

# Severe Aplastic Anemia and PNH

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## 77.1 Definition and Epidemiology

Severe aplastic anemia (SAA) is an autoimmune disorder (AID) due to the attack of autoreactive cytotoxic T lymphocytes to the hematopoietic component of the bone marrow. The triggering antigen is so far unknown. The incidence of SAA is about 2.34/million in Europe and the United States and threefold higher in East Asia, with two age peaks of incidence (in young adults and in the elderly) (Young and Kaufman 2008).

Paroxysmal nocturnal hemoglobinuria (PNH) is another bone marrow failure syndrome (BMFS) which is often embedded with SAA. PNH is a more heterogeneous disease since its clinical presentation includes hemolytic anemia and thrombophilia in addition to bone marrow failure.

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## 77.2 Diagnosis and Indication for Treatment for SAA

SAA is usually diagnosed in the setting of pancytopenia and a hypocellular BM. Diseases such as myelodysplasia, myelofibrosis, hypocellular acute leukemia, inherited BMF such as Fanconi's anemia (FA), or telomeropathies need to be excluded. Cytogenetic abnormalities can be found in up to 10% of true SAA (Rovo et al. 2016; Barone et al. 2015).

There is a close relationship between PNH and acquired SAA with a concomitant diagnosis in 40% of cases. SAA is diagnosed when marrow hematopoietic cellularity is <30%, and two of three of the following criteria are met: absolute neutrophil count <0.5 × 10<sup>9</sup>/L, absolute reticulocyte count <60 × 10<sup>9</sup>/L, and platelet count <20 × 10<sup>9</sup>/L (Camitta et al. 1976).

Treatment requires careful planning and may be prolonged. A watch and wait strategy is often used initially if there is milder pancytopenia. Conversely, in case of transfusion requirement or if the criteria for SAA are met, treatment should begin with no delay. Prior to treatment the patient should be stable clinically with control of bleeding and infections. Once the diagnosis is confirmed, and the disease severity is assessed, family HLA-typing and matched unrelated donor search should be done in the work-up phase. In the absence of sign of intravascular hemolysis, patient's treatment algorithm is similar with or without PNH.

## 77.3 Treatment of SAA

### 77.3.1 First Line Treatment for SAA

The choice of first-line treatment depends on the age of the patient and the availability of an HLA MSD (Fig. 77.1). The standard first-line treatments for a newly diagnosed patient with SAA are HSCT from a HLA-identical sibling donor or IS therapy (IST) using a combination of horse ATG and CSA (ATG + CSA). Early bone marrow HSCT after a conditioning regimen with CY, ATG, and GVHD prophylaxis combining CSA and MTX promotes excellent engraftment (95%) and OS (90% at 2 years) (Bacigalupo et al. 2012; Peffault de Latour 2016). This approach enabled also a very good long-term outcome with a rather limited number of late effects consisting in avascular necrosis, endocrine dysfunctions, and very rare

secondary malignancy (Konopacki et al. 2012). However, toxicity related to transplantation as well as increased risk of GvHD is still a problem for patients older than 40 years of age and for those with high comorbidity index (Marsh et al. 2011).

For these categories first-line IS with horse ATG + CSA is recommended. This combination showed both in prospective controlled studies (Scheinberg et al. 2011; Marsh et al. 2012) and in real-life surveys (Peffault de Latour et al. 2018) a response rate of about 60%. Frontline IST provided similar findings in children and adolescents (Dufour et al. 2014; Dufour et al. 2015a). After IST, responders might experience relapse (20–30%), CSA dependence (20–30%), or long-term clonal evolution (PNH, MDS, or AML) (Scheinberg and Young 2012), justifying regular follow-up and bone marrow evaluation every 12–18 months.

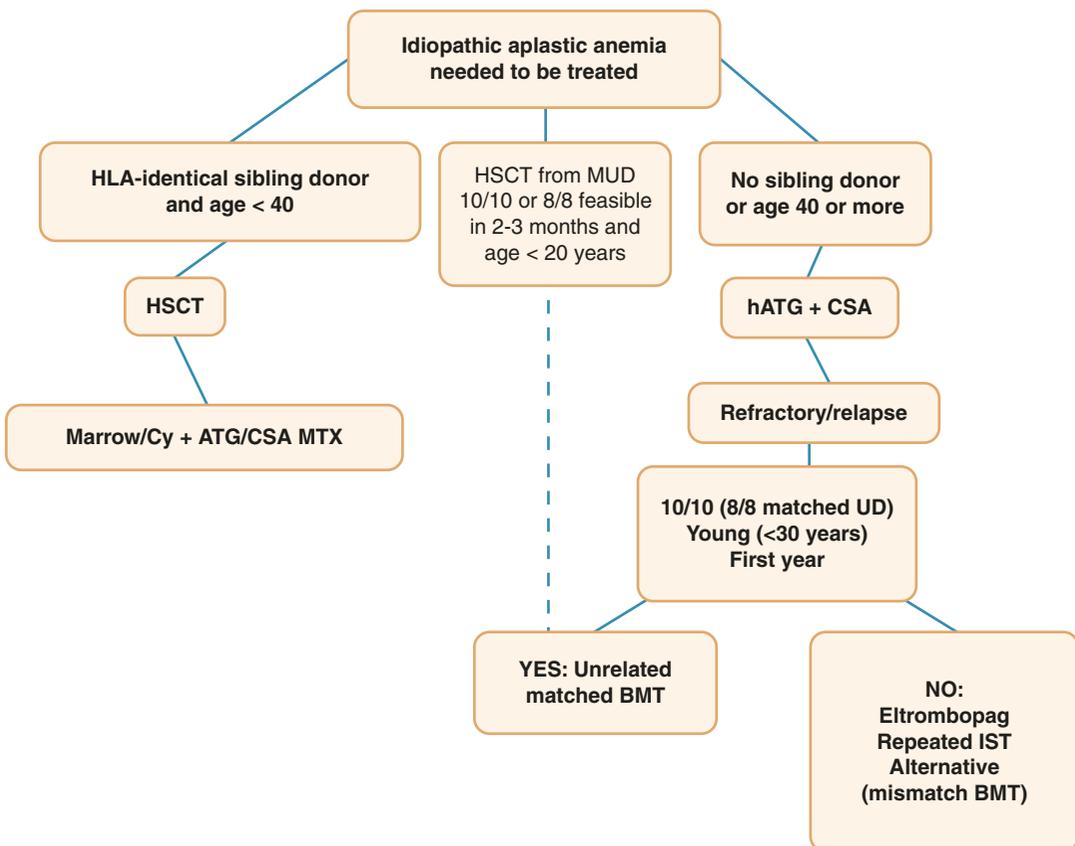


Fig. 77.1 Treatment algorithm of SAA in 2019

### 77.3.2 Second-Line Treatment for SAA

The choice of second-line treatment is also driven by age, by comorbidities, and by the presence of a matched related (MRD) or unrelated donor (MUD):

- In older patients with a MRD and confirmed refractory SAA, HSCT should be considered in the absence of significant comorbidities.
- In younger patients with a MUD and refractory or relapsed SAA, HSCT is recommended. Results of MUD HSCT have improved to such an extent that OS of idiopathic SAA are not statistically inferior to MRD transplants (Bacigalupo et al. 2015). This improvement has been largely attributed to better donor selection through allele matching, progress in supportive care, prophylaxis of GVHD, incorporation of FLU in conditioning regimens, and the addition of low-dose TBI. Recently some factors were found to positively affect OS after MUD HSCT including age  $\leq 30$  years, transplant within the first year after diagnosis (Devillier et al. 2016), use of BM vs PB, and CMV status (Bacigalupo et al. 2015).
- For patients older than 30 years, monotherapy with eltrombopag, an oral thrombopoietin-receptor agonist, produced in prospective studies in refractory patients an overall response of 40% with trilineage responses in some cases (Olnes et al. 2012; Desmond et al. 2014). A retrospective French study found similar results on patients with relapsed/refractory SAA. The overall rates of red blood cell and platelet transfusion independence were 7%, 33%, 46%, and 46 at 1, 3, and 6, months and last follow-up, respectively. No clonal evolution has been documented so far (Lengline et al. 2018). Other second-line options for patients not eligible to HSCT and who relapse or do not respond to frontline IST are a second course of ATG (rabbit) + CSA and alemtuzumab offering a response rate of 65% (Scheinberg et al. 2006) and 37% (Scheinberg and Young 2012), respectively.

### 77.3.3 Emerging Strategies for SAA

#### 77.3.3.1 Eltrombopag Added to the Standard Horse ATG + CSA First Line Treatment

Many efforts to improve results of the standard treatment with horse ATG and CSA have failed since 40 years (Scheinberg 2012). Excellent results obtained with eltrombopag in monotherapy in refractory patients prompted American colleagues from the NIH to test if the addition of eltrombopag to standard IST as the first treatment for SAA would have increased the rate of CR and improved the long-term outcome. In the best cohort (eltrombopag associated to ATG and CSA from day 1), complete and overall response rates at 6 months were 58% and 94%, respectively. After a median follow-up of 2 years, survival rate is 97% (Townesley et al. 2017). Rates of relapse and clonal evolution were similar to historical experience. Whether eltrombopag might substantially improve horse ATG + CSA platform is at the moment under investigation through a large, randomized, controlled, prospective European trial on behalf of the SAA working party of the EBMT (RACE trial; [ClinicalTrials.gov](http://ClinicalTrials.gov) number, NCT02099747).

#### 77.3.3.2 Up-Front Matched Unrelated Donor Transplantation

Although pediatric patients respond better to IST, the long-term risks of relapse, CSA dependence, and clonal evolution are high (Dufour et al. 2014). UK investigators reported an excellent estimated 5-year FFS of 95% in 44 consecutive children who received a 10-antigen (HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1) MUD HSCT; 40 of these children had previously failed IST. HSCT conditioning was with FLU, CY, and campath (FCC) (Samarasinghe and Webb 2012). Because of those excellent results, up-front MUD HSCT became an attractive first-line option in children. Between 2005 and 2014, a UK cohort of 29 consecutive children with idiopathic SAA received UD HSCTs (including five patients with 1 Ag mismatched transplants) as

first-line therapy after conditioning with FCC. Results were excellent, with OS and EFS of 96% and 92%, respectively, low GVHD rates, and only one death (from idiopathic pneumonia) (Dufour et al. 2015b). This cohort was then compared with historical matched controls who had received (1) first-line MRD HSCT, (2) first-line IST with horse ATG + CSA, and (3) MUD HSCT post-IST failure as second-line therapy. Outcomes for the up-front unrelated cohort were similar to MRD HSCT and superior to IST and UD HSCT post-IST failure. Similar results were observed in another pediatric study (Choi et al. 2017).

Currently a North American study aims to compare outcomes of children with SAA treated de novo with IST vs MUD HSCT (ClinicalTrials.gov number NCT02845596). While waiting the results of this trial, if a 10/10 MUD is available and the transplant appears feasible within 2–3 months since diagnosis, this type of HSCT has become a reasonable frontline option for young patients in many centers. Another option is to perform MUD HSCT early after failure of frontline IST within 4–6 months since diagnosis. This is why MUD donor search should be started at diagnosis in young patients who lack a MRD.

### 77.3.3.3 Alternative Donor Transplantation in SAA

Alternative HSCTs (MMURD, CB, and haplo-family donors) are possible for individuals with no suitable MUD. Alternative HSCTs may be curative, but the risks of graft rejection, infectious complications, and GVHD are higher than those for MRD or MUD HSCT. Patient age, comorbidities, and alternative HSCT specificities are thus important issues in the decision-making process. Age and comorbidities are the first barriers to this type of procedure. Most numerous cohorts (>50 patients) tend to mainly include pediatric patients. In older studies long-term OS of about 60% (Yagasaki et al. 2011; Horan et al. 2012; Peffault de Latour et al. 2011) compared to 5-year OS seen in refractory patients receiving only supportive care (Valdez et al. 2011). More recent studies with shorter follow-up showed OS and EFS >80% in unmanipulated haplo-HSCT with a high rate of cGVHD greater than 30% (Xu et al. 2016, 2017).

Based on this, alternative HSCT can be considered a salvage option that needs to be carefully balanced with best supportive care. The latter might be preferable for patients with comorbidities or advanced age (> 40 years or older) because of lower risks.

## 77.4 Treatment of PNH

Clinical presentation of PNH is extremely heterogeneous, including a variable combination of bone marrow failure, hemolytic anemia, and thromboembolism (Peffault de Latour et al. 2008). These clinical manifestations may change during the disease course of each individual patient so that the treatment of PNH should target the specific clinical presentation (Risitano 2017).

The treatment of marrow failure in PNH parallels that of SAA, and it has been described above; indeed, the presence of a PNH clone does not change the treatment algorithm of SAA.

In contrast, the treatment of complement-mediated hemolytic anemia and of thromboembolic PNH is based on complement inhibition through the anti-C5 MoAb eculizumab. Eculizumab has proven to be effective in inhibiting intravascular hemolysis of PNH, leading to hemoglobin stabilization and transfusion dependency in about half of patients (Hillmen et al. 2006; Brodsky et al. 2008). This dramatic effect on intravascular hemolysis, eventually resulting in improved quality of life, is also associated with a significant reduction of the risk of thromboembolic complications (Hillmen et al. 2007). Notably, eculizumab treatment leads to a significant improvement of overall survival of PNH patients, as documented by two independent long-term retrospective studies showing 5-year survival rates >90% (Kelly et al. 2011; Loschi et al. 2016). Based on this, eculizumab is currently the standard of care for all PNH patients presenting with symptomatic hemolytic and/or thromboembolic disease; occasionally, when this occurs concomitantly with a BMF, the anticomplement treatment may be considered also in combination with IST (i.e., sequential or concomitant treatment) (Pagliuca et al. 2018).

### 77.4.1 Emerging Strategies for PNH

Even if currently available anticomplement treatment addresses most clinical needs of patients with hemolytic (and thrombotic) PNH, a number of novel strategies of complement modulation are in their preclinical or clinical development (Risitano and Marotta 2016). These strategies may target specific unmet clinical needs pertaining PNH patients. Novel anti-C5 agents (either MoAb, small molecules or small interfering RNA) may represent an improvement of current eculizumab, mostly in terms of patient comfort due to long-lasting activity (with longer dosing interval) and/or self-administration (usually SC). In addition, a novel class of compounds targeting early steps of the complement cascade at the level of C3 or even upstream (inhibitors of complement factor B and factor B) may anticipate a better efficacy in terms of hematological response, due to possible effect on C3-mediated extravascular hemolysis. Ongoing clinical trials will reveal whether any of this strategy may lead to change in the standard of care of anticomplement treatment of hemolysis (and thrombophilia) of PNH patients (Risitano and Marotta 2018).

#### Key Points

- SAA is usually diagnosed in the setting of pancytopenia and a hypocellular BM when other diseases, especially inherited BMF such as Fanconi's anemia or telomeropathy, have been excluded.
- The preferred treatment of SAA is HSCT from HLA-identical sibling donor. Transplantation from a MUD may be considered for patients without a sibling donor after failure of IS therapy or up front in younger  $\leq 20$  years if feasible in 2–3 months since diagnosis.
- Eltrombopag might substantially change in the coming years the standard horse ATG + CSA platform.
- The role of alternative donor HSCT needs further validation to enter the current clinical practice.

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