

## REVIEW ARTICLE

# KIDNEY DAMAGE IN PATIENTS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

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**ABSTRACT**

The aim of the review is to present the most common renal complications after HSCT such as acute kidney injury, chronic kidney disease glomerulopathies. HSCT is a critical therapy for many cancer patients with cancer, as well as patients with some other nonmalignant hematologic disorders and certain congenital immune deficiencies. Kidney complications after HSCT in a form of acute kidney injury is associated with significant morbidity and worse patient outcome. In addition, risk of chronic kidney disease is also increased following HSCT. It is very important to be aware, prevent, early recognize and treat renal damage to improve kidney and patient survival.

**KEY WORDS:** stem cell transplantation, kidney function, chronic kidney disease, acute kidney injury, glomerulopathy

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**INTRODUCTION**

Hematopoietic stem cell transplantation (HSCT) is widely used in therapy of hematological diseases, cancer and amyloidosis. This is a breakthrough management of treatment-resistant diseases. About 50,000 treatments are performed annually around the world [1]. HSCT is divided into autologous HSCT and allogeneic HSCT. In autologous immunosuppressive HSCT treatment is not necessary. In the following years, thanks to modern treatment, the population of long-term survivors has been increasing. However, those who survive a bone marrow transplant are at risk of complications for many reasons such as cytoreductive therapy, conditioning, exposure to transfusion, infection, graft versus host disease (GVHD), immunosuppressants, antimicrobial drugs, thrombotic microangiopathy [2, 3].

One of these late complications is chronic kidney disease (CKD), which can lead to progressive loss of kidney function [4, 5]. According to the work of Abboud et al. CKD occurs in 13-66% of HSCT patients. CKD is caused by, among other things, chemotherapy treatment, occurrence acute and chronic GVHD [6]. It is worth emphasizing that in this area precise pathological changes, the long-term prognosis and optimal choice of HSCT immunosuppressants have not yet been fully determined.

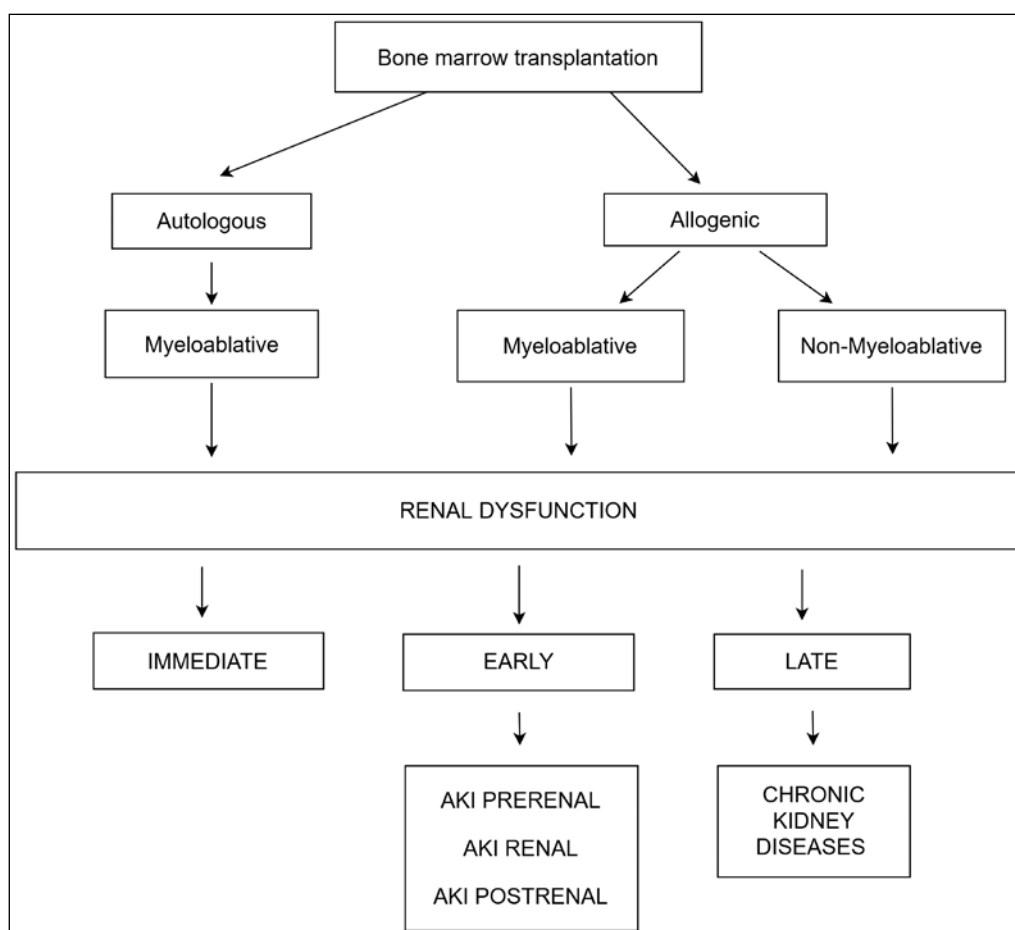
**THE AIM**

The aim of the review is to present the most common renal complications after HSCT such as acute kidney injury, chronic kidney disease glomerulopathies.

**REVIEW AND DISCUSSION****ACUTE KIDNEY INJURY**

Acute kidney failure is a common complication after transplantation. It is estimated that 20% to 75% of HSCT recipients have a complication of acute kidney injury (AKI) during HSCT. AKI risk depends on the type of transplant and conditioning regimen [3]. Renal dysfunction following bone marrow transplantation is presented in Figure 1. The epidemiology and prognosis of renal failure are different for the three main transplant procedures, such as myeloablative autograft, myeloablative allograft and non-myeloablative allogeneic transplant. However, what is common is that mortality increases as kidney failure worsens with each procedure. After allogeneic non-myeloablative HSCT is associated with a lower risk of AKI than myeloablative HSCT. This is related to treatment with high-dose chemotherapy and irradiation of the whole body, which is associated with complications such as nausea, vomiting, diarrhea, inflammation of the mucous membranes and hepatic vein occlusive disease [7,8].

The prevalence of AKI in autologous HSCT it is much lower than in allogeneic mainly due to the lack of acute and chronic GvHD, which may contribute to development AKI and chronic renal dysfunction [9,10]. It should be emphasized that the mortality rate is > 80% in patients with end-stage renal disease who are undergoing dialysis [11,12]. As is well known, acute kidney damage may be in the prerenal, renal and post renal form. Prerenal AKI can be caused by fluid loss – vomiting or diarrhea due to chemotherapy. It can also be caused by tumor lysis syndrome



**Fig. 1.** Renal dysfunction following bone marrow transplantation. Different causes for renal dysfunction.

in case of failure to achieve conditional remission. It is also worth emphasizing the role of Capillary Leak Syndrome (CLS) and implantation syndrome (release of pro-inflammatory substances) in the development of AKI. They can show up after autoHSCT and

alloHSCT as a form of fluid retention and fever. Treatment options are steroids

and anti-interleukin-6, which is currently under research [13]. Renal AKI may be caused by sepsis, toxic acute tubular necrosis. The causes of renal AKI can also include the toxic effects of the drugs which cause interstitial nephritis. Adenoviral infections also cause hemorrhagic cystitis which is a common cause of postrenal AKI. 90% of adenovirus patients develop acute kidney injury. the main symptoms are fever, hematuria and pain in the side. Kidney biopsy is necessary to establish a definitive diagnosis [14, 15]. The main treatment is to reduce immunosuppression during viremia to improve T-cell immunity answer. Antiviral therapy with cidofovir is only used for treatment severe cases of haemorrhagic cystitis [16].

### CHRONIC KIDNEY FAILURE

Chronic kidney disease (CKD) is a common complication after HCT. Up to 6-12 months after allogeneic HCT 20% patients develop CKD [17]. A retrospective cohort study by Weiss et al. confirmed that out of 120 patients after HSCT

CKD was found in 65%, and 22% had at least a doubling of the serum creatinine levels within 1 year of the transplant [18]. It is caused by many factors. In various studies, CKD was associated with older age, female gender, use of drugs such as fludarabine, amphotericin B, calcineurin inhibitors. Calcineurin inhibitors have been used in the prevention and treatment of GVHD in most studies were mainly associated with varying degrees of nephrotoxicity [19, 20]. Early research focused mainly on toxicity conditioning [21, 22]. As reported by I. Sekellari at al. there are much more factors associated with kidney damage after HCT. According to this study, the main influencing factors were nephrotoxic drugs, chemoradiotherapy or conditioning, severe infection, and presence of GVHD [23].

Radiation nephropathy is the cause of late renal dysfunction, affecting up to 20% of patients because radiation damages DNA [24]. Radiation can also cause endothelial damage and hemolysis. The incidence of toxicity and kidney damage after total body irradiation is increasing exponentially after a total dose of > 12 Gy [25]. It can be decreased the incidence of late kidney problems by using kidney sheath [26].

Improvements in the prevention of acute GVHD have been achieved in recent years, however, chronic graft versus host disease (GVHD) remains the most common late complication of allogeneic hematopoietic cell transplantation. The prognostic factors of survival in patients

with chronic GVHD have been analyzed in many studies. There were the presence of extensive chronic GVHD, poor performance status, thrombocytopenia, lichenoid changes in skin histology, increased serum bilirubin [27].

## NEPHROTIC SYNDROME AND GLOMERULONEPHRITIS

In patients after HCT, attention should also be paid to the development of nephrotic syndrome. Nephrotic syndrome and proteinuria are rare symptoms of graft versus host disease (GVHD). Only a few reports of cases of glomerulonephritis and nephrotic syndrome can be found in the literature.

Etiology and pathogenesis nephrotic syndrome after HSCT in patients with chronic GVHD remain unclear [28]. The most common histological diagnoses are membranous nephropathy (MGN) and minimal change disease [29]. MGN is poorly understood. Hiramatsu et al. examined 830 patients (621 patients receiving umbilical cord umbilical cord blood transplant (UCBT) and 208 patients after allogeneic bone marrow transplant) undergoing HSCT at Toranomon Hospital from 2000 to 2012. MGN was diagnosed in 5 patients after UCBT (MGN was not found in none after bone marrow transplantation) and has occurred concurrently with chronic graft versus host disease after cessation of immunosuppression. After treatment with immunosuppressants and angiotensin converting enzyme inhibitors was achieved complete remission after approximately 12 months in all patients [29].

Momoki et al. studied data of 1175 patients undergoing allogeneic HSCT (period 1986 to 2013). Nephrotic syndrome developed in 9 (7 men and 2 women). Average time by the time of diagnosis of nephrotic syndrome is 24 months after HSCT. If we look at the histological type (found after kidney biopsy), membranous nephropathy has become 8 (89%) of cases, a type of minimal change in 1 case [30]. Gomez-Garcia et al. reported 2 cases of nephrotic syndrome in the course of chronic GVHD in patients after allogeneic HSCT [31].

## CONCLUSIONS

HSCT is a critical therapy for many cancer patients with cancer, as well as patients with some other nonmalignant hematologic disorders and certain congenital immune deficiencies. Kidney complications after HSCT in a form of acute kidney injury is associated with significant morbidity and worse patient outcome. In addition, risk of chronic kidney disease is also increased following HSCT. It is very important to be aware, prevent, early recognize and treat renal damage to improve kidney and patient survival.

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**Conflict of interest:**

*The Authors declare no conflict of interest*

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