14/04/20 version

King's College Hospital guidance for adult aplastic anaemia/bone marrow failure patients during the COVID-19 outbreak

1. COVID-19

COVID-19 virus is highly infectious and produces severe life-threatening pneumonia. Patients with aplastic anaemia (AA) or bone marrow failure (BMF) disorders represent a vulnerable group at especially high risk.

If a patient becomes unwell, they should contact their haematology team immediately as per usual local practice.

General advice on COVID-19 can be found on: https://www.nhs.uk/conditions/coronavirus-covid-19/

The American Society for Haematology (ASH) has recently issued COVID guidance for AA treatment (the link to the current v1.0 is posted on the ASH website: https://www.hematology.org/covid-19/covid-19-and-aplastic-anemia This guidance has been written by Neal Young at NIH with contribution from King's College Hospital and others.

The European (EBMT) Severe Aplastic Anaemia Working Party has also issued similar guidance: https://www.ebmt.org/ebmt/documents/covid-19-bone-marrow-failure-and-pnh

2. Which patients with AA/BMF patients are at high risk?

i. All patients who are neutropenic, and especially those with severe and very severe neutropenia, as defined by neutrophil count < 0.5 and <0.2 x 10^9/l, respectively.
ii. All patients being treated with immunosuppressive drugs, notably antithymocyte globulin (ATG) and ciclosporin
iii. All patients who are lymphopenic: this will include patients with acquired AA being treated with ATG, ciclosporin, and also some patients with inherited/constitutional AA/BMF
iv. Constitutional AA/BMF:
    - Especially GATA2 deficiency patients who are monocytopenic, lymphopenic and often also neutropenic
    - Inherited telomeropathies/dyskeratosis congenita: some may have immunodeficiency with lymphopenia in the absence of neutropenia, affecting B, NK cells and T cells
    - Schwachmann-Diamond syndrome patients commonly are neutropenic, and may also have immune deficiency
    - Diamond Blackfan anaemia patients who are neutropenic, and/or lymphopenic
    - All patients on steroids
v. All patients undergoing allogeneic haemopoietic stem cell transplantation (HSCT) for AA/BMF, or who have had a HSCT

3. What treatments are possible for new patients?

Standard treatment options are HSCT or immunosuppressive therapy with antithymocyte globulin (ATG) and ciclosporin, which are life-saving. Potential transplant candidates should be discussed in a formal myeloid/BMT MDT setting to determine which are urgent and cannot be deferred. Availability of ICU beds may be restricted. Severe lymphopenia following ATG is usually short lived (1-2 weeks), and mild degree of lymphopenia occurs while on ciclosporin. ATG should be restricted to those with severe disease/cytopenias. For less severe AA, patients may be considered for single agent oral ciclosporin. Patients on ciclosporin should not suddenly stop the drug as there is a risk of relapse of the aplastic anaemia. Continue standard tapering of the drug in patients who have responded. All patients should be on prophylactic aciclovir. Blood monitoring of ciclosporin levels could be reduced/temporarily stopped in those patients with normal renal and liver function and well controlled/absent hypertension. Consideration of off-license use of eltrombopag with ATG or ciclosporin will require an urgent IFR to the CCG*. Corticosteroids should not be given to treat AA, other than as needed with ATG to prevent serum sickness.

**We are currently in urgent discussions with NHS England about possible rapid access to eltrombopag (with low dose ciclosporin) for new severe AA (SAA) patients, (i) as a bridge to later transplantation/ATG, for those patients in whom transplant/ATG can be safely deferred until the COVID-19 crisis is over and (ii) for refractory SAA patients.*

4. How should patients be monitored for COVID-19?

If AA patients are tested positive for COVID-19, it is advisable to defer treatment until (i) resolution of fever and (ii) **i**mprovement in respiratory symptoms and (iii) negative results of COVID-19 test from at least two consecutive nasopharyngeal swab specimens collected ≥24 hours apart; transplant recipients require 3 negative swabs (as per NICE and BSBMTCT guidelines).

5. Infection prevention and treatment

All AA/BMF patients who are severely neutropenic (neutrophils $<0.5 \times 10^9$/l) should be receiving prophylactic ciprofloxacin and posaconazole, as per NICE guidance. G-CSF is usually ineffective in severe and very severe aplastic anaemia

6. Transfusion support

In an attempt to reduce hospital attendance all red cell transfusion-dependent patients should be reviewed to assess if increased intervals between transfusions is possible without significant medical risk. Erythropoietin (EPO) is rarely of benefit in AA as endogenous serum levels are usually markedly elevated. Follow standard guidelines for prophylactic platelet transfusions ($<10 \times 10^9$/l, <20 if fever/infection/bleeding). For stable AA/BMF patients not on active treatment, if considering withholding prophylactic platelets, it is crucial to carefully assess the bleeding risk for individual patients by taking detailed bleeding history and examining for any bleeding and asking patients to report any new bleeding immediately. Use tranexamic acid where appropriate.