Pediatric Oncall Journal (January-March 2019)
Volume 16, Issue 1: 01-03
DOI: https://doi.org/10.7199/ped.oncall.2019.8

PEDIATRIC ONCALL
CHILD HEALTH CARE

REVIEW ARTICLE

MICROALBUMINURIA IN CHILDREN WITH SEPSIS

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ABSTRACT

Sepsis is a major problem which causes increased morbidity and mortality in critically ill children. Its incidence is increasing every year. The manifestations are varied, thus its diagnosis and determination of the severity are very important to prevent complications. Initially, the existence of albumin in urine was used as a predictor of the risk of renal disease and cardiovascular problem. However, it has developed into a marker of various inflammatory conditions as well as prognostic marker of death or even therapy evaluation. In sepsis, endothelial dysfunction will cause systemic capillary leakage which eventually results in the secretion of albumin in urine. Adult studies showed that microalbuminuria (ratio of urinary albumin/creatinine of 30-300 mg/gram) is a simple non-invasive test which not only indicates the systemic inflammatory response but also predict mortality with critical disease. The association of microalbuminuria with mortality in children with sepsis is still poorly investigated.

ARTICLE HISTORY

Received 13 February 2018

Accepted 22 October 2018

KEYWORDS

sepsis, microalbuminuria, urine albumin creatinine ratio

Introduction

Sepsis is derived from the Greek word "Sepo" which means damage. In 1989, sepsis was defined as a severe bacterial infection that caused damage to body tissues.[1,2] The reaction to sepsis is very complex and includes inflammatory and non-inflammatory processes, humoral and cellular reactions and circulatory abnormalities. The incidence of sepsis increases almost nine percent each year.[3] The highest incidence of sepsis is seen in infants, i.e. 5.6 cases per 1000 population whereas the lowest incidence rate in adolescents is 0.2 cases per 1000 population.[2] The manifestations of sepsis vary widely. The diagnosis and determination of sepsis severity is very important to prevent complications. In the last 40 years, the presence of albumin in urine has been found in patients with sepsis. It was initially used to predict risk of kidney and cardiovascular disease, and has progressed to be used as a prognostic marker to predict mortality or as a therapeutic evaluation criteria in diabetes mellitus, hypertension, renal failure, and even acute inflammatory conditions.[4] Measurement of the urine albumin/creatinine ratio is widely used as a marker of endothelial dysfunction.[5] In sepsis, endothelial dysfunction is caused by inflammatory processes and oxidative stress which gives rise to systemic capillary leakage and eventually results in increased albumin secretion in urine.[6] Until now there is no agreement on the range of values that distinguish pathological and physiological albuminuria.[7] Research has shown that microalbuminuria (urine albumin/creatinine ratio of 30-300 mg/gram is a simple, non-invasive test that may indicate the occurrence of systemic inflammatory response syndrome (SIRS), and is useful for predicting mortality rates in children with critical illness.[8,9]

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Sepsis

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. In Indonesia, there is a national guideline for medical services of the Indonesian Pediatric Society (IDAI) to diagnose sepsis so as to reduce morbidity and mortality from sepsis.[10] According to the guidelines, diagnosing sepsis can be done within 2 steps.

The first step is to identify evidence or suspected infection.[10] One needs to look for predisposing factors of infection such as genetic factors, age, nutritional status, immunization status, history of therapy and comorbidities (asplenia, chronic disease, congenital disease). Then assess for signs and evidence of ongoing infection according to clinical examination and laboratory tests. Clinically look for fever or hypothermia, or presence of focal infection. Laboratory tests include leucocyte count, platelet count, neutrophil: lymphocyte ratio, peripheral blood examination, C-reactive protein and procalcitonin. Inflammatory response consists of a) fever (core temperature >38.5°C or axilla temperature >37.5°C or hypothermia (core temperature <36°C); b) tachycardia with mean heart rate above normal for age in the absence of external stimulus, chronic medication, and pain, or an unexplained increase in heart rate rate for over 0.5 to 4 hours; c) bradycardia (for children age <1 year old) i.e. heart rate of below normal range for age without any external vagal stimulus, beta blocker, and congenital heart disease or unexplained decreased heart rate for over half an hour; d) tachypnea (mean respiratory rate above normal limit).

The second step is to look for organ dysfunction. Warning sign is established when one of three clinical signs is present: a) awareness loss by AVPU (alert, voice, pain, unresponsive) method; b) cardiovascular disorders by looking for abnormalities in pulse, peripheral perfusion or mean arterial pressure; c) respiratory disturbance by checking for increased or decreased work of breathing.

Cell dysfunction in sepsis

Endothelial cells are the outer layer of the blood vessels. Endothelial vascular plays an important role in maintaining adequate blood supply to vital organs. Endothelial cells are also important in regulating vascular tone, maintaining nutritional circulation between intravascular and extravascular space and maintaining coagulation function. Inflammatory processes cause endothelial cell damage, impaired function and occurrence of apoptosis leading to subendothelial edema in damaged areas and impairment of endothelial permeability.[11] Apoptic endothelial cells will induce an inflammatory reaction by generating cytokines and free oxygen radicals and activating complement systems. Cytokines such as interleukin (IL) [1] and tumor necrosis factor (TNF) alpha generated by the inflammatory cells interfere with the endothelial cell activity leading to inhibition of thrombomodulin, antithrombin III, tissue plasminogen activator and heparan sulphate resulting in blockade of plasmin formation and fibrinolysis and interfere with coagulation function and trigger exogenous coagulation cascade.[12] Disrupted endothelial cells will produce Von Willebrand factor, which is important for adhesion and activation of platelets, resulting in adhesion of platelets and monocytes in the endothelium to form microthrombus which will interfere with the microcirculation of the capillaries and cause perfusion defects of the vital organs.[12] Various inflammatory mediators cause changes of endothelial cell cytoskeleton and also an increase of intracellular calcium resulting in endothelial cell defense disorders as well as extravasation of fluids and proteins in the interstitial space known as capillary leaks.[12]

Albuminuria and urine albumin/creatinine ratio

Small amounts of albumin in the urine can be found in normal people but it can be excreted in excessive amounts in certain circumstances.[13] Albuminuria is thought to be caused by impaired endothelial function.[6] Levels of albumin in the urine can vary from normal, microalbuminuria and macroalbuminuria.[14] However, the Kidney Disease Improving Global Outcome (KDIGO) has composed new terminology that divides albuminuria into [3] categories (Table 1).[15]

Increased urinary albumin excretion is a result of increased vascular permeability in renal glomeruli associated with endothelial damage.[14] The urinary albumin/creatinine ratio may be a marker of endothelial dysfunction caused by systemic inflammation and on reduction of inflammation, there will be a decrease in the urinary albumin/creatinine ratio.[16] Microalbuminuria examination is a simple, non-invasive, bedside, time- and cost-effective examination, which can be measured with every urination, or even every minute using a urinary catheter.[9]

Increased urine albumin/creatinine ratio in patients with sepsis

In acute inflammatory conditions, an increase in urinary albumin-creatinine ratio is thought to be caused by glomerular endothelial leakage in the kidney which is a manifestation of increased systemic capillary permeability resulting from persistent inflammation of the endothelium. It is also suspected that inflammation causes a defect in the glycocalyx layer of the endothelium that causes microalbuminuria in sepsis.6 In renal glomeruli, vascular permeability is regulated by a complex structure known as the glomerular filtration barrier (GFB). The GFB maintains the balance of albumin and high-weight endogenous molecules in the urine.[17] Glycocalyx damage is associated with increased paracellular permeability and displacement of albumin or fluid to the interstitial space through endothelial gaps.[18,19] It causes loss of vascular tone, degradation of heparan sulfate and increased expression of adhesion molecules with increased leukocytes and loss of antioxidants that will exacerbate endothelial damage. Renal impairment occurring during sepsis is thought to be due to perfusion disorders that cause changes in the GFB structure.[19]

Currently, there have been several studies analyzing the association between sepsis and microalbuminuria. Research in adult patients with sepsis in India reported that microalbuminuria in the first 24 hours can predict the survival value in patients.[20] Another study comparing the value of microalbuminuria in septic patients found a higher value of microalbuminuria in septic patients and as a prognostic marker for mortality.[21] Research on adults in India found a significant correlation between APACHE (Acute Physiology and Chronic Health Evaluation) II score and SOFA (sequential organ failure assessment) values with microalbuminuria.[22,23] Research in 2010 found elevated levels of microalbuminuria within the first 24 hours in patients who died of sepsis.[6] The association of microalbuminuria with mortality in children with sepsis has been studied[24] but more studies are still required.

Table 1. Terminology of albuminuria[13]

Old terminology	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
KDIGO terminology	Normal to mild increased albuminuria (category 1)	Moderately increased albuminuria (category 2)	Severely increased albuminuria (category 3)
Urine albumin/creatinine ratio	< 30 mg/gram or <3 mg/mmol	30–300 mg/gram or 3-30 mg/mmol	>300 mg/gram or >30 mg/mmol
24 hours urine albumin	<30 mg/day	30-300 mg/day	>300 mg/day

Note: KDIGO - Kidney Disease Improving Global Outcome

Compliance with Ethical Standards

Funding: None

Conflict of Interest: None

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