Sepsis and Acute Kidney Injury; Interventions that Attenuate Acute Kidney Injury in Patients with Sepsis

Essay

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بِسْمِ اللّهِ الرّحمَنِ الرّحيمِ

(...رَبِّ أوزِعنِي أن أشكُرَ نِعمَتَكَ
الّتِي أنْعَمْتَ عَلَيَّ و عَلى والِدَيَّ

و أنْ أعْمَلَ صَالِحاً تَرْضَاهُ و أدْخِلْنِي
بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ)

صدق الله العظيم

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Eslam Abu-bakr Ali Mohammad

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List of Abbreviations

ACA : Activated tricarboxylic acid
ADP : Adenosine di-phosphate
ADPKD : Autosomal dominant polycystic kidney disease
AKI : Acute kidney injury
AKIN : Acute Kidney Injury Network
ANP : Atrial natriuretic peptide
APC : Activated protein C
aPTT : Activated partial thromboplastin time
ARDS : Acute respiratory distress syndrome
ARF : Acute renal failure
ATN : Acute tubular necrosis
ATP : Adenosine tri-phosphate
BNP : Brain natriuretic peptide
BUN : Blood urea nitrogen
CAVH : Continuous arteriovenous haemofiltration
CDK : Chronic kidney disease
COP : Cardiac output
CRRT : Continuous renal replacement therapy
CVVH : Continuous venovenous haemofiltration
CyC : Cystatin C
DNA : Deoxyribonucleic acid
ECF : Extracellular fluid
ELISA : Enzyme linked immunesorbent assay
ESKD : End-stage kidney disease
GFR : Glomerularfiltration rate
HVHF : High Volume Haemofiltration
ICU : Intensive care unit
IHD : Intermittent hemodialysis
IL-18 : Interleukin

List of Abbreviations *(Cont...)*

iNOS : Inducible nitric oxide synthase
JG : Juxtaglomerular
JGA : Juxtaglomerular apparatus
KIM : Kidney injury molecule
L-FABP : Liver fatty acid binding protein
LPS : Lipopoly saccharide
MMP : Matrix methaloproteinase
MODS : Multiple organ dysfunction syndrome
mRNA : Massenger ribonucleic acid
MV : Mechanical ventilation
NADPH : Nicotinamide adenine dinucleotide phosphate
NGAL : Neutrophil gelatinase associated lipocalin
NHE_3 : Sodium/ hydrogen exchange isoform 3
NO : Nitric oxide
NSAIDs : Nonsteroidal anti-inflammatory drugs
RBF : Renal blood flow
RCTs : Randomized controlled trials
rhTM : Recombinant human soluble thrombomodulin
rhTM : Recombinant human thrombomodulin
RIFLE : Risk-injury-failure-loss-end stage kidney disease
RNOS : Reactivenitrogen-oxygenspecies
RRT : Renal replacement therapy
SCr : Serum creatinine
TCA : Tricarboyxlic acid
TM : Thrombomodulin
TV : Tidal volumes
Tv : Tindal volume
UO : Urine output
UTI : Urinary tract infection

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Introduction

Acute kidney injury (AKI) is a frequent and serious complication of sepsis in intensive care unit (ICU) patients, particularly in the elderly. Moreover, there is strong evidence that sepsis and septic shock are the most important causes of AKI in critically ill patients, which account for 50% or more of cases of AKI in ICUs, and are associated with a very high mortality***(Ishani, 2009).***

AKI is a broad clinical syndrome encompassing various etiologies, including pre-renal azotemia, acute tubular necrosis, acute interstitial nephritis, acute glomerular and vasculitic renal diseases, and acute postrenal obstructive nephropathy. More than one of these conditions may coexist in the same patient and epidemiological evidence supports the notion that even mild, reversible AKI has important clinical consequences, including increased risk of death***(Kellum and Lameire, 2013).***

Sepsis develops when the initial, appropriate host response to an infection becomes amplified and then dysregulated. Because of very high mortality rates, it is fundamental to promptly recognize sepsis-induced AKI and to choose the most appropriate therapeutic modality.It is well established that the kidney is a commonly affected organ during sepsis, and its involvement carries a high risk of mortality***(Bagshaw et al., 2009).***

The pathophysiology of AKI in sepsis is complex and multi-factorial and includes intrarenal hemodynamic changes, endothelial dysfunction, infiltration of inflammatory cells in the renal parenchyma, intraglomerular thrombosis, and obstruction of tubules with necrotic cells and debris***(Wan et al., 2008).***

Accurate diagnosis of AKI in an ICU setting is challenging.Indeed, the characteristic swings in renal function over time in critically ill patients largely reduce the validity of a sole creatinine-based AKI assessment. This has stimulated researchers to establish multidimensional classification systems that use specific criteria to grade AKI severity. At present, the RIFLE classification represents the most widely accepted tool to "score" AKI severity***(Honore et al., 2007).***

Physiopathological model of AKI have delayed the development of successful drug treatments, and at present much of the treatment of AKI in sepsis focuses on the support of kidney function. The management of AKI in septic patients is complicated, due to the existing hemodynamic instability and associated multi organ dysfunction.As a result, in recent years, both continuous and intermittent renal replacement therapy (RRT) techniques have been developed***(Pannu, 2008).***

Aim of the Work

In this essay we will discuss the fundamental mechanisms of sepsis-induced AKI, early recognition and biomarkers of renal damage and recent potential therapies.

Chapter (1): Physiology of the Kidney

Most people are familiar with one important function of the kidneys to get rid of the body waste materials that are either ingested or produced by metabolism. A second function that is especially critical is to control the volume and composition of the body fluids. For water and virtually all electrolytes in the body, the balance between intake (due to ingestion or metabolic production) and output (due to excretion or metabolic consumption) is maintained in large part by the kidneys. This regulatory function of the kidneys maintains the stable environment of the cells necessary for them to perform their various activities. The kidneys perform their most important functions by filtering the plasma and removing substances from the filtrate at variable rates, depending on the needs of the body. Ultimately, the kidneys clear unwanted substances from the filtrate (and therefore from the blood) by excreting them in the urine while returning substances that are needed back to the blood***(Guyton and Hall, 2006).***

The kidneys play a dominant role in regulating the composition and volume of the extracellular fluid (ECF). They normally maintain a stable internal environment by excreting appropriate amounts of many substances in the urine. These substances include not only waste products and foreign compounds, but also many useful substances that are present in excess because of eating, drinking, or metabolism***(Tanner, 2003).***

The nephron is the basic unit of renal structure and function

Each human kidney contains about one million nephrons**(Figure 1),**which consist of a renal corpuscle and a renal tubule. The renal corpuscle consists of a tuft of capillaries, the glomerulus, surrounded by Bowman's capsule. The renal tubule is divided into several segments. The part of the tubule nearest the glomerulus is the proximal tubule. This is subdivided into a proximal convoluted tubule and proximal straight tubule. The straight portion heads toward themedulla, away from the surface of the kidney. The loop of Henle includes the proximal straight tubule, thin limb, and thick ascending limb. The next segment, the short distal convoluted tubule, is connected to the collecting duct system by connecting tubules. Several nephrons drain into a cortical collecting duct, which passes into an outer medullary collecting duct. In the inner medulla, inner medullary collecting ducts unite to form large papillary ducts. The collecting ducts perform the same types of functions as the renal tubules, so they are often considered to be part of the nephron. The collecting ducts and nephrons differ, however, in embryological origin, and because the collecting ducts form a branching system, there are many more nephrons than collecting ducts. The entire renal tubule and collecting duct system consists of a single layer of epithelial cells surrounding fluid (urine) in the tubule or duct lumen. Cells in each segment have a characteristic histological

appearance. Each segment has unique transport properties***(Tanner, 2003).***

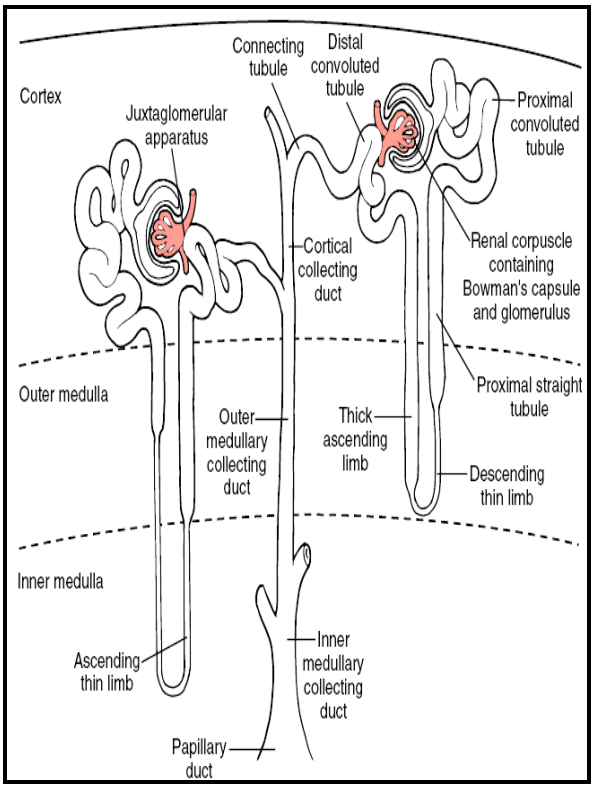

Figure (1): Components of the nephron and the collecting duct system. On the left is a longlooped juxtamedullary nephron; on the right is a superficial cortical nephron***(Tanner, 2003).***

Three groups of nephrons are distinguished, based on the location of their glomeruli in the cortex: superficial, midcortical, and juxtamedullary nephrons. The juxtamedullary nephrons, whose glomeruli lie in the cortex next to the medulla, comprise about one-eighth of the nephron population. They differ in several ways from the other nephron types: they have a longer loop of Henle, longer thin limb (both descending and ascending portions), larger glomerulus, lower renin content,