ERN-EuroBloodNet

European Reference Network on Rare Hematological Diseases

Care Pathways

2. CLINICAL CARE

2.1.3. (Core) The ERN has developed recommendations for care pathways based on the needs of patients, clinical evidence, and on the available organizational, professional, and technological resource

Supporting Document 16. List of care pathways recommendations developed

2.1.4 (Extended) The ERN has worked on recommendations for cross-border care pathways to ensure equality in the access to care within its area of expertise, according to the legislation applicable

Supporting Document 17. Recommendations for care pathways including cross-border elements developed

2.1.5 (Extended) The ERN follows up the implementation of care pathways to encourage consistent use across its Members

Supporting Document 18. Results of the follow-up of the implementation of care pathways

INTRODUCTION

Care pathways may serve as useful and evidence-based tools to reduce variations in clinical practice and improve quality and outcomes of healthcare interventions. Care pathways incorporate clinical guidelines in that the latter are embedded into the pathway itself. However, their development and Implementation at the EU level Is challenging due to differences in the 27 EU-MS National Health systems. This Is especially true when It comes to Highly specialized procedures (HSP) for rare disorders.

HSP are defined in the context of the network as those procedures that, for a number of reasons e.g. economical, lack of expertise or awareness, are not available at the same level in all EU-MS. HSP are usually core elements of the available Clinical Practice Guidelines (CPG) or other Clinical Decision Making Tools (CDMT), involving interventions for prevention, diagnosis and treatment. Their complexity can rely on technological advances or multidisciplinary team expertise of multidisciplinary team, or both. In the worst scenario, a HSP may not be available at all in a given country, thus requiring of cross-border health delivery.

METHODOLOGY

ERN-EuroBloodNet Identified a first group of 5 RHD for which important variations in clinical practice across Europe is anticipated although the existence of a CPG or other CDTM. For each disorder, main clinical areas of assessment were defined based on minimal requirements (standard of care) and HSPs related (Table 1). The performance of diagnosis of Pyruvate Kinase Deficiency, and performance of Transcranial Doppler and bone marrow transplant as HSPs in Sickle Cell Disease were targeted as first priorities for the conduction of three European mapping exercises.

In the specific case of bone marrow transplant it was agreed by experts to expand the mapping exercise to non-oncological disorders.

Moreover, the establishment of a cross-border bilateral agreement was initiated between two ERN-EuroBloodNet members from Italy and Ireland, for the performance of bone marrow transplant for SCD pediatric patients as a HSP for these population.

Disease/condition selected	**Pyruvate kinase deficiency (PKD)**	**Sickle Cell Disease (SCD)**	**HFE-hemochromatosis**	**Anemia due to genetic disorders of iron metabolism and heam disorders**	**Myelodysplastic syndromes (MDS)**
CPG and other CDMT selected	Addressing the diagnostic gaps in pyruvate kinase deficiency: Consensus recommendations on the diagnosis of pyruvate kinase deficiency	ENERCA clinical recommendations for disease management and prevention of complications of sickle cell disease in children	Key-interventions derived from three evidence based guidelines for management and follow-up of patients with HFE haemochromatosis	Practice guidelines for the diagnosis and management of microcytic anemias due to genetic disorders of iron metabolism or heme synthesis	Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet
Why this disease/CPG/CDMT have been selected for assessment of implementation?	PKD patients are undiagnosed /misdiagnosed due to the lack of facilities or expertise. In some countries, they are likely to not being genotyped due to economical shortages in the national health systems.	Although international guidelines exist for SCD holistic clinical care they are not completely implemented across EU due to: a) budget limitations, b) drug availability, c) lack of disease awareness and/or standard health care policies and d) lack of adequate health professionals training.	Key interventions for HFE - hemochromatosis have been developed and published by a team from Belgium and the Netherlands. Outcome parameters need to be discussed in ERN team; evidence based guidelines and clinical outcome parameters for the more rare forms of HH need to be developed and discussed	Currently the only evidende based guidelines on the topic; guideline developed by a multidisciplinary team of Dutch (only) professionals from different hospitals in the Netherlands. More specific and SMART defined outcome parameters should be defined and discussed for all 14 diseases of the guideline.	Cytogenetic analysis represents a mainstay for diagnosis and risk assessment and should be available for any patient with MDS. Erythropoiesis stimulating agents, lenalidomide, azacititine and allogeneic stem cell transplantation are the standard of care for patients with MDS. Somatic mutation analysis through NGS and clinical trials should be available.
Clinical areas of assessment: It would be preferable to have some pointing to the minimal requirements (standard of care) and 1 or 2 related to highly specialized procedures. They should ideally cover several areas	1. PKD Diagnosis activity – Part A PK enzyme activity	1. Newborn screening	1. Screening of first degree relatives of patients	1. Diagnosis within 6 months after presentation	1. Cytogenetic analysis
	2. PKD Diagnosis activity – Part B PKLR genetic analysis	2. Vaccination (meningococcus, streptococcus pneumoniae, capsulated cocci)	2. HFE-gene testing when both TSAT and ferritin are increased	2. Screening of family members	2. Erythropoiesis stimulating agents for lower risk MDS
	3. Availability of genetic counselling for PKD	3. Antibiotic prophilaxis until 5 ye at least	3. Phlebotomise (bi) weekly when ferritin are increased to target ferritin between 50 and 100 ug/l	3. Timely start of treatment	3. Lenalidomide for lower risk MDS with del 5q
	4. Availability of prenatal diagnosis for PKD	4. Transcranial Doppler starting at 2 ye	4. Patients with suspected overlaod: TSAT and ferritin testing, and only HFE testing when TSAT is increased		4. Azacitidine for high risk MDS
		5. Availability of Hydroxyurea treatment	5. liver, heart, endocrine organs, joints screening before phlebotomy patients		5. Allogeneic stem cell transplantation for high risk MDS
		6. Bone marrow transplantion			6. Mutation analysis by next generation sequencing
					7. Access to clinical trials

Table 1. RHD identified for assessment of variations in clinical practice across Europe.

RESULTS

PERFORMANCE OF DIAGNOSIS FOR PYRUVATE KINASE DEFICIENCY (PKD) ACCORDING TO AVAILABLE RECOMMENDATIONS

Pyruvate kinase deficiency (PKD) is an ultra-rare chronic hereditary hemolytic anemia of variable severity, ranging from mild anemia to life-long transfusion dependence. Lack of standardized diagnostic procedures combined with a low prevalence results in a significant number of undiagnosed or misdiagnosed patients.

The aim of this study was to assess the distribution of PKD patients in Europe in order to better understand variability on PKD diagnosis performance.

The study was conducted through RADeep, which is endorsed by ERN-EuroBloodNet. Up to 145 centres dealing with RADs from 16 European countries were included in the study. Data on PKD patients in follow-up was requested, stratified by age range, adult and paediatric (<18) and by severity according to two main variables: splenectomy and regular transfusion, which was defined as >6 transfusions per year. Data on number of diagnosis in the last 25 years was requested only from diagnostic centres. Data was correlated to a country's total population (2020). Based on highest frequency, estimations were calculated for the expected number of PKD patients in all participating countries.

Data on 499 PKD patients in follow-up and 611 diagnosed PKD patients retrieved from 84 medical centres from 15 European countries is shown on figure 1. Highest frequency for both PKD patients in follow-up and PKD diagnosis was found in Denmark, respectively 4,47 and 4,81 per million. This is in line with previous published data on PKD prevalence, with estimations ranging between 3,2 and 8,5 per million. Based on the PKD diagnosis frequency in Denmark, we calculated the expected number of PKD patients in the rest of participating countries. Results showed an expected number of PKD patients of 1.995, meaning that our study is covering on average 25% of PKD patients in follow-up and 31% of diagnosed PKD cases. Important differences on PKD patients in follow-up coverage are found among countries, from 63% in France to less than 25% in most of participating countries. Diagnostic coverage was highest in the Netherlands, France and Portugal. According to stratification of PKD patients based on severity, 267 adult patients were stratified as follows; 18% splenectomised on regular transfusion, 4% non-splenectomised on regular transfusion, 43% splenectomised on occasional or non-transfusion and 35% non-splenectomised on occasional or non-transfusion. Finally, % of PKD patients genotyped was found to be on average 90% and 86% for adults and pediatrics respectively (range 20-100%).

National recognition of centres of expertise for PKD for follow-up (i.e. France), centralized diagnosis (i.e. Netherlands) and/or existing registries (i.e. France, Netherlands, Denmark) dramatically improve disease coverage. Therefore, important efforts are needed in most other European countries to improve PKD diagnosis and follow-up rates.

> This study clearly shows the need to improve and standardize PKD patients' pathway at the national level across Europe in order to ensure adequate and timely diagnosis, and proper access to best treatment for any PKD patient.

Figure 1. European distribution of PKD patients and estimations on expected number of PKD patients based on reference frequency

Country	Population	Nº Centres	Nº PKD patients follow-up	Frequency PKD patients follow-up per million	PKD diagnosis last 25 years	Frequency PKD diagnosis last 25 years per million	Nº Expected PKD patients based on reference frequency	% PKD patients follow-up vs Expected PKD	% PKD diagnosis vs Expected PKD
DK	5.822.800	3	26	4,47	28	4,81*	28	93%	100%
LT	2.794.100	1	2	0,72	2	0,72	13	15%	15%
IE	4.963.800	1	7	1,41	0	0,00	24	29%	0%
FI	5.525.300	1	2	0,36	0	0,00	27	8%	0%
PT	10.295.900	6	21	2,04	25	2,43	50	42%	50%
SE	10.327.600	3	5	0,48	2	0,19	50	10%	4%
CZ	10.693.900	3	11	1,03	21	1,96	51	21%	41%
GR	10.709.700	3	6	0,56	0	0,00	51	12%	0%
BE	11.549.900	6	11	0,95	27	2,34	56	20%	49%
NL	17.407.600	5	30	1,72	66	3,79	84	36%	79%
ES	47.330.000	17	55	1,16	103	2,18	228	24%	45%
IT	60.244.600	12	52	0,86	104	1,73	290	18%	36%
UK	67.025.500	5	31	0,46	7	0,10	322	10%	2%
FR	67.098.800	8	203	3,03	167	2,49	323	63%	52%
GE	83.166.700	10	37	0,44	59	0,71	400	9%	15%
Total	414.956.200	84	499	1,20	611	1,47	1.995	25%	31%

PERFORMANCE OF TRANSCRANIAL DOPPLER (TCD) SCREENING FOR STROKE PREVENTION PROGRAMS SICKLE CELL DISEASE (SCD) CHILDREN

Children with sickle cell disease (SCD) are at increased risk of cerebrovascular events such as stroke, silent infarcts and neurocognitive impairment. The role of Transcranial Doppler ultrasound scanning (TCD) to identify sickle cell anemia (SCA) children at high risk of stroke is well established. Adam et al in 1998 recommended those with abnormal cerebrovascular flow velocities are offered prophylactic blood transfusion therapy to prevent stroke between ages 2 to 16 years. Therefore, TCD screening for stroke prevention in now is a mandatory in all guidelines for the management of children with SCA. However, there is still no uniform implementation of the program globally and in European countries. Moreover, the information available on the quality of the TCD screening is limited to educational experiences in a few countries but to evaluation of stroke prevention programs has been performed in Europe. As more disease modifying therapies become available for children with SCD, it is mandatory to know TCD availability, screening practices, and real-world data on stroke prevention in Europe.

The aim of this study was to assess the state of the art of TCD screening and stroke prevention programs in European Expert Centers.

An online survey was developed by SCD experts in 5 European countries and sent to all Representatives of the Health Care Providers (HCP) and the Red Cell Disorder representatives in each HCP within the EuroBloodNet network, as well as to National Representatives of Scientific Societies within European Countries.

81 hematologists or pediatricians from 77 centers in 16 European countries responded to the survey (14/16 in Western Europe); 39/77 (51%) were EuroBloodNet Expert centers, 14/77 (18%) were under evaluation as being recognized; 67/77 specified their expertise: 24% were pediatric, 3% adult, 58% both; 12 centers had >200 patients in the age range 1-16 years.

36% Physicians reported not having a dedicated TCD/TCDi service for children with SCD so exams had to be performed by cardiologists (10%), general radiologists (28%), TCD is not performed (31%), or patients have to be sent in another center (31%). 74% reported requesting annual TCD for their patients, but to the question "What percentage of your patients receives annual TCD" only 28% confirmed that all their patients managed to actually receive annual TCD, due to lack of trained staff (43%), lack of TCD instruments (11%), refusal of patients due to logistical difficulties (22%) (i.e TCD in another city), lack of funds for dedicated staff or equipment (11%), or other reasons.

Only 74% of hematologists were aware of the protocol in use at their center by the staff performing TCD; the STOP criteria were applied by 64% of the physicians, mainly due non evaluation of the Internal Carotid Artery. The extracranial part of the carotid artery was evaluated only in 30% of the respondents.

In case of abnormal/conditional TCD results, the approach varies and is not uniform across centers.

Our data show that less than 30% of children with SCD followed in European Centers receive annual TCD according to recognized guidelines.

> “This first multinational European survey allowed the identification of issues related to the lack of access to TCD, lack of trained staff, lack of adequate protocols for implementation of TCD and treatment afterwards, which will need to be addressed through dedicated care pathways.”

The abstract "Limited Access to Transcranial Doppler Screening and Stroke Prevention for Children with Sickle Cell Disease in Europe: Results of a Multinational Eurobloodnet Survey" presenting the results from the mapping was selected to be presented during the American Society of Hematology (ASH) 2021 edition for an oral presentation provided. A peer review publication is under preparation.

PERFORMANCE OF BONE MARROW TRANSPLANT IN SICKLE CELL DISEASE (SCD) AND OTHER NON-ONCOLOGICAL CONDITIONS.

Bone marrow transplant Is a highly specialized procedure, standard of care as unique curative treatment for severe non-oncological conditions. Its performance requires of specific multidisciplinary teams trained In non-oncological disorders.

A survey was designed in order to assess diseases for which the respondent consider the BMT for the correct management of the patients, analyze for which non-malignant RHDs and patients' age the respondent's center offers the BMT, and assess if referrals to other centers are ever considered when necessary and if a standardized procedure is in place in such cases.

A total of 18 answers from 14 countries were gathered. Comparison between need for BMT per disease declared by the centres and availabilty of BMT is shown in Table 2.

Comparison BMT need / BMT availability			
	Need	**Availability**	**Difference**
SCD	70,4%	48,1%	22,2
THAL	74,1%	59,3%	14,8
METAB	48,1%	44,4%	3,7
AA	77,8%	74,1%	3,7
ID	51,9%	59,3%	-7,4

Table 2. Comparison between need for BMT per disease declared by the centres and availabilty of BMT. SCD: Sickle cell disorders, THAL: Thalassaemia syndromes, METAB: Metabolic Disorders, AA: Inherited or acquired aplastic anemia, ID: Immune Deficiencies

As a result of the analysis, SCD is the condition for which the availability of BMT (48,1%) is the lowest, 22,2 points below the need (70,4%), followed by Thalassaemia syndromes in which availability of BMT (59.3%) is 14,8 points below the need (74.1%). In 7 centres which consider BMT for SCD patients, the procedure is not available, 5 of them belonging to the red blood cell subnetwork. From the 7 centres, 6 confirmed that they refer patients to another centre, 5 in the same country and one abroad. However, only 2 have a standardised procedure for referral of patients, being one of the two the centre referring patients abroad.

> This study showed the need to establish national care pathways for adequate delivery of bone marrow transplant in sickle cell disease in a timely and standardized manner as well as the establishment of cross-border agreements in concrete cases.

BILATERAL AGREEMENT FOR BONE MARROW TRANSPLANT (BMT) FOR SICKLE CELL DISEASE PEDIATRIC (SCD) PATIENTS BETWEEN TWO EUROPEAN MEMBER STATES: CHALLENGES AND BARRIERS

A proposal to standardize the referral of patients with SCD and an HLA matched sibling donor from two ERN-EuroBloodNet members from Dublin to Padova for BMT was performed in 2019, and multiple steps in the process undertaken including: letter of Intent from both institutions, Dublin Team visit to Padova to agree on the Medical and Logistic Protocols and approval of the agreement by the Regional Health Authority of the Veneto Region.

Major challenges and barriers found during the process were: a) Financial barriers: accomodation was not covered by the E11 module, b) The translation for patients speaking a language that is different from the hosting country is not covered, c) Different reimbursement procedures for countries and d) Different costs in the countries involved.

> Due to the delay in activating the final steps of the agreement and the insurgence of the COVID-19 Pandemic, further discussion was made in Ireland to allow on site BMT for patients with SCD. Therefore, although the agreement was eventually not finalized, discussions and round tables between Irish and Italian experts promoted by ERN-EuroBloodNet, served as a driving force to obtain previous unavailable treatment to Irish patients.

https://ec.europa.eu/health/ern_en

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As of the 1st of April 2021 the Consumers, Health, Agriculture and Food Executive Agency (CHAFEA) ceased to exist. The portfolio of actions managed by CHAFEA under the 3rd HP was transferred to the Health and Digital Executive Agency (HaDEA).