Clinical Guidelines for the diagnosis and management of Aplastic Anaemia (AA) and Bone Marrow Failure (BMF) in adults and young people >16 years

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**Version History**

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GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF APLASTIC ANAEMIA (AA) AND BONE MARROW FAILURE (BMF) IN ADULTS AND YOUNG PEOPLE ≥16 YEARS

Authors: Snowden/Kaur/Francis/Greenfield/Fernando/Barker

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Background

AA is a rare disease with an incidence of 1-2 per million per annum. It is comprised of acquired AA and inherited BMF syndromes (eg Fanconi anaemia, Dyskeratosis congenita), and there is an overlap with hypoplastic myelodysplastic syndrome (MDS), especially in older patients. AA has a biphasic age distribution showing peaks at 15-24 years and ≥ 65 years of age; about 1/3 cases occur in children. Morbidity and mortality are substantial and treatments are complicated, often with multiple hospital admissions for infection or bleeding. The disease is classified as very severe, severe or non-severe depending on blood counts and clinical outcomes and treatments vary according to disease severity. AA may evolve into other haematological conditions such as paroxysmal nocturnal haemoglobinuria (PNH), MDS or acute leukaemia where prompt recognition and management are required. Treatment is different for immune, constitutional and MDS subtypes and precise diagnosis is critical in order to avoid inappropriate and costly treatments.

On behalf of the British Society for Haematology, the British Committee for Standardisation in Haematology (BCSH) has recently published consensus guidelines for diagnosis and management of aplastic anaemia in adults (Killick et al 2016). The South Yorkshire Network Haemato-oncology Network and BMT Programme have agreed to follow the national guidelines. The following is a summary with local adaptations aimed at providing a high quality specialised service for management of adults with all severities within the South Yorkshire region.

Modern diagnosis of AA, BMF and hypoplastic MDS

The diagnosis of AA and other forms of BMF is not always straightforward and there is much overlap with hypocellular MDS. Constitutional forms are easily missed, especially in adults. In addition to established diagnostics, molecular techniques are now available via the Haematology Diagnostic Service (HODS), including Next Generation Sequencing (NGS) which will enable better distinction between constitutional, MDS and immune mediated aplastic anaemia. Identification of inherited subtypes is critical to avoid toxicities and for family testing.
Treatment of AA, BMF and hypoplastic MDS

Treatments are often challenging, high risk and resource intensive. Therapeutic decisions for different age groups are not always straightforward. Patients may receive inappropriate therapy, especially older patients with severe and very severe disease.

In addition to transfusion and antibiotic support, the main treatment options are

(i) immunosuppressive therapy (IST) with antithymocyte globulin (ATG) and ciclosporin (CSA), with about 2/3 of patients responding

(ii) BMT also known as haemopoietic stem cell transplantation (HSCT)

(iii) other established therapies such as androgens and danazol

(iv) new therapies likely to be available for both acquired and constitutional AA, such as eltrombopag and alemtuzumab

(v) specific non-transplant therapies for hypocellular MDS

All patients require long term follow up because of the risk of relapse (in 30%) and later clonal disorders such as MDS/acute myeloid leukaemia (in 15% patients) and PNH (in 10%), following treatment with ATG. Although HSCT is curative of AA with no increased risk of later clonal disorders, there are differences in how HSCT is performed for AA compared with other BMF syndromes and different risks of complications. Prolonged transfusion support, and frequently with more special support (e.g. HLA matched platelet transfusions) are frequently required. It is important to identify 'late effects' of both the specific disease and HSCT and non-HSCT treatment.

Service configuration

AA and related BMF diseases are rare diseases and some hospitals in North Trent see only a few patients per year, limiting the ability to acquire specialist expertise in the diagnosis and treatment. Delayed and incorrect diagnosis may lead to inappropriate complex treatments, inadequate long term monitoring for evolution and in efficient use of resources. Although there have been MDT level discussions and mandatory BMT registrations, there is little data on the total local incidence and prevalence and also on the use and outcomes after ATG and other non-HSCT treatments, supporting the case to consolidate the expertise within the region and create a comprehensive service combining modern diagnostics, clinical care, data collection and potentially research.

A single South Yorkshire network regional referral service has been agreed for:

(i) early and accurate diagnosis of all new cases of AA by modern techniques

(ii) treatment of severe and very severe AA patients with HSCT or ATG.

(iii) To provide a treatment plan for all newly diagnosed patients avoiding toxicities due to inappropriate therapies through specialist MDT discussion

(iv) Family testing will be provided where necessary for the inherited BMF syndromes.

(v) To provide a plan for long term monitoring of all patients, including
a. Immune AA treated with ATG – for response and evolution
b. Immune AA treated with HSCT – for HSCT related late effects
c. Hypocellular MDS

This service will be based around the Tuesday am BMT (Prof Snowden, Dr Kaur, Dr Francis) and Late Effects clinic (Prof Greenfield) and ward O2 day ward (for stable new and follow up patients), with in-patient isolation facilities available on wards P3/P4/O1 for unstable and high risk patients, in alliance with HODS for the modern morphological, flow cytometric, cytogenetic and molecular diagnostics. An appropriate key worker/clinical nurse specialist will be allocated depending on whether transplantation is a current or future option.

All new patients will be routinely discussed in the regional weekly MDT, with the ability for patients to be reviewed when further management decisions require multidisciplinary support (such as changes in treatment). The MDT will be open for review of existing AA/BMF patients, including all AA/BMF patients transitioning from Sheffield Children’s Hospital or other paediatric facilities. All patients under the age of 25 will also be discussed in the MDT meetings for Teenagers and Young Adults (TYA, haematology lead Dr Morley). Where necessary, the established liaison with other national centres (such as Kings College Hospital and Leeds Teaching Hospitals NHS Trust) will be coordinated in complex cases by the Sheffield specialist clinicians (Snowden, Kaur, Francis, Greenfield) working with the MDT.

The potential for shared cared between the central service and the referring base will be considered on an individual case-by-case basis.

REFERENCES

British Journal of Haematology 2016; 172(2):187-207


International Fanconi Anemia Treatment Resource Guide: STH is a listed specialist referral centre for Fanconi Anaemia.