Diagnosis and management of neutropenia in children: consensus audit of the "Associazione Italiana Ematologia Oncologia Pediatrica" (AIEOP) experts

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Abstract

SUMMARY Neutropenia is a generic term that indicates a reduction of neutrophils below the threshold for age and race. This condition encompasses a number of diseases with a wide range of duration and severity. In the present paper, the approach to diagnosis and treatment of neutropenia has been reviewed and implemented with the knowledge acquired during the last decade, by a group of experts, 10 years after the first publication. The diagnostic itinerary highlights the most important tools available to define the type of neutropenia and updates the list of genes causative of the disease. In addition, the present paper underlines the progresses towards a better definition of "primary autoimmune neutropenia" without remission which often hides different diseases. Moreover, indications on how to speed up neutropenia diagnosis and the indications to perform the bone marrow examination in the genetic forms, are given. The management and treatment of the "well-known" diseases and "special situations" are also reviewed giving literature derived and expert opinion-based suggestions tailored on the single patient/diagnosis.

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Table IV G-CSF therapy and doses according to neutropenias diagnosis

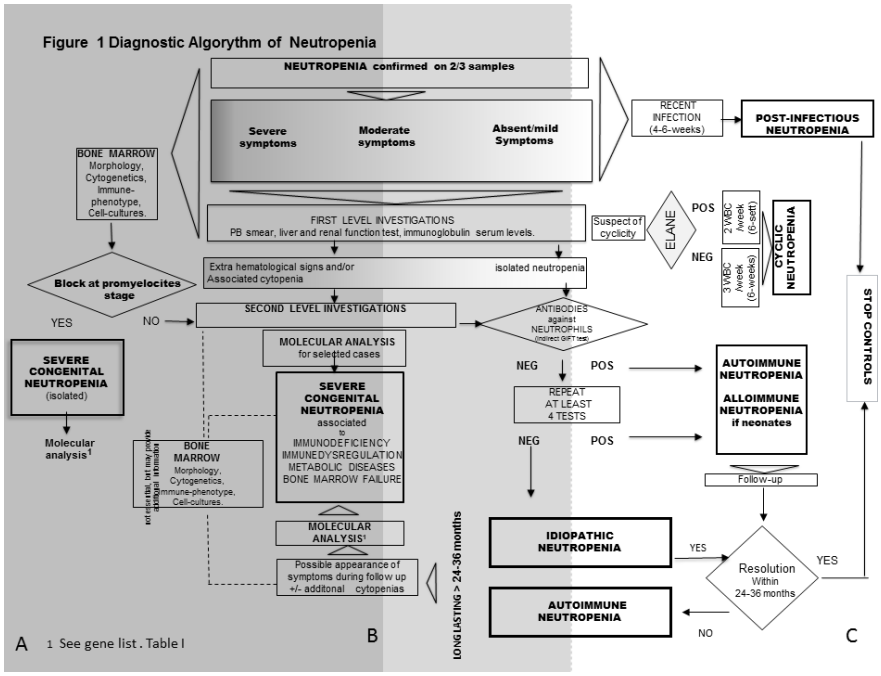
Np Type	Starting dose	Primary goal ANC between 1.0 x 10^9/L and 5.0 10^9/L	Increasing dose if ANC< 1.0x10^9 /L	Lowering dose if ANC >5.0x10^9	Special situation
SCN	5 γ/kg/day *EO 8.4B*	If reached within 5-7 days mantain starting dose. *EO 9A*	After 7days increase of 2.5 γ/kg/day every 5-7 days. *EO8.4B*	G-CSF has to be lowered empirically in any type of neutropenia with ANC >5.0x10^9. *EO 8.8 B*	In case of torpid or severe infections in any type of neutropenias, increase of G-CSF depends on patient clinical conditions. *EO 8.6 B*
CyN	2 γ/kg/day *EO 8.1B*	If reached within 2-4 Np phases maintain starting dose. *EO 8.3B*	After the next neutropenia phases increase of 2γ/kg/day every 2-4 np phases. *EO 8.1 B*		
GSD 1b	1-3 γ/kg/day *EO8.3B*	If reached within 5-7 days mantain starting dose. *EO 8.7 B*	After 7days increase of 2 γ/kg/day every 5-7 days. *EO 8.4 B*		
SDS	1-3 γ/kg/day *EO7.8 B*	If reached within 3-5 days mantain starting dose. *EO 8.4B*	After 5 days increase of 2γ/kg/day. *EO 7.5 B*		
IN and AN	1-3 γ/kg/day *IN EO8.3B AN EO 8.6B*	If reached within 5-7 days mantain starting dose. *EO8.8B*	After 7 days increase of 1-2γ/kg/days. *EO8.7B*		

Table V Type and timing of controls according to the different type of neutropenia even during G-CSF treatment

The consensus was assessed for any statement and the votes were all 8 or 9 B/C. Only the scores that were different are included in the table and in the legend.

	Full blood count	Biochemical[1] parameters	Bone marrow[2]	Abdomen Ultrasound Scan	Bone density	Further consideration
SCN G-CSF	At least 3/y	At least every 2/y months.	Every 12-18 months[3].	12 months *EO 7.9 C*	12-24 months.	If morphological dysplasia or any abnormal cytogenetic clone during follow up occurs, repeat bone marrow more frequently[4]. If an isolated mutation of G-CSF-r without RUNX1 associate mutation occurs, repeat bone marrow analysis every 12 months [5]. If CSFR3 clone is associated to RUNX1 mutation the follow up has to be tailored on single case . HSCT may be a recommended .
CyN G-CSF	At least 3/y	At least 1/y.	Not indicated routinely.	12 -24months.	24 months.	-----
AN/IN G-CSF Treated Continuously	IN G-CSF Treated At least 3/y	At least every 3 (IN) or 2 (AN)/y.	At least once (AN) Suggested periodically (IN).	12 -24months. *EO 7.7 D*	24 months.	If neutropenia is persistent and strongly suggestive of AN repeat indirect antibodies against muetrophils even to define a ID (at least 4 times) .If a spontaneous resolution of neutropenia does not occur after standard time, consider to perform an enlarged panel of autoimmunity[6].
AN / IN/ Cy Without G-CSF therapy	At least 3/y	Not indicated except CyNp at least 1/y.	Not indicated routinely see the clinic.	-----	---------	In both AN and ID lasting more than 36 months or with a delayed onset (>5 years) think of immune deficiency/dysimmunity and perform Genetic test for PID according to the availability of the center.

Legend to Tab V
1 Biochemical parameters (hepatic and renal function, ALP, LDH uricemia, hemoglobin F (in case of neutropenia at risk of transformation to mds/aml) and urine analysys
2 Bone marrow analysis for morphology, cytogenetics, FISH cr 7 and 8, immunophenotype and marrow biopsy (according to the each centre policy)
3 G-CSF receptor mutation and RUNX 1 analysis on bone marrow aspirate every 12 months ***(EO, 8,4, B).***
4 Bone marrow aspiration for morphology, cytogenetics, FISH cr 8 and 9, ***(EO, 9, A)*** Haemotopietic stem cell transplantation procedures must be activated .
5 Bone marrow aspiration: morphology, cytogenetics, FISH cr 8 and 9 and immunophenotype In this case, if an identical sibling is available, HSCT has to be considered.
6 Enlarged panel of autoimmunity has to be done periodically and includes tests for thyroiditis, celiac disease and autoimmune lymphoproliferative syndrome-ALPS.



Keys to Figure 1

The degree of severity is depicted according to the grey nuance of the background. The dark side on the left indicates the highest degree of severity whereas the lighter the least severe situation (from A to C).
The experts suggest for diagnosis to proceed according to three main scenarios :

A) When neutropenia (prefentially ANC< 500/cmm), either isolated or associated to any signs of complex syndromes, is accompanied with severe (namely sepsis , meningitis, osteomyleitis, deep abscesses /flemmons or pneumonia) or recurrent/torpid infections (i.e. otitis, masthoiditis, skin abscesses, urinary tract infections, enteritis) and appears in early infancy (< 1 year of age), the panel suggests to confirm ANC count (2 or 3 times according to the severity), to perfom the first level investigations and the bone marrow examination. If a block at promyelocytes leve is identified, a targeted genes analysis is suggested.

B) When neutropenia, once confirmed, is patently associated to signs or symptoms (i.e. deficiency of lymphocyte subset(s)) a targeted route has to be taken. When phenotype is suggestive for associated conditions, molecular analysis may be performed even before bone marrow examination.

C) When neutropenia is found by chance, neither accompanied by clinical signs nor symptoms or previous history of infections, it has to be confirmed at least on 3 samples performed not more frequently than one week apart (e.g one test evrey week forthree weeks). The panel suggests to perfom first level investigations followed by search of antibodies against neutrophils. The diagnosis will be probable Autoimmune or Idiopathic Neutropenia. Re-evaluations are periodically needed in case of long lasting neutropenia (longer than 24-36 months)

A peculiar diagnsis usually belonging to the mild phenotype classification is the so called « cyclic neutropena» which by definiton has a tipical oscilaltion of ANC reaching the nadir values every 21-28 days. Mutations in *ELANE2* gene have been found associated in 60 % of cases. The confirmation of ciclicity has always to be proven by repeating ANC more frequently (3 ANC/week for 4-6 weeks) in subjects in whom no genetic lesion is found and in patients in whom an *ELANE2* gene mutation is found (2 times/week for 4-6 weeks)

* Every procedure has to be fastened when the cinical picture is very severe since the beginning or get worse over time