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# MANAGEMENT OF ADENOSINE DEAMINASE DEFICIENCY: A REVIEW ARTICLE

**Amnah Alhazmi [1], Bushra Alhazmi [2], Dhabiah AlQahtani [2]**

[1]College of Medicine, Almaarefa University, Riyadh., [2]King Saud bin Abdulaziz University for Health Sciences, College of Medicine, Riyadh.

**Abstract:**

*Adenosine deaminase 1 [ADA] deficiency is a very rare condition inherited in an autosomal recessive pattern. Dysfunctional ADA enzyme activity result in toxic metabolite buildup within the cells compromising many body systems, most importantly the immune system integrity. Majority of patients with ADA deficiency suffer from severe combined immune deficiency [SCID]. If left untreated, patients usually succumb to infection before the age of two years. The management of ADA-SCID is complex and require both supportive measures to boost the immune system along with definitive treatment. The aim of this paper is to present an overview of ADA deficiency and the available treatment modalities.*

**Key words:** *adenosine deaminase deficiency, enzyme replacement therapy, hematopoietic stem cell transplantation, gene therapy, immunity.*

**Corresponding author:**

**Amnah Alhazmi,**

College of Medicine, Almaarefa University, Riyadh.

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## INTRODUCTION:

Adenosine deaminase 1 [ADA] deficiency is a systemic autosomal recessive disorder where a defective ADA gene that causes severe combined immune deficiency [SCID] along with other physiological systemic impairments[1]. SCID is mainly a result of malfunctioning T-lymphocytes, B-lymphocytes, natural killer and humoral immunity[2]. ADA deficiency is extremely rare, affecting 1 child per 200,000 livebirths[3]. ADA is one of most common causes of SCID accounting for 15-25% of all cases[1]. ADA enzyme is an ubiquitously expressed intracellular enzyme that is also found on the cell surface of some cell types and the serum[1]. ADA is critically important in the purine salvage pathway which regulates purines availability in the cells. It enables the deamination of adenosine into inosine, and deoxyadenosine into deoxyinosine which ultimately get processed to waste metabolites and get excreted [1-4]. Faulty mutations in ADA1 gene located on 20q13.11 result in dysfunctional ADA enzyme causing adenosine and deoxyadenosine to build up inside the cells[2]. This accumulation leads to phosphorylation of adenosine and deoxyadenosine to 5'-deoxyadenosine triphosphate [dATP]. DATP eventually inhibits *de novo* synthesis of deoxynucleotides, integral substrates in DNA synthesis, decreasing DNA synthesis. Cells with high replication and turnover are the most affected[1-4]. Several studies have been conducted attempting to reveal the exact mechanism by which ADA deficiency causes aberrant immune and non-immune organ systems, the subject of which is beyond the scope of this review. The clinical manifestation of ADA deficiency may vary depending of the severity of the disease. The severity of the ADA1 mutations correlates with the enzymes activity and hence the resulting metabolic disturbance[1]. Majority of the patients typically present within the first months of life with SCID phenotype[2]. The condition can ultimately lead to death if left untreated within the first two years of life. The most common presenting complaint in these patients include failure to thrive, severe infections and chronic diarrhea. The following are the most frequent infections in ADA-SCID phenotype affected children: Pneumocystis jirovecii pneumonia [PCP]; Candidal infection of the gastrointestinal tract and skin; cytomegalovirus [CMV], Epstein-Barr virus and varicella-zoster virus infections; and enterovirus and parainfluenza infections[2]. Other clinical manifestations include, but not limited to, central nervous system abnormalities such as bilateral sensorineural hearing loss, cognitive and behavioral abnormalities, and gait disturbances [2, 5, 6]. Moreover, lymphoma has been documented in patients presenting late and in those who underwent enzyme replacement therapy[2, 7]. Patients with ADA-SCID might develop dermatofibrosarcoma protuberans, a rare mesenchymal malignancy of the skin[8]. Another rare disorder seen in high frequency in children with ADA-SCID is pulmonary alveolar proteinosis in which surfactant-derived components accumulate in the lungs[2]. In one study, 7 out of 16 patients [43.8%] had pulmonary alveolar proteinosis[9]. There is compelling evidence that lung abnormalities seen in ADA-SCID individuals are mainly due to metabolic insufficiency[10]. ADA deficiency might also predispose patients to skeletal system abnormalities such as costochondral defects and skeletal dysplasia[1]. Although less frequent than other organ systems, renal abnormalities including mesangial sclerosis, global sclerosis, and increased mesangial matrix were observed in patients with ADA-SCID[11]. Small percentage of patients with ADA deficiency have milder form of the disease and present at older age [2].

## METHODOLOGY:

A PubMed search was conducted up to October 2018. The following terms were used individually or in combination: adenosine deaminase deficiency, severe combined immune deficiency, enzyme replacement therapy, hematopoietic stem cell transplantation, gene therapy. Relevant articles written in English were reviewed and included in making this overview. In addition, references lists were scanned for additional related articles. Studies based on non-human subjects were excluded.

## RESULTS AND DISCUSSION:

**Treatment overview:**

The management of ADA deficiency is complex and requires a multidisciplinary team of experienced and well-trained health care providers. General supportive measures should be taken in all patients with ADA-SCID to prevent infections[12-14]. These measures include avoiding contact with patients with contagious illness. Vaccines containing live or live-attenuated viruses, like measles, mumps and rubella [MMR], rotavirus, adenovirus, varicella, herpes zoster and bacillus calmette–guérin [BCG] should not be given. Nonirradiated blood products are contraindicated to reduce the risk of transfusion-associated graft versus host disease and the risk of CMV transmission. Similarly, if the mother is positive for CMV antibodies, breastfeeding should be ceased. Another important supportive measure is immune globulin replacement therapy as it may provide a passive protection to certain diseases. Patients should also receive respiratory syncytial

virus [RSV] prophylaxis and PJP antibiotic prophylaxis. Along with these general measure, ADA-SCID specific treatment should be provided based on individualized level. Current treatments include enzyme replacement therapy, allogenic hematopoietic stem cell transplantation, and gene therapy.

**Enzyme replacement therapy [ERT]:**

Because of their ability to exit the cells, ADA substrates, adenosine and deoxyadenosine, can be metabolized by serum ADA or ADA-positive red blood cells [RBC][15]. Periodic frozen irradiated RBC transfusion was one of the earliest techniques to deliver ERT[16]. This technique is not used any more due to its adverse effects of iron overload and the introduction of a bovine derived ADA, polyethylene glycol-modified bovine ADA [PEG-ADA][17, 18]. PEG-ADA is delivered intramuscularly and have a half-life of 2-3 days. It has shown to be effective in augmenting the immune system sometimes to normal levels. While, PEG-ADA treatment has also shown to resolve pulmonary alveolar proteinosis, hepatocellular damage was not corrected in treated patients[9, 19]. On the long term, PEG-ADA had less mortality rates than haploidentical hematopoietic stem cell transplantation, yet many patients with PEG-ADA injections die due to lymphomas, opportunistic and life-threatening infections[20]. In addition, PEG-ADA replacement therapy is extremely expensive, costing around one hundred to three hundred US dollars per year in the United States[21]. Enzyme replacement therapy is usually used to stabilize the patients until they receive a definitive treatment[22]. It is also a good therapeutic alternative for treating ADA-deficient patients who were not suitable for stem cells transplant[23, 24].

**Hematopoietic stem cell transplantation [HSCT]:**

HCST from a matched sibling donor or matched family donor can provide a cure for ADA-SCID[18, 25, 26]. Many retrospective studies reported a survival rate up to more than 80%[12, 25, 27-29]. Matched unrelated or haploidentical donors have shown less successful results[27, 28]. In a multicenter retrospective study, **Hassan *et al.*** studied the outcome of 119 hematopoietic stem cell transplants in 106 ADA-SCID affected patients [27]. The overall survival was 67%. Several factors were investigated for their potential impact on the outcome, one of which is the source of stem cells. The same authors noted a better overall survival of 86% and 81% with matched sibling donors [MSD] and matched family donors [MFD]-derived HSCT, respectively. Moreover, HSCT from MSD had a significantly superior survival when compared to HSCT from matched unrelated donors [67%, P<0.05] and haploidentical donors [43%, P<0.001].The ADA-positive donor lymphocytes are more likely to survive than the recipient ADA deficient lymphoid cells. In addition, the transplant rejection is less likely when the recipient is almost devoid of lymphoid cells. Thus, in most cases, there is no need for immunosuppressive conditioning[12, 24]. **Hassan *et al.*** demonstrated a high engraftment rate of 90% among unconditioned MSD and MFD transplantations [27]. Unconditioned transplants were significantly associated with better overall survival compared to preparative myeloablative conditioning [81% vs 54%, P<0.003]. Notably, non-engraftment was a major concern in unconditioned HSCT from haploidentical and matched unrelated donors, with 1 successful engraftment in each group out of 6 and 3 transplantations, respectively[30].

The literature addressing the long-term outcomes of HSCT in ADA deficient patients is limited. In one study, nine patients were assessed between 18 and 212 months following transplantation[30]. Majority of patients had robust T-cell engraftment. Most of the patients also had a sufficient B cell engraftment with normal B-cell counts. Beside the immune system, HSCT have shown to improve other organ dysfunctions including pulmonary alveolar proteinosis and bone defects[9, 31]. It is postulated that ADA positive cells improve purine hemostasis leading to multi systemic improvements. Neurological abnormalities on the other hand were not reversed with hematopoietic stem cell transplantation[32]. Although stem cell transplantations from matched donors yield excellent, roughly 15% of all patients have matched sibling donors necessitating the quest for alternative therapies[18].

**Gene therapy:**

Gene replacement therapy has revolutionized the management of ADA deficiency[33]. The principle of gene replacement relies on introducing the gene of interest, ADA-expressing gene, to the patient via genetically engineered viruses[34]. Enhanced gene transfer efficacy and nonmyeloablative pre-transplantation conditioning have improved the success rates of gene therapy reaching up to 70% success rates[12, 18, 35-37]. **Aiuti *et al.*** studied the outcome of autologous genetically engineered CD34+ hematopoietic stem cell infusion [37]. The CD34+ cells where transduced with ADA-containing retroviral vector. All patients in the trial received busulfan regimen, a nonmyeloablative conditioning, prior to the infusion. ERT was stopped after complete infusion of treated cells. 10 children with ADA-SCID

were treated. The study reported a 100% survival rate after a median follow up of 4 years. The immune system was sufficiently restored in eight patients while two patients required resuming their ERT. In another study, 10 patients were treated with CD34+ transduced with ADA-containing retroviral vector[38]. In four patients, the cells were infused without preconditioning regimen and patients remained on ERT. The outcome was not shown to be successful in these patients. The remaining six patients included in the study received busulfan and had their ERT stopped before the infusion. Three out of six had successful results. Other studies have also highlighted the importance of reduced-intensity conditioning before transplantation[39, 40]. Gene therapy appear to have a good safety profile with very low risk of malignant transformation in ADA-deficient patients[18, 24, 33]. ADA-gene therapy is treatment of choice in case of unavailable matched family donor for HSCT and ERT is not effective[26]. To date, over 100 patients with ADA-SCID have been treated with gene therapy[22].

**Other treatment:**

Other treatment modalities such as deoxycytidine kinase inhibitors, thymic and fetal liver grafts have been used to treat ADA deficiency. Howeverthe authors reported that outcomes are unpromising and short-lasting[18, 41-43].

## CONCLUSION:

The management of ADA deficiency has significantly advanced over the last years with more breakthroughs expected to come. The management of ADA deficiency is delicate and require a good health care facility with an experienced team. Patients with ADA-SCID should be urgently admitted for prompt assessment and management. Appropriate supportive measures such as RSV, PJP prophylaxis, and immune globulin therapy should be administered. Moreover, live or live-attenuated vaccines should be avoided in all patients. ERT is given to stabilize the patients while waiting for definitive treatment [i.e. HSCT or GT]. HSCT from matched family donors remains the definitive treatment of choice.

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