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Acute Kidney Injury in Hospitalized HIV-Infected Patients in the HAART Era: An Epidemiological View

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1. Introduction

Actually, more than 30 million people are affected with human immunodeficiency virus (HIV) infection worldwide [1]. Since the introduction of the highly active antiretroviral therapy (HAART) at the end of 1995, overall mortality of patients with HIV infection decreased dramatically as well as mortality caused by HIV infection or by an Acquired Immunodeficiency Syndrome (AIDS)-defining disease. Conversely, mortality due to kidney disease, liver disease, heart disease, and non-AIDS-defining cancers has proportionally increased [2,3,4].

Renal disorders in HIV-infected patients can present as an acute or chronic condition and they are associated with increased morbidity and mortality in this population [5,6,7,8,9]. Acute kidney injury is a common complication in ambulatory HIV-infected patients treated with HAART and has been associated with prior renal impairment, lower CD4 levels, AIDS, hepatitis C virus (HCV) co-infection, and liver disease [10,11]. HIV-infected patients are also at increased risk for AKI development within hospitalization, related to volume depletion, sepsis, and the acute administration of nephrotoxic medications or radiocontrast. Before the advent of HAART, studies addressing AKI on HIV-infected patients typically included only severe cases of AKI which were identified through hospital records or biopsy databases [12,13,14]. The epidemiology of AKI in hospitalized HIV-infected patients in the HAART era has also not been extensively analyzed. In fact, few studies have focused on the clinical characteristics of AKI in hospitalized HIV-infected patients in the HAART era [15,16,17,18]. In this chapter, we provide a critical and contemporary review of AKI in hospitalized HIV-infected patients in the HAART era, focusing on the incidence, risk factors, and outcome.

2. Incidence of AKI in hospitalized HIV-infected patients

Three recent studies [15,16,17] have addressed specifically the incidence of AKI in hospitalized HIV-infected patients (Table 1). Wyatt et al [15] compared the incidence of AKI in HIV-infected patients before and after the introduction of HAART. For this purpose, all adult patients who were discharged from acute care hospitals in New York State during 1995 (pre-HAART era) and during 2003 (post-HAART era) were evaluated. The presence of AKI was determined by a diagnosis code 584 of the International Classification of Diseases, 9th Revision (ICD-9), which identified AKI based on the clinical judgement of the treating physician. There were 52.580 patients with documented HIV infection discharged from hospital in 1995, and 25.114 in 2003. Acute kidney injury was reported significantly more often during hospitalizations for HIV-infected patients than for uninfected patients in both 2003 (6% versus 2.7%) and 1995 (2.9% versus 1.0%). After adjusting for other covariates, HIV infection remained associated with an increased risk of AKI both in 2003 [adjusted odds ratio (OR) 2.82, 95% confidence interval (CI) 2.66-2.99) and in 1995 (adjusted OR 4.62, 95% CI 4.3-4.95). Lopes et al [16] conducted a cohort study including 489 HIV-infected patients hospitalized in a tertiary and teaching Portuguese Hospital between 2005 and 2007 to characterize AKI in this population. Acute kidney injury was defined and categorized according to "Risk Injury Failure Loss of kidney function End-stage kidney disease" (RIFLE) classification [19], and it was considered if there was an increase of baseline serum creatinine × 1.5 or in patients with baseline serum creatinine > 4 mg/dl if there was an acute rise in serum creatinine of at least 0.5 mg/dl. They found that 18% of patients had AKI within the hospitalization which was much higher than the incidence previously reported (6%) in hospitalized HIV-infected patients in HAART era [15]. It should be remembered that in the study of Wyatt et al [15] the diagnosis of AKI was determined by a diagnosis code 584 of the ICD-9 based on the clinical judgement and documentation of the treating physician, and laboratory values were not reported. Administrative databases may be a powerful tool for the study of AKI, although the low sensitivity of the AKI codes still remains an important caveat [20]. Therefore, in the study of Wyatt et al [15] the utilization of diagnostic code to identify AKI could not have captured an important number of cases.

In a previous report, Lopes et al [17] have also studied AKI in a small cohort of critically ill HIV-infected patients hospitalized in a tertiary and teaching Portuguese Hospital between 2002 and 2006. In this retrospective study, 47% of patients had AKI (defined by the RIFLE criteria) during the intensive care unit (ICU) stay.

3. Risk factors of AKI in hospitalized HIV-infected patients

In the HAART era, clinical conditions commonly associated with increased risk of AKI in the general population such as older age, Male, Black race, diabetes, prior hypertension, liver disease and pre-existing chronic kidney disease have also been reported as independent risk factors of AKI in hospitalized HIV-infected patients [15,16,17] (Table 1). Accordingly, renal function should be closely monitored during the hospitalization, and an adequate control of glycemia and blood pressure as well as the appropriate management of patients with acute or chronic liver insufficiency and/or chronic kidney disease could prevent the occurrence of AKI.

	N	Design	Setting	Year of hospitalization	Definition of AKI	Incidence of AKI	Risk factors of AKI	Mortality (AKI versus non-AKI)
Wyatt et al [15]	25.114	Retrospective, multicenter	Hospitalized	2003	Code 584 of the ICD-9	6%	Age (per year above mean) (adjusted OR 1.03, 95% CI, 1.02-1.04), Male (adjusted OR 1.16, 95% CI 1.04-1.30), diabetes mellitus (adjusted OR 1.27, 95% CI 1.08-1.49), chronic kidney disease (adjusted OR 5.48, 95% CI 4.58-6.56), liver disease (adjusted OR 1.59, 95% CI 1.40-1.79)	In-hospital mortality [27% versus 4.5% (adjusted OR 5.83; 95% CI, 5.11-6.65, P<0.0001)]
Lopes et al [16]	489	Retrospective, single-center	Hospitalized	2005-2007	↑> 1.5X SCr or ↑ SCr ≥0.5mg (if baseline SCr >4mg/dl)	18%	Pre-existing hypertension (adjusted OR 2.4, 95% CI 1.04-5.6, P=0.04), AIDS (adjusted OR 2.7, 95% CI 1.2-6, P=0.02), sepsis (adjusted OR 23, 95% CI 11-45.3, P<0.001), and nephrotoxic drugs administration (adjusted OR 2.8, 95% CI 1.4-5.8, P=0.004)	In-hospital mortality [27.3% versus 8% (adjusted OR 2.7, 95% CI 1.3-5.6, P=0.008)]
Lopes et al [17]	97	Retrospective, single-center	Intensive care unit	2002-2006	↑> 1.5X SCr or ↑ SCr ≥0.5mg (if baseline SCr >4mg/dl)	47%	Age >60 years (adjusted OR 5.32, 95% CI 1.23-23, P=0.025), HCV co-infection (adjusted OR 3.42, 95% CI 1.08-10.85, P=0.037), SAPS II >50 (adjusted OR 2.35, 95% CI 1.2-5.9, P=0.008)	60-day mortality (65% versus 24%, P<0.0001)

Table 1. Studies reporting the incidence, risk factors and mortality of acute kidney injury in the highly active antiretroviral therapy era. AKI- acute kidney injury. ICD-9- International Classification of Diseases, 9th Revision. OR- odds ratio. CI- confidence interval. HCV- hepatitis C virus. SCr- serum creatinine. AIDS- Acquired Immunodeficiency Syndrome. SAPS II- Simplified Acute Pathophysiology Score version II.

Hepatitis C virus co-infection has also been associated with increased risk for AKI (Table 1). Hepatitis C virus co-infection is an increasingly important cause of morbidity and mortality in patients with HIV [2], and affects approximately 30% of HIV-infected individuals [21]. Studies have demonstrated that co-infection with HIV and HCV translates into higher morbidity and mortality related to end-stage liver disease [22]. A recent meta-analysis of 27 studies including data of more than 18.000 HIV-infected patients has also demonstrated that HCV co-infection was associated with an increased risk of AKI by 64% [23]. Therefore, the association between HCV co-infection and risk for acute and chronic kidney disease supports existing guidelines for the diagnosis and management of kidney disease in patients with HIV [5].

Only two studies have specifically analyzed the etiology of AKI in hospitalized HIV-infected patients [16,17]. In the study of Lopes et al [16], the etiology of AKI was multifactorial in 48.9% of patients. The most common etiologies of AKI in this cohort were sepsis (59%), nephrotoxic drugs administration (i.e. aminoglycosides, amphotericine B, vancomycin, acyclovir, gancyclovir and foscarnet) (37.5%), volume depletion (21.6%), and use of radiocontrast (20.5%). Other less common causes of AKI were tumour lysis syndrome, hemorrhage, acute urinary tract obstruction and thrombotic microangiopathy. In the ICU setting, Lopes et al [17] have also identified sepsis as the most common cause of AKI (86%) in HIV-infected patients. Therefore, prompt recognition and aggressive treatment of sepsis, adequate hydration, avoidance and serum monitoring of nephrotoxic drugs, and prophylaxis of contrast induced nephropathy could be important in diminishing the occurrence of AKI in this population [24,25].

The influence of HIV-related variables namely type of HIV, HAART, CD4 lymphocyte count, viral load and AIDS diagnosis in the development of AKI in hospitalized HIV-infected patients still remains to be established. In fact, only one study has attempted to study the impact of those variables on renal function in hospitalized HIV-infected patients [16]. In this study, only AIDS-defining conditions were independently associated with AKI and none association was found with type of HIV, HAART, CD4 lymphocyte count and viral load. However, the limited number of studied patients did not allow the authors to conclude definitively about the influence of those variables in the development of AKI. Therefore, prospective and randomized studies with a large number of patients are still warranted to better determine the precise impact of those HIV-related variables on renal function among HIV-infected patients who are hospitalized.

4. Impact on outcome of AKI in hospitalized HIV-infected patients

Acute kidney injury is a risk factor for short- and long-term mortality, and there is a graded relationship between severity of AKI and increased mortality [26,27,28,29,30,31,32]. The mechanism by which AKI contributes to increased mortality is not completely understood. Volume overload, coagulation abnormalities, an increased incidence of sepsis with multi-organ failure, and cytokine or immunemediated major organ dysfunction are other possible explanations for poor survival among AKI patients. The permanent injury to other vital organs caused by AKI, although the potential reversible nature of clinical AKI, in which serum creatinine can return to baseline after the

acute episode, could account for decreased long-term survival of patients who developed AKI [33,34,35]. Moreover, CKD disease with subsequent hypertension, proteinuria and increased cardiovascular disease has been appointed as a possible cause of poor long-term outcome among AKI patients [36].

The development of AKI during the hospitalization also portends an ominous outcome among HIV-infected patients (Table 1). In the study of Wyatt et al [15], hospitalizations of HIV-infected patients that were complicated by AKI were also complicated by much higher in-hospital mortality that seen in admissions of HIV-infected patients without AKI and, furthermore, AKI independently increased in-hospital mortality of those patients. In the study of Lopes et al [16], the development of AKI was associated with lengthened time of hospitalization and increased in-hospital mortality. In fact, patients who developed AKI within the hospitalization had higher in-hospital mortality than those patients who did not develop AKI. After adjusting for other covariates, AKI still remained associated with increased in-hospital mortality. Furthermore, there was a relationship between more severe AKI and increased in-hospital mortality. In critically ill HIV-infected patients [17], AKI has also been associated with increased mortality, and there was a graded relationship between AKI severity and mortality.

The detrimental impact of AKI on patient outcome seems to persist after hospital discharge even in those patients who exhibit renal function recovery. Recently, Choi et al [17] conducted an observational cohort study in a national sample of 17.325 HIV-infected persons receiving care in the Veterans Health Administration who survived at least 90 days after discharge from their first hospitalization to examine the association between AKI experienced during their first hospitalization with the development of heart failure, atherosclerotic cardiovascular events, end-stage renal disease (ESRD), and death over a period of 2 decades. They found a graded and independent association between severity of AKI with heart failure, cardiovascular disease, ESRD, and death.

5. Conclusions

Acute kidney injury is a common complication in hospitalized HIV-infected patients in the HAART era. Older patients, Male, Black race patients, diabetic and /or hypertensive patients and patients with pre-existing chronic kidney disease, HCV co-infection and/or liver disease are at increased risk for AKI within the hospitalization and, therefore, renal function should be closely monitored in those patients. Sepsis is the most common etiology of AKI in this setting and should be promptly diagnosed and treated. The occurrence of AKI is associated with both increased short- and long-term mortality. Therefore, prevention of AKI should be an important task to accomplish in order to improve morbidity and mortality in this specific population.

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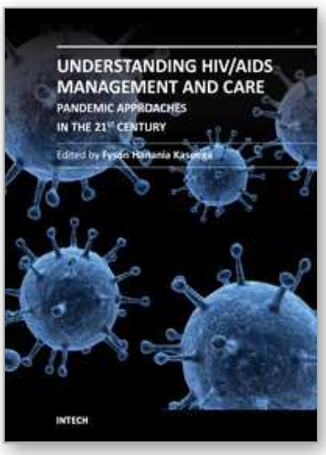
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Like any other book on the subject of HIV/AIDS, this book is not a substitute or exhausting the subject in question. It aims at complementing what is already in circulation and adds value to clarification of certain concepts to create more room for reasoning and being part of the solution to this global pandemic. It is further expected to complement a wide range of studies done on this subject, and provide a platform for the more updated information on this subject. It is the hope of the authors that the book will provide the readers with more knowledge and skills to do more to reduce HIV transmission and improve the quality of life of those that are infected or affected by HIV/AIDS.

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