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ORIGINAL ARTICLE

# Factors influencing the treatment response of cyclosporine-a therapy in aplastic anemia patients in resource-limited settings

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**ABSTRACT**

**Background and aim:** Cyclosporine-A (CsA) is the preferred treatment for Aplastic Anemia (AA) in developing countries with restricted access to Antithymocyte Globulin (ATG) and Matched Sibling Donor Hematopoietic Stem Cell Transplantation (MSD HSCT). Treatment response to CsA is variable, and this study aims to determine the factors influencing the treatment response of CsA in AA patients.
**Methods:** A cross-sectional analytical observational study included 40 AA patients diagnosed according to Camitta criteria, who had CsA therapy for 3 months at the Hematology-Oncology Outpatient Clinic at Wahidin-Sudirohusodo Hospital, Indonesia, from June 2023 to June 2025. The treatment response was evaluated using the British Society for Haematology's 2024 Guideline. The examined factors comprised age, body mass index (BMI), diagnosis-to-treatment interval, number of blood transfusions preceding therapy, corticosteroid administration, comorbidities (hypertension and diabetes mellitus), and disease severity. Multivariate logistic regression analysis was used to identify variables influencing CsA treatment response.
**Results:** This study reported a 40% response rate (RR) to CsA therapy (27.5% partial response and 12.5% complete response). A significant correlation was identified between the number of blood transfusions preceding therapy (P = 0.022; OR = 7.328; CI 1.341-40.056) and disease severity (P = 0.040; OR = 12.081; CI 1.122-130.054) concerning CsA treatment response within 3 months.

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**Conclusions:** Our findings suggest that AA patients who received ≥3 blood transfusions preceding therapy and exhibited severe disease were less likely to respond to CsA therapy. This highlights the prognostic importance of transfusion history and disease severity in predicting treatment outcomes. (www.actabiomedica.it)

**Key words:** aplastic anemia, cyclosporine-a, immunosuppresive therapy, prognostic factors, resource-limited settings

## Introduction

Aplastic Anemia (AA) is a chronic hematological disorder characterized by pancytopenia and bone marrow hypoplasia or aplasia. AA is classified as non-severe, severe, or very severe based on the presence of pancytopenia and bone marrow cellularity (1) Every year, there are 0.6 to 6.1 incidences per 1 million individuals worldwide (2). Annually, there are 2 to 3 occurrences of AA per million individuals in the U.S. and Europe. Asian nations exhibit a higher incidence of AA cases. China reports 7 incidents per 1 million individuals, whereas Korea, Malaysia, and Thailand report 5 (3). Indonesia experiences 2 to 5 incidents per million individuals each year. Aplastic Anemia, while rare, can be life-threatening (4). At present, Antithymocyte Globulin (ATG) and Cyclosporine-A (CsA) serve as the primary treatments for severe or very severe AA in cases where Matched Sibling Donor Hematopoietic Stem Cell Transplantation (MSD HSCT) is not available (1,5). CsA shown equivalent efficacy to ATG in patients with severe AA in a randomized trial (6). In comparison to ATG, CsA is more affordable, easily accessible, suitable for outpatient administration, and exhibits reduced toxicity. In developing countries, when ATG is limited and costly, this method serves as an effective initial treatment for AA. In developed countries, immunosuppressive therapy (IST) serves as the primary treatment due to the scarcity of donors for allogeneic transplantation among most patients. Conversely, allogeneic transplantation is often not feasible in many developing countries (1,5). The response of CsA treatment in AA has been thoroughly studied. Al Ghazaly et al. in Yemen, Matsuda et al. in Japan, Mandal et al. in East India, Li et al. in China, and Awan et al. in Pakistan suggest that CsA may serve as an effective treatment, particularly in developing nations with restricted access to ATG and MSD HSCT, leading to its frequent use as a standalone treatment (6-10). While its effectiveness is established, the response of patients to CsA varies considerably and is influenced by multiple factors. Key components include patient characteristics (age, genetics), disease characteristics (severity, duration from diagnosis to treatment), and management-related factors (transfusion history, comorbidities) (5,11). Clinicians require an immediate comprehension of elements influencing treatment response. Finding key indicators could lead to better risk assessment and tailored treatment plans, ultimately enhancing the likelihood of successful therapy (11,12).

## Materials and methods

An analytical observational study employing a cross-sectional design, gathering patient medical record data from June 2023 to June 2025 at the Hematology-Oncology Outpatient Clinic at Wahidin Sudirohusodo Hospital, Indonesia. Informed consent was not necessary for this study, as there was no direct interaction with participants and the data was obtained through patient medical records. A total of 85 patients, aged 18 to 78 years, received treatment over a two-year period (June 2023 to June 2025) and 40 patients met the inclusion criteria. Inclusion criteria comprised: (1)

men and women aged 18 years or older, (2) diagnosed with AA based on Camitta criteria, having undergone a physical examination and complete blood count, and having received Cyclosporine-A therapy (Sandimmun®, Novartis Pharma, Basel, Switzerland) at an initial dose of 5 mg/kg BW/day, divided into 2 doses for 3 consecutive months. The drug was procured and dispensed in Makassar, Indonesia. Patients who were not observed for ≥1 month, passed away preceding 3 months of treatment, discontinued medication, or were transferred to a different medical facility were excluded from this study. Patients presenting with pregnancy, lactation or immunodeficiency conditions, such as malignancies, HIV infection, were designated as exclusion criteria. The dependent variable is the treatment response of AA patients following 3 months of CsA therapy, categorized into no response (NR), partial response (PR), and complete response (CR) according to the British Society for Haematology Guideline. The independent factors comprise age, body mass index (BMI), diagnosis-to-treatment interval, number of blood transfusions preceding therapy, corticosteroid administration, comorbidities, and disease severity. Age is classified as ≤40 years and >40 years based on the eligibility criteria for patients undergoing MSD HSCT according to the British Society for Haematology Guideline. The patient's BMI is determined according to WHO guidelines for Asians and classified into two categories: non-obese (BMI < 25 kg/m²) and obese (BMI ≥ 25 kg/m²). The diagnosis-to-treatment interval refers to the period from AA diagnosis to the initial dose of CsA. The number of blood transfusions was a total of Packed Red Cells (PRC) units administered from the diagnosis of AA to the initiation of CsA therapy. Corticosteroid administration refers to patients who have received corticosteroid medications (Methylprednisolone, Prednisone, or Dexamethasone) at any dosage within 1 month preceding and during the 3 months period of CsA therapy. Comorbidities refer to the chronic diseases of the patient, specifically Hypertension and Diabetes Mellitus. Disease severity is categorized as not severe, severe, or very severe according to the Camitta criteria. The British Society for Haematology Guideline classifies treatment response as no response, partial response, or complete response, as illustrated in Table 1.

**Table 1.** Treatment Response of Cyclosporine-A in Aplastic Anaemia

| **Respons Criteria following IST in Severe AA** | |
|---|---|
| **None** | Still fulfill severe disease criteria |
| **Partial** | Transfusion independent<br>No longer meet criteria for severe disease |
| **Complete** | Hemoglobin concentration normal for age and gender<br>Neutrophils >1.5x10$^9$/L<br>Platelets >150x10$^9$/L |
| **Respons Criteria following IST for Non Severe AA** | |
| **None** | Blood count are worse, or do not meet criteria below |
| **Partial** | Transfusion independent (if previously dependent)<br>or doubling or normalisation of at least one cell line<br>or increase of baseline<br>Hemoglobin concentration >30g/L (if initially <60)<br>Neutrophils >0.5x10$^9$/L (if initially <0.5)<br>Platelets >20x10$^9$/L (if initially <20) |
| **Complete** | Same criteria as for severe disease |

Descriptive statistics evaluated qualitative data using frequency and percentage distributions and quantitative data using means, standard deviations, medians, and ranges. Shapiro–Wilk and Kolmogorov–Smirnov tests determined data normality. We use the Pearson Chi-Square Test for categorical variables and the Paired T-Test for numeric-categorical variables in bivariate analysis. The multivariate analysis will use binary logistic regression. A p-value < 0.05, type I error rate of 5%, and 80% statistical power indicate the study's significance. Statistical analysis will utilize SPSS 22.0.

## Result

This study involved 40 AA patients. The patients' ages varied from 18 to 78 years, with a mean age of 46.7 ± 16 years. Of these, 18 (45%) were male and 22 (55%) were female. A total of 60% of patients were transfusion dependent, requiring up to 10 bags, with a median of 3 bags. A total of 29 patients (72.5%) exhibited non-severe illness severity, while 11 patients (27.5%)

had severe disease severity. The complete distribution of patient characteristics is presented in Table 2.

This study reported a 40% response rate (RR) to CsA therapy, comprising 11 patients (27.5%) with PR and 5 patients (12.5%) with CR. Three factors significantly influenced the CsA treatment response in AA patients according to the bivariate analysis: comorbid Hypertension (P = 0.025), the number of blood transfusions preceding therapy (P = 0.013), and disease severity (P = 0.014), as outlined in Table 3. Multivariate analysis revealed that Hypertension did not significantly impact on the responsiveness to CsA therapy in AA patients (P = 0.151). Two factors significantly influenced the CsA treatment response in AA patients: the number of blood transfusions preceding therapy (P = 0.022; OR = 7.328; 95% CI: 1.341–40.056) and disease severity (P = 0.040; OR 12.081; CI: 1.122-130.054) as illustrated in Table 4.

**Table 2.** Patient Characteristics

| Variable | Result |
|---|---|
| Age (mean ± SD, years) | 46.7 ± 16 |
| Sex, n (%) | |
| Male | 18 (45) |
| Female | 22 (55) |
| Body Mass Index (mean ± SD, kg/m$^2$) | 22.3 ± 3.64 |
| Diagnosis and treatment Time Interval (median, days) | 30 (30-60) |
| Blood Transfusion (median, bag) | 3 (0-10) |
| Transfusion Dependent, n (%) | 24 (60) |
| Hypertension, n (%) | 10 (25) |
| Diabetes, n (%) | 6 (15) |
| Corticosteroid Use, n (%) | 13 (32.5) |
| Bleeding, n (%) | 18 (45) |
| Haemoglobin Level (mean ± SD, g/dL) | 8.2 ± 2.7 |
| Reticulocyte Count (mean ± SD, %) | 1.04 ± 1.13 |
| Leucocyte Count (mean ± SD, per µL) | 3439 ± 1921 |
| Absolute Neutrophil Count (mean ± SD, per µL) | 1594 ± 1475 |
| Thrombocyte Count (mean ± SD, per µL) | 64000 ± 80967 |
| Severity, n (%) | |
| Non-Severe | 29 (72.5) |
| Severe | 11 (27.5) |

## Discussion

### *Age and treatment response*

Cyclosporine-A shown efficacy in 67% of patients aged ≤40 years, compared to only 32% in those >40 years. The findings indicated no association between age and treatment response (P = 0.064). Although no

**Table 3.** Bivariate Analysis of Factors Influencing Treatment Response

| Variable | Treatment Response: Response n (%) | Treatment Response: No Response n (%) | Total | p value | Unadjusted OR |
|---|---|---|---|---|---|
| **Age** | | | | | |
| ≤ 40 y. o | 6 (67) | 3 (33) | 9 | 0.064 | 4.200 |
| > 40 y. o | 10 (32) | 21 (68) | 31 | | |
| **Body Mass Index** | | | | | |
| Non-Obese | 12 (40) | 18 (60) | 30 | 1.000 | 1.000 |
| Obese | 4 (40) | 6 (60) | 10 | | |
| **Diagnosis-treatment Time Interval** | | | | | |
| ≤ 30 days | 15 (39) | 23 (61) | 38 | 0.767 | 0.652 |
| > 30 days | 1 (50) | 1 (50) | 2 | | |
| **Blood Transfusion** | | | | | |
| ≤ 3 bags | 13 (43) | 10 (57) | 23 | **0.013** | **6.066** |
| > 3 bags | 3 (18) | 14 (82) | 17 | | |
| **Corticosteroid Use** | | | | | |
| No | 10 (37) | 17 (63) | 27 | 0.581 | 0.686 |
| Yes | 6 (46) | 7 (54) | 13 | | |
| **Hypertension** | | | | | |
| No | 15 (50) | 15 (50) | 30 | **0.025** | **9.000** |
| Yes | 1 (10) | 9 (90) | 10 | | |
| **Diabetes Mellitus** | | | | | |
| No | 15 (44) | 19 (56) | 34 | 0.206 | 3.947 |
| Yes | 1 (17) | 5 (83) | 6 | | |
| **Severity** | | | | | |
| Non-Severe | 15 (52) | 14 (48) | 29 | **0.014** | **10.714** |
| Severe | 1 (9) | 10 (91) | 11 | | |

**Table 4.** Multivariate Analysis of Factors Influencing Treatment Response

| Variable | Treatment Response Response N (%) | No Response N (%) | p value | Adjusted OR (95% CI) |
|---|---|---|---|---|
| **Hypertension** | | | | |
| No | 15 (37.5) | 15 (37.5) | 0.151 | 5.934 (0.521-67.623) |
| Yes | 1 (2.5) | 9 (22.5) | | |
| **Blood Transfusion** | | | | |
| ≤ 3 bags | 13 (32.5) | 10 (25) | **0.022** | **7.328 (1.341-40.056)** |
| > 3 bags | 3 (7.5) | 14 (35) | | |
| **Severity** | | | | |
| Non-Severe | 15 (37.5) | 14 (35) | **0.040** | **12.081 (1.122-130.054)** |
| Severe | 1 (2.5) | 10 (25) | | |

statistically significant link was seen, the treatment response was twice as high in the ≤40 age group (67% compared to 32%), indicating that younger age is a robust predictor of improved CsA response. Wang et al. identified a significant association between IST failure and patients aged ≥60 years in a meta-analysis (12). Younger patients exhibit superior responses to IST, making the age of commencement critical. The 15-year overall survival rate diminishes with advancing age (11,12).

### Body Mass Index and treatment response

The study found no significant correlation between BMI and treatment response (P = 1.000), supporting Walter et al.'s 2023 findings that obese and non-obese patients had comparable 5-year overall survival rates (13). In contrast to the 2024 Thai study by Somprasertkul et al., a low BMI is associated with diminished treatment success in SAA or VSAA patients, but a BMI of ≥24.9 kg/m² signifies a better outcome. Chronic immunosuppression and malnutrition in low-BMI patients impede bone marrow regeneration and exacerbate treatment outcomes. Conversely, Leptin and adiponectin, synthesized by adipose tissue in individuals with high BMI, may facilitate hematological repair or mitigate the immunological dysregulation that leads to AA (14).

### Diagnosis-to-Therapy interval and treatment response

The diagnosis-to-therapy interval did not influence treatment response in AA patients (P = 0.767). Nevertheless, the diagnosis-to-therapy interval for IST is a critical factor influencing prognosis and treatment success. The 2024 European Group for Blood and Marrow Transplantation (EBMT) RACE research indicates that early commencement of CsA-based IST enhances hematological response and OS (15). A 2023 study by Nakamura et al. revealed that treatment failure or infection-related complications are the primary causes of mortality during the first year, underscoring the necessity for early initiation of IST. Delays in treatment elevate the risk of severe infections and hemorrhaging, frequently resulting in premature mortality (15,16).

### Number of transfusions preceding therapy and treatment response

The number of transfusions preceding therapy shown a significant correlation with treatment response (P = 0.013). Multivariate analysis indicated that the responsiveness to CsA treatment in AA patients was predicted by the number of transfusions preceding therapy (P = 0.022; OR = 7.328; 95% CI: 1.341–40.056). These observations corroborate the literature associating elevated blood transfusion requirements prior to IST with worse treatment outcomes. Higher transfusion requirements augment HLA alloimmunization, prolong illness duration, and precipitate hematological failure, while diminishing the efficiency of IST (17,18). This immune sensitization can stimulate cytotoxic T cells and natural killer cells, thereby further inhibiting residual hematopoiesis. Since CsA primarily functions by suppressing T-cell activation, an existing condition of elevated immune activation may diminish its therapeutic effectiveness (18). In 2025, Leyu et al., discovered that patients receiving fewer transfusions exhibited a superior outcome. In contrast, a history of numerous transfusions before to IST correlates with a reduced RR, signifying a more severe and resistant condition (17,19). Excess iron resulting from frequent transfusions induces oxidative stress and disturbs the bone marrow microenvironment, potentially compromising the survival and functionality of stem cells. Since the microenvironment has been damaged, CsA may not reestablish hematopoiesis (20).

### Corticosteroid administration and treatment response

The administration of corticosteroids did not influence the treatment outcome (P = 0.581). These data corroborate the literature indicating that corticosteroids are utilized solely as short-term adjunctive therapy for the symptoms of ATG infusion (serum illness or allergic reactions) (21). Corticosteroids are not utilized alone due to their ineffectiveness without ATG/CsA (19,21). Routine, high-dose, or extended use may elevate toxicity and yield a minimal partial response without any discernible advantages (21,22).

### Hypertension and treatment response

Bivariate analysis revealed a significant association between Hypertension and treatment response (P = 0.025); however, subsequent multivariate analysis revealed no significant association (P = 0.151). This aligns with the literature indicating that Hypertension is not an independent predictor of treatment failure. Confounding variables such as advanced age and comorbidities, including Diabetes Mellitus, exacerbate prognosis and treatment efficacy, potentially elucidating the adverse consequences of Hypertension shown in the bivariate study. Research indicates that CsA is nephrotoxic and may induce Hypertension by renal vasoconstriction and sodium retention. Hypertension is a consequence of treatment, rather than a variable that directly influences the efficacy of CsA therapy (23,24).

### Diabetes mellitus and treatment response

The presence of Diabetes Mellitus comorbidity did not influence treatment response (P = 0.206). Although no statistically significant correlation was found, the non-DM group exhibited a fourfold greater treatment response (44% vs to 17%), indicating that DM may serve as a substantial predictor of treatment success. Hyperglycemia, chronic inflammation, and immunosuppression in people with diabetes mellitus may adversely affect hematopoietic stem cells and the bone marrow microvascular environment, impede bone marrow regeneration and compromise the immune system's response (25).

### Disease severity and treatment response

A significant correlation was identified between the disease severity and the treatment response (P = 0.014). Multivariate analysis indicated that disease severity influenced the CsA treatment response in AA patients (P = 0.040; OR 12.081; CI: 1.122-130.054). Previous study indicates that illness severity is a critical prognostic factor that adversely affects therapeutic outcomes (26). More severe conditions exhibit poorer treatment responses and prognoses. Severe disease correlates with a significantly elevated risk of premature mortality from infection, resulting in treatment failure preceding the efficacy of IST being realized. Secondly, very severe severity indicates greater BM damage and diminished stem cell reserves, constraining the regeneration capacity to attain a complete response (26,27). Severe immune dysregulation, characterized by increased activation of cytotoxic T cells, results in extensive and frequently irreversible marrow injury that CsA alone cannot sufficiently reverse. Patients also depend on blood transfusions, which cause alloimmunization and iron overload, and delayed diagnosis damages bone marrow, making CsA therapy unresponsive to severe disease (26,28).

### Study limitation

This single centre study's medical record data raises concerns regarding selection bias, information bias, and the generalizability to other populations or healthcare systems.

## Conclusion

Our findings suggest that AA patients with a history of over three blood transfusions preceding treatment and present with severe disease were less likely to respond to CsA therapy. These results emphasize the importance of transfusion history and disease severity as potential predictors of treatment outcome, underscoring the need for early diagnosis and timely therapeutic intervention.

**Ethics approval:** Ethical approval was granted by the Biomedical Ethics Committee on Human Research, Faculty of Medicine, Hasanuddin University, under clearance number 166/UN 4.6.4.5.31/PP36/2025. Patient confidentiality was preserved by excluding personal identifiers from all research material.

**Conflict of interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

**Authors contribution:** SSBK, AFB, and MI composed the manuscript. SSBK, AFB, and SB designed and conceptualized the study. SSBK and AS gathered, evaluated, and interpreted the data. AFB, MI, SB, and SA meticulously revised the manuscript for significant intellectual substance. All authors contributed to the production of the final draft, manuscript correction, and critical assessment of the intellectual content. All writers have reviewed and endorsed the manuscript's content and verified the accuracy and integrity of every aspect of the work.

**Declaration on the Use of AI:** No artificial intelligence methods were employed to produce scientific material, analyze data, or formulate conclusions. The authors assume all responsibility for the integrity, accuracy, and originality of the manuscript's scientific content.

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