THE DIAGNOSTIC PROCESS OF THE ACUTE KIDNEY INJURIES

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KEYWORDS

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ABSTRACT

Acute kidney injury (AKI) is very common disease and large number of people is suffering from AKI. This research aims to visualize entire concept and diagnostic process of AKI. Different procedure to diagnose, Physical Checkup, Blood Tests, Urinary Tests & further Novel Biomarkers, are the tests which are uses to diagnose AKI. Among these processes Physical Checkup, Blood Tests and Urinary Tests are most popular techniques which are widely used for the diagnostic process. For making the healthier society it is necessary to access this disease at initial level. In future researches effectively of all kinds of tests will examined in Pakistan and same like countries and examine the prerequisites to avoid this dangerous disease.

INTRODUCTION

As per the studies of Stapleton, Jones and Green (1987) and Hentschel, Lodige and Bulla (1996), the AKI-Acute Kidney Injury has been witnessed and founded in 8% to 24% of preterm neonates who has been admitted to neonatal ICU's. Latterly, Bellomo, Ronco, Kellum, Mehta and Palevsky (2004) said that in current era only RIFLE System is being used to diagnose AKI and due to that there is an increasing trends of AKI intensity such as risk, injury, failure, and loss and in end, stage kidney disease. Further, this system was modernized with certain inputs from the acute kidney injury network (Mehta, Kellum & Shah, 2007). On beginning stage, sign of AKI possibility consist of 50% rise in creatinine of serum ("or ≥ 0.3 mg/dl" under period of 48 hours), and/or a urine output is less than 0.5mg/kg/hr within six hours (Bellomo et al., 2004; Mehta et al., 2007), which indicates that there is identifiable reduced GFR. To define categorically AKI within the particular neonatal populated environment although it was not created.

The reasons for "AKI in preterm neonates are specifically pre-renal in source or origin, happen due to the renal perfusion like hypotension, hypoxia and sepsis" (Stapleton et al., 1987; Cataldi et al., 2005). Such conditions become the reason for such inflammatory procedures, secondly apoptotic, and in last necrotic presence in the kidney's (Bonventre, 2007; Ueda & Shah, 2000). Particularly, AKI is a major reason for long-lasting chronic renal diseases particularly in the preterm neonates (Abitbol, Bauer, Montane, Chandar, Duara & Zilleruelo, 2003). There is a study, conducted by Cataldi et al. (2005) within the 172 preterm neonates and it was founded that AKI happen due to the administration of the drugs related to the neonatal and maternal "(non-steroidal anti-inflammatory drugs (NSAIDs) and the antibiotics, mainly ceftazidime)" such decreased Apgar score and such type patent ductusarteriosus. But surprisingly age gestational do not have any impact over AKI, although heavy quantity of identified AKI patients 79% weighted less than one and half kg at the time of the birth (Cataldi et al., 2005).

A study was conducted over 281 preterm neonates and result were founded multiple risk factors for AKI. The factors were consisting on administration of maternal like NSAID, decreased Apgar score, the respiratory distress syndrome, neonatal drug administration (antibiotics & NSAID'S) and multiple clinical interventions (catheterization, intubation

at birth, phototherapy and mechanical ventilation). There was much more importance given to the early identification and cure of AKI but in recent times such concentration to unhide biomarkers of such novel urinary and its occurrence of latest biomarker provides an assistance to identify the rapid decline in the renal functioning ahead to cellular like injury. For instance, the creatinine of the serum un-elevated till and far the 48 hours to 72 hours behind acute injury happened (Moran & Myers, 1985) and it has been identified that as much as time taken to diagnose and curing of AKI always become the major reason for the further renal injury. This study is being conducted at Children Hospital Lahore to check AKI in neonates.

LITERATURE REVIEW

Acute Kidney Injury (AKI) is the condition which really based on different other kind of renal disease. Due to that there is a quick decline in kidney functioning. There is other much different aetiology, but the major reasons of the "AKI are sepsis, volume depletion, haemodynamic imbalance and nephrotoxic drugs". AKI one of most common diseases diagnosed in the patients who got admitted at hospitals particularly with the patients of Intensive care unit. Such happening & prospects really based on particular number of patients, the availability of combined factors & altogether deep intensity of diseases but other variables to elaborate and identify AKI. Altogether, clear symptoms are available that AKI is linked temporary and other long periodic medical issues, before time deaths and very costly healthcare in current era (Cataldi et al., 2005). The description of AKI suggest that it happen due to risk, injury, failure, loss and end stage criteria in 2004 to AKI Network classification in 2007. In 2012, both were indulged as the outcome in the kidney disease with improved global outcomes classification as presented in numerous studies.

The generation of creatinine heavily based on liver like functioning and muscle buildup. That's why, "patients with liver problem, muscle wasting and sepsis", a real decrease in GFR may not give true picture through mixer of serum based on creatinine. Serum based on the creatinine which shows significant consistent impact on drugs without any impact on renal function. In addition to that, the processing methodology at the laboratory may affect serum creatinine concentrations. Substances such as bilirubin or drugs have some impact with particular analytical techniques and more frequently with Jaffe based assays (Thomas, Blaine & Dawnay, 2015). In the last, mixer of serum based on creatinine being analyzed and due to that it may has effected by differentiation in the volume frequency. It is being observed that patients of AKI may face the late or even don't happen the rapid mixer accretion. All recent categorizations of AKI consist on urine criteria. Urine output is one of most critical clinical indication but as like as creatinine, it is not particularly related to renal. Actually, outflow of urine which is available tills renal functioning which almost stopped.

Table 1 "Short and Long-term Complications of AKI".

"Short-term complications"	**"Long-term complications"**
"Uraemia"	"Proteinuria"
"Fluid accumulation"	"CKD/ESRD"
"Dosing errors renally excreted medications"	"Risk of cardiovascular morbidity"
"Non-recovery of renal function"	"Risk of strokes"
"Prolonged stay in hospital"	"Hypertension"
"Organ crosstalk (effects on organ systems)"	"Risk of fractures"
"Healthcare costs"	"Risk of infections/sepsis"
"Recurrent AKI"	"Reduced quality of life"

The successfully treated AKI patients represent the most critical group of society, who is particularly facing the chronic health issues consisting on the CKD, "cardiovascular and cerebrovascular activities, infections and premature mortality", like risk of premature death rate is high especially in the AKI survivors and particular in the high intense AKI patients. Follow up analyzing the RENAL research, a multicentre RRT research work, showing the result of that only one third of patients with acute RRT who were admitted in ICU's were survived for 3.5 years after cure and treatment (Gallagher, Cass & Bellomo, 2014). "A prospective cohort evaluation 2010 ICU patients in a tertiary care centre discover the even survivors of AKI stage it had particularly lesser than 10-year survival rates than matched significantly ill patients without AKI" (Linder, Fjell, Levin, Walley, Russell & Boyd, 2014).

Definition and Classification of Acute Kidney Injury

AKI which based on rapid dis-functioning of kidney, categorized by quick decrease in the "glomerular filtration rate (GFR)", whole process may happen within the hours. A non-functioning of the kidney is also the reason for production of metabolic waste products such as urea, creatinine, destructed running liquid, other products which based on acid homeostasis (Lameire, Biesen & Vanholder, 2005). AKI, it is not any distinctive health issue although it is a syndrome like the heterogeneous linked to the vast assemblage of pathophysiologic procedure of certain factors high intensity and etiology. From another point of view, AKI is frequently considered as three broad pathophysiologic categories such as pre-renal, the intrinsic & the post renal. The first, Pre-renal type of AKI happens when hypo-perfusion of the kidneys reasons for the decrease in glomerular filtration rate without having any impact on the overt the parenchymal disaster. Such etiologies related to pre-renal AKI consist on both conditions to reduce volume and condition of reduced impactful arterial blood volume.

Intrinsic AKI become reason for the diverse diseases including "renal parenchyma, acute and quick reformist glomerulonephritis, acute interstitial nephritis, acute tubular injury and acute vascular syndromes and atheroembolic disease". However, high intensive post renal AKI happen with blockage in the bladder or both side ureteral blocking or even one side ureteral blockage with the loss or non-functionality of contralateral kidney, low and falling functioning in kidney and it can be watched with unilateral ureteral blockages, moreover with availability of normal contralateral kidney. For example, prerenal AKI is linked such clinical parenchymal like injury and real time consistent pre-renal & post renal conditions may impact as the parenchymal affectation. This concept of AKI has replaced the older concept of the "acute renal failure (ARF)". Thus certain emergence of the terminologies shows the real consideration and link among the proper functional kidney and its functionality & over the organ non-functioning is not dichotomous but also the other way like smaller to medium acute reduction in the kidney functionalities are linked with severe results.

However, the latest concept really unhide the bigger view of AKI related disease and real time effect but these terms still are not perfect and don't give a complete impact. The terminology "Injury" reflects presence of parenchymal organ loss, however parenchymal like issue is not categorized as acute non-functionality of the kidney is linked with the perennial and post renal AKI (Mehta et al., 2007; KDIGO, 2012). Sometimes this terminology AKI is being used as parallel as the ATN, however these terminologies are not with the same meaning. ATN is being considered the one of the renowned condition of intrinsic AKI significantly in high level of illness patients; this reflects only one factor of different etiologies of AKI. Moreover, "still in patients with a standard presence of AKI in the setting of sepsis and ischemia reperfusion injury, there may be non-presence of

concordance among the clinical syndrome and also the histopathologic outcomes defined by the terminology of ATN" (Rosen &Heyman, 2001; Lameire, 2005).

AKI Definitions and its Validation

To check the validation of the AKI description with optimal level which may be consists on an undeniable "gold standard" to analyze. Unluckily, this kind of the standard is not available.

Table 2 "Pediatric Modified RIFLE Criteria for Diagnosis & Classification of AKI in Children"

"Class"	"eCCl"	"Urine output"
"Risk"	"eCCl decrease by >25%"	Urine output <0.5 mL/kg/h for >8 h
"Injury"	"eCCl decrease by >50%"	Urine output <0.5 mL/kg/h for >16 h
"Failure"	"eCCl decrease by >75% or eCCl<35 mL/min/1.73 m2"	Urine output <0.3 mL/kg/h for >24 h; Anuria for >12 h
"Loss"	"Failure for >4 weeks"	
End-Stage Disease	"Failure for >3 months"	

"AKI acute kidney injury, eCrClestimated creatinine clearance using Schwartz formula, RIFLE risk, injury, failure, loss end-stage disease". Change in blood mixer of creatinine is being identified as replacement in kidney functionality and considered as the extensive face authority. A consistency of urine outcome criterion & such clinical factors to provide a base for particular benchmark being adopted were less vigorous. The cross verification of multiple categorization schemes has been described as predicted variance in diagnosis and the conditions. It has been explained through an example as the analysis was done over the 14,356 significantly ill patients and among them 5093 (35%) were identified as the AKI patients through the RIFLE criterion from whole 14,356 selected patients but in comparison 4093 (28%) were identified by utilizing the AKIN definitions and the system of staging from the whole 14,356 patients (Joannidis, Metnitz, Bauer, Moreno, Druml & Metnitz, 2009).

At the same time, from the 9263 patients who were treated and processed through the RIFLE criteria as AKI negative but later own from same 9263 patients there 504 (5%) were identified as the AKI positive by utilizing the AKIN definition system. And on the other hand 1,504 (15%) patients from the 10,263 patients who were AKI negative as per the AKIN definition system among them 781 patients were identified at RIFLE Risk, 452 patients were known at RIFLE Injury and 271 patients were diagnosed as RIFLE Failure as per the RIFLE criteria and system. Many of researchers and their studies who tried to validate the AKI definitions concluded with death. As across analysis as discussed above increased intensity of AKI even analyzed through RIFLE and AKIN was linked with an enhanced frequency of hospital based death rate (Joannidiset et al., 2009). Same studies have identified that even at further "broader level including sepsis, trauma, post cardiac surgery and the hematopoietic cell transplant patients" (KDIGO, 2012; Lopes, Goncalves & Jorge, 2008).

Currently, the acute kidney injury epidemiologic prospective investigation research has analyzed "KDIGO definition and staging condition system over the 1802 ICU admitted patients particularly in 97 ICU's in 33 countries in North and South America, Europe, Africa, Asia and Australia" (Hosteet al., 2015). Enhanced AKI with high intensity was linked with gradual increased risk for hospital mortalities with certain adjusted factors. The chances of the death level "enhanced from 1.68 (95% CI 0.89 3.17; $p = 0.11$) at stage 1 AKI to 2.95 (95% CI 1.38–6.28; $p = 0.005$) at stage 2 AKI and 6.88 (95% CI 3.88–12.23; $p < 0.001$) at stage 3 AKI" in comparison with non AKI patients. Just diagnosed patients with AKI may had highly critical condition for kidney performance particularly

on discharging from hospital with "eGFR<60 mL/min/1.73 m2 in 47.7% (95% CI 43.6–51.7)" with AKI positive patients in comparison to only 14.8% (95% CI 11.9–18.2) AKI negative patients (Hoste et al., 2015).

The Process to Diagnose

Different Procedure to Diagnose

AKI is the most happening clinical condition being classified as the sudden loss of the kidney functioning. Here, we will discuss in detail about the different procedure to diagnose of AKI as well as the physical exam and their results and different laboratory tests that can be utilized to analyze the patients with AKI. In the last, there will be a detailed discussion about the utilization of the broader "list of novel biomarkers which are directly linked with the betterment in the diagnosis, risk stratification and outcome prognostication of the patients which are admitted at hospital with AKI issues" (Koyner & Parikh 2013).

Differential Diagnosis

Commonly the different procedure to diagnose of the AKI has been categorized into pre-renal, intrinsic rena or intrarenal & post-renal reasons (Thadhani, Pascual & Bonventre al., 1996). Typically, this process has able the practitioners to analyze about the different variables which have some impact on "renal functionality into factors which appeared before the kidney (prerenal), within kidney and also after the kidney (post renal along remaining on genitourinary system)". This structural and categorization process is being used from decade of years, yet latest techniques have been emerged like the pre, intra, and post renal are constant with clinical decision making. Numbers of practitioners do trust on that such variables are really critical for prerenal and post renal reasons of AKI and with the passage of time those become the intrinsic/intrarenal AKI. In addition to that, if diagnosis process is done then it is possible to stop pre and post renal AKI with respect to variation in glomerular function/serum creatinine and hence process may not only intimate about intensity of the AKI but possible indicate about death rate which are really linked.

"Prerenal reasons of AKI is outcome from improper renal perfusion from either correct intravascular volume depletion (GI losses, hemorrhage or burns) and from the reduction in the impactful circulating volume (decompesated congestive heart failure with reduced ejection fraction or end stage liver disease with cirrhosis)". In addition to that different medicines which have some impact on renal vascular autoregulation have been linked with prerenal AKI. "These are included nonsteroidal anti-inflammatory drugs (NSAIDs) and calcineurininhibitors (CNIs), angiotensin-converting enzyme inhibitors (ACE-I), and angiotensin II receptor blockers (ARBs), all of them amend the renal vascular auto regulation". "NSAIDs can become the reason for the afferent arteriole vasoconstriction which direct to the decrease in renal blood flow and hence a decrease in the glomerular filtration rate (GFR)/increase in creatinine". Moreover, "CNIs consisting tacrolimus and cyclosporine are also considered as the reason for the renal arteriolar vasoconstriction directed towards enhancement which is linked with AKI as analyzed by enhanced serum creatinine".

In addition to that the drugs which affect the rennin-aldosterone system (Like CE-I and ARBs) also being considered as the renal hemodynamics and hence effect the "functional biomarkers of AKI (serum creatinine and cystatin C) but not the biomarkers that report structural nephron injury/loss". However, "ACE-I and ARBs" direct to replacement of serum creatinine the level where that is really AKI being under analysis. If the current biomarker fails on the accounts of the AKI to grow further in nephrology to basically the change in the pattern which have been discussed as differential diagnosis of AKI (New

AKI paradigm is available). The kidnies have tendency to in-flow and outflowto regulate GFRand renal blood by alteration in “afferent & afferent arteriolar tone”. Although, pre-renal stage if it is high intensive then it can be overpowering such supportive procedure and can be directed to a very severe decrease in GFR. Moreover, in the situation of AKI such autoregulatory structure can be diverse direction to exacerbation of starting injury furthermore gentle reduction in blood pressure and suddenly possibly the conversion into intrarenal injury (Kelleher, Robinette & Conger, 1984).

In hospital scenario, disruptive uropathy (post-renal) counted around 10% of the cases of AKI (Nolan & Anderson 1998). A post renal reason for the “AKI can find from hurdles anywhere from the urinary tract but is well know from bladder outlet obstruction as seen in prostatic hypertrophy in men” (Sacks, Aparicio, Bevan, Oliver, Will & Davison, 1989). ATN is estimated by clinical assessment regardinginherent chronic renal injury that is not resulting to ischemic “(cardiac surgery or septic shock) or nephrotoxic insults”. The “histopathologic results of ATN are commonly patchy”. However, terminology of ATN may be considered as the “misnomer and concept of acute tubular injury may show the physiopathologic not linked with individual” (Rosen & Stillman 2008). Acute phosphate nephropathy result in phosphate “bowel consisting bowel preparation”. General agent and factors are included antimicrobial agents (sulfonamides, β lactams, antiviral agents, quinolones), antiulcer agents (H2 antagonists, proton-pump inhibitors), no steroidal anti-inflammatory drugs, allopurinol and the anticonvulsants (Perazella & Markowitz, 2010).

Laboratory Tests

Blood Tests

The laboratories analysis of the patients with AKI should be derived from their clinical process and their risk factors for kidney injury. Laboratory tests conduct for diagnosis of serum creatinine, blood urea nitrogen (BUN) andincorporated other serum electrolytes, chloride, sodium and bicarbonate (CO2) and potassium levels. In pre-renal situations findings from increased salt & water greed, there is possibility about unbalancing the ratio of BUN to creatinine (twenty to one). The enhancement in BUN might be in high level due to existence of the ADH (Perazella & Markowitz 2010). In the condition of AKI laboratory tests willindicate hyponatremia. Hyponatremia is frequently discovered in the existence of AKI with diverse researches with linkage two entities, in one of prospective observational research of all patients who got admitted to the city located hospital with hyponatremia among them AKI was present in 32% patients (Adams, Jonge, Cammen, Zietse & Hoorn, 2011). In another research of “hyponatremia, AKI was existing in 16% of hospitalized cohort with AKI rates exceeds more than 20% in older patients like with 74 years” (Turgutalp, Ozhan & GokOguz, 2013). Multicenter observational research showed that over the 923 patients affected of hyperkalemia > 6.5 mEq/L.

AKI was found in twenty-two people with usual “core line renal functioning and in over than half” (51.8%) of them with already chronic kidney disease (An, Lee & Jeon, 2012). In another research, hyperkalemia, even renowned as the most severe condition of AKI had a little impact on the size and linkage among the “admitted patients’ mortality than metabolic acidosis and cumulative fluid balance” (Libório, Leite, Neves, Teles & Bezerra, 2015). Certain benchmark and cure options are not as vigorous for metabolic acidosis and volume overload. In a prospective “randomized multicenter trial analyzing the upper and down intensity of running RRT, severe acidosis, defined as a pH < 7.2 was exist in 34.9% of concepts”. Same likely in a post hoc measurement of the “Finnish Acute Kidney Injury (FINNAKI) studyfifty two percent perception had pH less than 7.15 earlier to RRT. Andacidosis is reported sign of RRT in 35.8 percent (Bellomo et al., 2009; Vaaraet al., 2014). Metabolic acidosis is considered to affect with normal functions of different

procedures in body and concludes the severe output with progression of hemodynamic uncertainty through the reduced cardiac outcome and vasodilatation.

Urinary Test

Analysis of urine residue is critical part in procedure of different procedure to diagnose in the condition of AKI (Bagshaw et al., 2012). There is enough evidence which described that analyzing the urine and existence of cellular casts and renal tubular epithelial cells that are associated to pre examination of AKI and for severity of AKI (Perazellaet al., 2008; Schinstock et al., 2013). Current research described that greater urine microscopy intensive rate, as analyzed by the enhance existence of muddy brown casts and urinary granular that are associated with highrate of existence as compare tosuperiordanger of development of the AKI (Bagshawet et al., 2012). While is the resurgence of impact in microscopic analysis of urine, such clinical technique has not been well interacted into current bigger level latest biomarker analysis (Parikh et al., 2013). Instead of different types of already written scoring systems, there have not been bigger level the multicenter validating researches to state the performance of the urine microscopy (Perazella et al., 2008).

In pre renal AKI, urine deposit investigation results in hyaline casts. 'Hyaline casts' are round shapemold of rapid Tamm Horsfall protein which iscreated in the 'distal tubule'. In "ATN, muddy brown, roughcast are classified seen with extra freely "renal tubular epithelial cells". RPGN (Rapid production of glomerulonephritis) is the main source of differential diagnosis of AKI. And it is classified by 'urine sediment included RBC casts'. These casts are consisting of "red cells in matrix of Tamm-Horsfall protein". Schrier and colleagues described that sodium can be examined in absence of CKD (serum creatinine <1.6) and (less than 500 ccs of urine/day) (Miller et al., 1978). A "FEUrea< 35% has been believed as indicatorof prerenal AKI, however, if its value>35% is believed as indicator intrinsic AKI (ATN) (Kaplan & Kohn 1992). Also, FEUrea stated in far lesser researches in comparison with FENa. In a study, FEUrea less than 35% was seen in 90, 89, and 4% for prerenal with diuretics, and ATN patients, respectively". (Carvouniset al., 2002). In addition to that the FENa, conduct to analyze the "FEUrea as a diagnostic/prognostic technique in situation of early AKI have failed to disclose its clinical utility" (Koyneret al., 2008).

Table 3 "Summary of Three Previously Published Urinalysis Severity Scores

"Study"	"Scoring system"
Chawla et al., 2008	"Grade 1: no casts or RTE" "Grade 2: at least 1 cast or RTE but <10% of LPF" "Grade 3: many casts or RTEs (amid 10 & 90% of LPF)" "Grade 4: sheet of muddy brown casts and RTEs"
Perazella et al., 2010	"0 points: no casts or RTE seen" "1 point each: 1–5 casts per LPF or 1–5 RTEs per HPF" "2 points each: ≥6 casts per LPF or ≥6 RTEs per HPF"
Bagshaw et al., 2012	"0 points: no casts or RTE seen" "1 point each: 1casts or 1 RTEs per HPF" "2 points each: 2–4 casts or RTEs per HPF" "3 points each: ≥ 5 casts or ≥ 5 RTEs per HPF"

CONCLUSION

Acute kidney injury (AKI) is very critical disease and many people are suffering from AKI especially in third world countries. Different procedure to diagnose, Physical Checkup, Blood Tests, Urinary Tests & further Novel Biomarkers, are the tests which are uses to

diagnose the AKI. Among these processes Physical Checkup, Blood Tests and Urinary Tests are most popular techniques which are widely used for diagnostic process. For making the healthier society it is necessary to access this disease at initial level. At large scale above scores can described with biomarkers of the 'tubular injury' to increase the prognostication of AKI (Perazella et al., 2010; Bagshaw et al., 2012; Schinstock et al., 2013). In future researches effectively of all kinds of tests will examined in Pakistan and same like countries and also examine the prerequisites to avoid this dangerous disease.

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