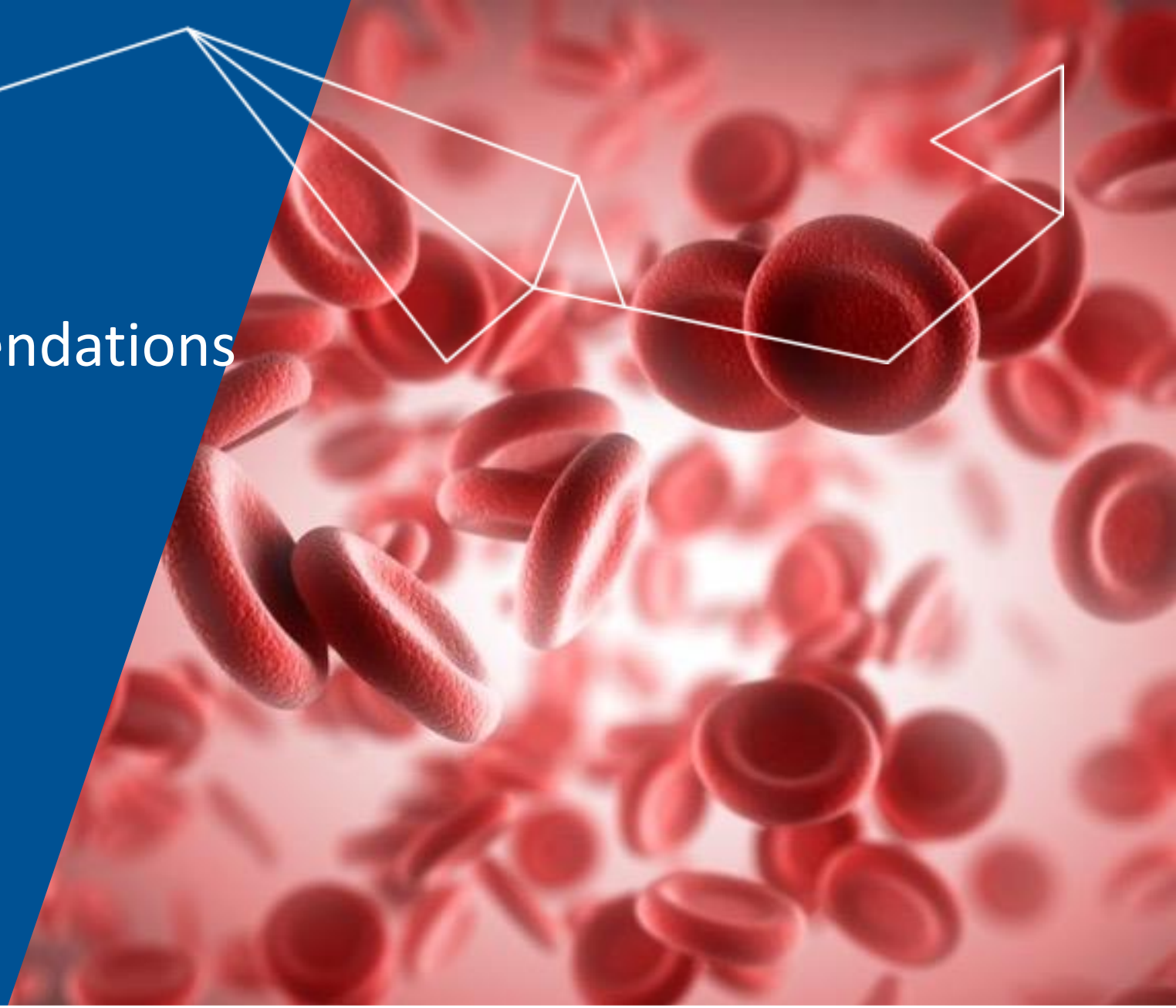
EUROPEAN HEMATOLOGY ASSOCIATION

Guidelines and Recommendations on the management and treatment of Chronic Neutropenias



Chairs: Helen Papadaki, Francesca Fioredda

1) G-CSF Indications: Congenital Neutropenia (CN) and Cyclic Neutropenia (CyN)

Statement 1

Overall, the panel considers that G-CSF treatment either in CN or in CyN might be beneficial because it reduces the frequency and severity of infection and improves the quality of life (reduced use of antibiotics, hospitalization and infection-related complications).

Consensus 100% yes

CN: congenital neutropenia; CyN: cyclic neutropenia; G-CSF: granulocyte colony-stimulating factor.

1) G-CSF Indications: Congenital Neutropenia (CN) and Cyclic Neutropenia (CyN)

Statement 2

The panel recommends the use of G-CSF in severe CN.

Consensus 100% yes

CN: congenital neutropenia; CyN: cyclic neutropenia; G-CSF: granulocyte colony-stimulating factor.

1) G-CSF Indications: Congenital Neutropenia (CN) and Cyclic Neutropenia (CyN)

Statement 3

The panel recommends the use of G-CSF in CyN, particularly in those with recurrent or severe infections.

Consensus 100% yes

CN: congenital neutropenia; CyN: cyclic neutropenia; G-CSF: granulocyte colony-stimulating factor.

1) G-CSF Indications: Congenital Neutropenia (CN) and Cyclic Neutropenia (CyN)

Statement 4

The panel does not recommend the use of G-CSF in ADAN due to the lack of infection propensity.

Consensus 100% yes

ADAN: ACKR1/DARC-associated neutropenia; CN: congenital neutropenia; CyN: cyclic neutropenia; G-CSF: granulocyte colony-stimulating factor.

1) G-CSF Indications: Chronic Idiopathic Neutropenia (CIN) and Autoimmune Neutropenia (AIN)

Statement 5

The panel does not recommend the continuous use of G-CSF, based only on the ANC, in patients with CIN or AIN.

Consensus 100% yes

AIN: autoimmune neutropenia; CIN: chronic idiopathic neutropenia; G-CSF: granulocyte colony-stimulating factor.

1) G-CSF Indications: Chronic Idiopathic Neutropenia (CIN) and Autoimmune Neutropenia (AIN)

Statement 6

The panel recommends an individual approach for patients with CIN or AIN and the final decision regarding continuous G-CSF should be based on the history and severity of infections rather than the ANC.

Consensus 100% yes

AIN: autoimmune neutropenia; ANC: absolute neutrophil count; CIN: chronic idiopathic neutropenia; G-CSF: granulocyte colony-stimulating factor.

1) G-CSF Indications: Chronic Idiopathic Neutropenia (CIN) and Autoimmune Neutropenia (AIN)

Statement 7

The panel encourages the use of G-CSF in the rare patients with CIN or AIN who present with frequent and/or severe infections. The panel also suggests evaluating the occasional use of G-CSF in CIN or AIN patients during severe infectious episodes.

Consensus 100% yes

AIN: autoimmune neutropenia; CIN: chronic idiopathic neutropenia; G-CSF: granulocyte colony-stimulating factor.

1) G-CSF Indications: Chronic Idiopathic Neutropenia (CIN) and Autoimmune Neutropenia (AIN)

Statement 8

The panel believes that the inability of the available studies to prove a clear survival benefit, improvement in quality of life or reduced infective complications in populations with CIN or AIN is because only a minority of those patients will need treatment with G-CSF.

Consensus 91% yes, 9% no

AIN: autoimmune neutropenia; CIN: chronic idiopathic neutropenia; G-CSF: granulocyte colony-stimulating factor.

2) Primary Goal of Treatment

Statement 9

G-CSF is able to enhance the ANC in almost 90% of neutropenia patients thus maintaining ANC over 1.0 x 10^9/L which is regarded as the threshold towards protection from infections. For CyN, the nadir may be lower, but should be as brief as possible.

(SDS is discussed separately)

Consensus 100% yes

ANC: absolute neutrophil count; CyN: cyclic neutropenia; G-CSF: granulocyte colony-stimulating factor; SDS: Schwachman-Diamond syndrome.

3) G-CSF Types

Statement 10

Filgrastim and lenograstim may be interchangeably used in patients with severe CN. Pegfilgrastim might be considered in cases of poor adherence to G-CSF treatment.

Consensus 100% yes

CN: congenital neutropenia; G-CSF: granulocyte colony-stimulating factor.

4) G-CSF DOSES and FREQUENCY

Statement 11

As a general concept, the panel suggests using the lowest effective dose of G-CSF for infection control (usually coinciding with ANC ≥ 1.0 x 10^9/L) and to minimize marrow stimulation and potential side effects (bone pain, splenomegaly).

Consensus 93% yes, 7% no

ANC: absolute neutrophil count; G-CSF: granulocyte colony-stimulating factor.

4) G-CSF DOSES and FREQUENCY

Statement 12

In CN the panel suggests initiating treatment with the standard dose of 5 µg/kg/day.

Consensus 94% yes, 6% no

CN: congenital neutropenia; G-CSF: granulocyte colony-stimulating factor.

4) G-CSF DOSES and FREQUENCY

Statement 13

In CyN G-CSF doses may be lower than CN. Standard dose should be ≤ 3 µg/kg/day. continuously. G-CSF may be given every other day. Dosage may be adjusted to avoid nadir <500 and clinical conditions such as mouth ulcers, fevers, or infections.

Consensus 94% yes, 6% no

CN: congenital neutropenia; CyN: cyclic neutropenia; G-CSF: granulocyte colony-stimulating factor.

4) G-CSF DOSES and FREQUENCY

Statement 14

In SDS and GSD1b particular attention should be paid to use minimal effective dose of G-CSF to prevent infections.

Consensus 100% yes

G-CSF: granulocyte colony-stimulating factor; SDS: Schwachman-Diamond syndrome.

4) G-CSF DOSES and FREQUENCY

Statement 15

In AIN and CIN, no studies have established what G-CSF dose to use. If G-CSF is needed, we suggest beginning at a low dose i.e. 1 µg/kg/day.

Consensus 93% yes, 7% no

AIN: autoimmune neutropenia; CIN: chronic idiopathic neutropenia; G-CSF: granulocyte colony-stimulating factor.

4) G-CSF DOSES and FREQUENCY

Statement 16

Neutrophil counts of > 5.0 x 10^9/L are usually not necessary to prevent infections. In patients with cyclic neutropenia higher ANC at peak can be expected.

Consensus 93% yes, 7% no

ANC: absolute neutrophil count; G-CSF: granulocyte colony-stimulating factor.

4) G-CSF DOSES and FREQUENCY

Statement 17

Sporadic therapy is reserved for those patients (mainly with AIN or CIN) who require a transient boost of the ANC but are generally infection-free without intervention.

Consensus 87% yes, 13% no

AIN: autoimmune neutropenia; ANC: absolute neutrophil count; CIN: chronic idiopathic neutropenia; G-CSF: granulocyte colony-stimulating factor.

4) G-CSF DOSES and FREQUENCY

Statement 18

Continuous *therapy is indicated for those patients persistently at risk of developing severe infections due to intrinsic/severe impairment of neutrophil production/ maturation.*

Consensus 80% yes, 7% no, not sure 13%

G-CSF: granulocyte colony-stimulating factor.

4) G-CSF DOSES and FREQUENCY

Statement 19

In G-CSF treated patients with AIN and CIN, the possibility of spontaneous remissions of the neutropenia, and hence no further need for GCSF treatment, should be taken into consideration by cautiously interrupting the treatment for 1-3 weeks

Consensus 87% yes, not sure 13%

AIN: autoimmune neutropenia; CIN: chronic idiopathic neutropenia; G-CSF: granulocyte colony-stimulating factor.

5) CORTICOSTEROIDS

Statement 20

The panel does not recommend the use of corticosteroids in any type of neutropenia as the lymphocytolytic effect may worsen propensity to infections.

Consensus 93% yes, 7% no

6) GRANULOCYTE TRANSFUSION

Statement 21

The panel considers that, at present, due to lack of knowledge on efficacy and possible side effects, granulocyte transfusions should not be considered as a therapeutic option for severe infections in any chronic neutropenia condition outside well designed clinical trials.

Consensus 86% yes, 14% no

7) SUPPORTIVE MEASURES: ANTIBIOTICS

Statement 22

Infections in neutropenic patients should be promptly evaluated as treatment with broad-spectrum antibiotics and hospitalization may be needed. The choice of antibiotics depends on the local policies, hospital bacterial flora, and antibiotic resistance patterns and possible known colonization of patient with specific microbes.

Consensus 100% yes

7) SUPPORTIVE MEASURES: PROPHYLACTIC ANTIBIOTICS

Statement 23

Based on lack of data on efficacy and risk of microbiological resistance, the panel suggests avoiding antibiotic prophylaxis in any type of neutropenia.

Consensus 87% yes, 7% no, not sure 7%

7) SUPPORTIVE MEASURES: DENTAL HYGIENE

Statement 24

Given the increased incidence of periodontal inflammation in severe CN and cyclic neutropenia, frequent periodontal examinations and maintenance of good oral hygiene is recommended. The panel suggests maintaining a target ANC of ≥ 1.0 x10^9/L for optimal dental health.

Consensus 87% yes, 13% no

ANC: absolute neutrophil count; CN: congenital neutropenia.

7) SUPPORTIVE MEASURES: PSYCHOLOGICAL SUPPORT

Statement 25

Psychological support is highly advisable in chronic neutropenia patients to improve quality of life.

Consensus 93% yes, not sure 7%

7) SUPPORTIVE MEASURES: PSYCHOLOGICAL SUPPORT

Statement 26

Special support and rehabilitation programs for patients with neurodevelopmental disabilities is suggested.

Consensus 100% yes

7) SUPPORTIVE MEASURES: VACCINATION

Statement 27

Subjects affected with chronic neutropenia in whom underlying T-cell, B-cell, and NK-cell immunodeficiency/dysregulation have been ruled out, should receive all routine inactivated and live attenuated vaccines according to specific national schedules.

Consensus 100% yes

NK: natural killer.

7) SUPPORTIVE MEASURES: VACCINATION

Statement 28

Consultation with an immunologist is indicated in neutropenic patients with an underlying immunodeficiency.

Consensus 100% yes

7) SUPPORTIVE MEASURES: VACCINATION

Statement 29

All patients with chronic neutropenia should be advised to receive an approved influenza and COVID-19 vaccine.

Consensus 100% yes

7) SUPPORTIVE MEASURES: VACCINATION

Statement 30

Whenever possible, it is worth considering immunization of close contacts of a patient with neutropenia against all vaccine preventable diseases.

Consensus 100% yes

8) HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Statement 31

The panel suggests carefully evaluating the pros and cons of HSCT, tailoring the decision on an individual case basis and sharing the decision with the patient/family. The expertise of the Center in performing HSCT and in managing CN patients is an important consideration in the final decision.

Consensus 93% yes, 7% not sure

CN: congenital neutropenia; HSCT: hematopoietic stem cell transplantation.

8) HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Statement 32: Strong indications for HSCT include

1) Established transformation to MDS/AML or BM dysplastic features with high-risk acquired cytogenetic abnormalities (monosomy 7, trisomy 8, trisomy 21) or with a combination of acquired leukemia-associated somatic mutations (e.g. RUNX1, ASXL1, SETBP1). CSF3R mutations alone are not an indication for HSCT. 2) CN due to mutations carrying an intrinsic high risk of leukemic transformation per se i.e., GATA2 mutations, high-risk ELANE mutations, or clones with biallelic TP53 mutations in SDS. 3) No response to G-CSF (doses >20 µg/kg/day to reach ANC 1.0 x10^9/L), poor response to G-CSF (doses between 10 and 20 µg/kg/day failing to reach ANC of 1.0x10^9/L) or poor control of infection irrespective of the G-CSF dose.

Consensus 100% yes

AML: acute myeloid leukemia; ANC: absolute neutrophil count; BM: bone marrow; CN: congenital neutropenia; G-CSF: granulocyte colony–stimulating factor; HSCT: hematopoietic stem cell transplantation; MDS: myelodysplastic syndrome .

8) HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Statement 33: Potential indications to HSCT

Adequate management of infections with G-CSF at "intermediate doses" (10 µg-15 µg/kg/day) with availability of a healthy HLA-identical sibling or HLA identical matched donor.

Consensus 93% yes, 7% no

G-CSF: granulocyte colony–stimulating factor; HLA: human leukocyte antigen; HSCT: hematopoietic stem cell transplantation.

8) HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Statement 34: Weak indication to HSCT

G-CSF response at doses up to 10 µg/kg/day, good tolerability and compliance to daily subcutaneous injections, infections control and unavailability of HLA-matched donors.

Consensus 100% yes

G-CSF: granulocyte colony–stimulating factor; HLA: human leukocyte antigen; HSCT: hematopoietic stem cell transplantation.

Thank you

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