicates a noninfectious insult (eg: acute pancreatitis, pulmonary contusion). Current theories about the onset and progression of sepsis and SIRS focus on dysregulation of the inflammatory response, including the possibility that a massive and uncontrolled release of proinflammatory mediators initiates a chain of events that lead to widespread tissue injury. This response can lead to multiple organ dysfunction syndrome (MODS), which is the cause of the high mortality associated with these syndromes.

DEFINITIONS

Systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock were initially defined in 1991 by a consensus panel convened by the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) **(American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference, 1992)** These definitions were reconsidered in 2001 during an International Sepsis Definitions Conference that included representatives from the ACCP, SCCM, American Thoracic Society (ATS), European Society of Intensive Care Medicine (ESICM), and Surgical Infection Society (SIS) **(Levy et al., 2003).** A practical modification of the definitions has since been published, which provides exact hemodynamic definitions for septic shock **(Annane et al., 2005).**