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Perspective
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The EHA Research Roadmap: Anemias

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In 2016, the European Hematology Association (EHA) published the EHA Roadmap for European Hematology Research[1] aiming to highlight achievements in the diagnostics and treatment of blood disorders, and to better inform European policy makers and other stakeholders about the urgent clinical and scientific needs and priorities in the field of hematology. Each section was coordinated by one to two section editors who were leading international experts in the field. In the five years that have followed, advances in the field of hematology have been plentiful. As such, EHA is pleased to present an updated Research Roadmap, now including eleven sections, each of which will be published separately. The updated EHA Research Roadmap identifies the most urgent priorities in hematology research and clinical science, therefore supporting a more informed, focused, and ideally a more funded future for European hematology research. The eleven EHA Research Roadmap sections include Normal Hematopoiesis; Malignant Lymphoid Diseases; Malignant Myeloid Diseases; Anemias and Related Diseases; Platelet Disorders; Blood Coagulation and Hemostatic Disorders; Transfusion Medicine; Infections in Hematology; Hematopoietic Stem Cell Transplantation; CAR-T and Other Cell-based Immune Therapies; and Gene Therapy.

Anemia is still the most common disease among the world population, and it affects 1.6 billion people worldwide.[2] In various ages of life, it seems to be particularly prevalent: childhood, females of childbearing age, and old age. In most cases, these are anemias due to acquired causes, while cumulatively the hereditary causes make up about 7% of the total.

Among these, thalassemias and other hemoglobinopathies have acquired considerable importance in Europe in consideration of the globalization and the arrival of immigrants from regions with a significant incidence. For these reasons, one of the problems of public health in many European countries is represented by these pathologies which require transfusion interventions and management of chronic and acute pathologies.

One of both today's and future goals of these pathology treatments is represented by precision diagnostics, considering that it is no longer enough to identify the causative gene only, but the identification of the cohort of genes that significantly modify the phenotype is mandatory mainly for the outcome definition (Figure 1).

A particular emphasis is given to the search for new effective therapies in hereditary diseases. Among them were new stem cell transplantation techniques and new approaches such as gene therapy and genome editing, which allow to solve the problem of transplant rejection and the scarcity of donors.

The consequences of morbidity associated with chronic anemia extend to loss of productivity from impaired work capacity, cognitive impairment, increased susceptibility to infection, and in the elderly, a huge contribution to comorbidities, which

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exerts a very substantial economic burden on healthcare systems.[3] Nevertheless, anemia frequently goes unrecognized and untreated, causing high direct and indirect costs at both the individual and national levels.

Healthcare services in these countries have to deal with increasingly culturally diverse populations. It is noteworthy that, due to the immigrant movements in Europe, there is a new epidemiology of acquired and inherited anemias.[4] It is important for planning for health intervention to know exactly the distribution of the different form of anemia in each country. To carry out this, it appears mandatory to have European guidelines for diagnosis and establish a common and more sustainable therapeutic approach.

Moreover, clinical trials on new drugs and therapeutic procedures could ameliorate the quality of patients affected with the diseases, mainly in the inherited form, and enhance the quality of their life and life expectancy.

Coordinated efforts should be made to develop strategies for prevention of acquired and inherited anemias in individuals at risk in Europe. Detailed epidemiological studies in all countries, especially western countries, are a prerequisite for the implementation of effective prevention programs.

For a correct diagnosis is mandatory to have a shared diagnostic flowchart for each of the main form of anemias. Thus, the development of new tools to reliably diagnose anemias is urgently needed and fits well with the needs of personalized medicine. We expect that the development of such a diagnostic tool will improve timely diagnosis throughout Europe, especially in those countries where it is difficult to gain access to "classical" diagnostic tests.

In the last 15 years, hematology research has made a big leap forward. The emergence of sophisticated genetic and molecular tools (ie, next-generation sequencing [NGS] technique) allowed spectacular progresses in our understanding of the structure and function of the blood cells in health and disease. Our general aim will be to solve several hematologic problems using these new approaches.[5,6]

Research on rare genetic iron-related diseases that are informative biological models may contribute to further understanding of iron metabolism. Their precise diagnosis might lead to avoid unnecessary and costly diagnostic tests and possibly harmful treatments.

New technologies for anemia and related disorders

Where we are now

Anemia, defined as a decreased amount of hemoglobin, can result from blood loss but also from decreased synthesis of hemoglobin, decreased erythrocyte (RBC) production, or increased RBC destruction. The clinical cost and socio-economic impact of these disorders is tremendous. Anemia of inflammation (AI), chronic kidney disease (CKD), myelodysplastic syndromes (MDS), hemolytic anemias, and some forms of BM failure represent a growing and pressing medical and socioeconomic issue in Europe. Children affected by hemoglobinopathies require long-life transfusion for survival but, eventually, a considerable morbidity develops leading to a decreased lifespan.

Clinical management includes administration of anti-inflammatory molecules in AI, erythropoiesis-stimulating agent and iron in CKD, blood transfusion, administration of hematopoietic growth factors, low-intensity chemotherapy, and BM transplantation in MDS. Hemoglobinopathies represent the most frequent disorder worldwide, with at least 300,000 children born with these disorders every year. Clinical management has been focusing on supportive therapy such as blood transfusion, iron chelation and management of pain. Recently, a novel drug, Reblozyl (luspatercept-aamt) that modulates TGFβ-like pathways and improves RBC synthesis as well transfusion regimen, and has been approved for the treatment of β-thalassemia and MDS. BM transplantation has also been utilized as a definitive, although not without risk, curative option. Additional anemias are due to dietary limitation, such as folate, vitamin B12, and ID, while others are due to infections or exposure to toxic agents.

Plans for the future

Advances have been made in our understanding of molecules and pathways that could be targeted to improve anemia. B-cell-CLL/lymphoma-11A (BCL11A) modulates the production of fetal hemoglobin (HbF), is an important modifier of clinical severity in β-globinopathies.[7] Furthermore, small molecule inhibitors inducing HbF, such as epigenetic enzymatic inhibitors, or directly inducing HbF or targeting transcription factors, are currently being evaluated for their therapeutic efficacy.[8] Molecules that control dietary iron absorption in the gut and hepcidin production in the liver, such as ferroportin (FPN), transferrin, erythroferrone (ERFE) and type-two transmembrane-serine-protease (TMPRSS6) have also been investigated for their contribution to iron overload and anemia in β-thalassemia.[9] Gene therapy either via gene addition of β-globin[10] or γ-globin gene[11] and gene editing approaches have been introduced as realistic alternatives to treat β-globinopathies.

Drugs that limit iron absorption and improve anemia are showing very promising results in preclinical studies.[12] Additional drugs that target oxidative stress (like peroxiredoxin-2 agonists) and erythroid cell metabolism (like Glycine Transporter Type I Inhibitor or Pyruvate kinase agonists) are being investigated. Preclinical studies indicate that combinatorial therapies could further improve anemia.[13] Gene therapy and gene editing trials for the cure of β-thalassemia and SCD show very promising results.[7] These approaches are now waiting for the development of nontoxic myeloablative regimens. Genetic variability will likely influence the efficacy of these new therapeutics or therapies. For this reason, we recommend:

- The use of next-generation (-omics technologies) to assess the role of genetic makeup of the patients, modifiers, and environment, leading to personalized treatment for each individual *affected by hereditary anemias*.[14]
- To invest in these new lines of investigations and technologies to validate their potential, and transform them into effective and safe ways of treatment (Figure 1).

Efforts to develop new scientific discoveries and therapeutics can have a major impact, at multiple levels on the growing and aging population in Europe. Moreover, many additional incurable disorders could benefit from the development of gene therapy and gene editing technologies designed for β-thalassemia, SCD, and many other diseases that require management of RBC production.

Iron deficiency anemia

Where we are

Iron deficiency anemia (IDA) is the most common form of anemia worldwide. IDA (and ID without anemia, which is even more common) poses a major burden to the society: they may cause cognitive defects in children, increased morbidity and mortality in pregnancy, reduced physical performance in workers, and are common comorbidities in the elderly. Etiology, populations at risk, and algorithms for diagnosing absolute ID/IDA are overall well established. More recently, also whole blood donors are identified as being at risk to develop ID, especially

Figure 1. Graphical representations of the aims of the Research Roadmap for Anemias in Europe during the period 2020–2025.

at fast donation rates.[15] Major challenges are diagnosing ID in nonerythropoietic tissues (eg, heart, kidney, and lungs) and in the context of inflammation. It is well known that microorganisms compete with the human host for iron. An emerging issue in the field is the role of microbiota. Studies in mouse models suggest that gut microbiota might modulate iron absorption, counteracting the positive effect of duodenal HIF-2 alpha thus contributing to systemic iron homeostasis.[16]

Iron and iron proteins have a profound effect on erythropoiesis, and erythroid expressed ferroportin, exporting iron, protects red cells from oxidative stress and contributes to the levels of serum iron in ID.[17] BM transferrin receptor 2 (TFR2) in complex with the erythroid receptor (EPOR) senses ID and modulates erythroid differentiation accordingly. Both genetic and acquired ID increase megakaryocyte commitment in mice,[18] providing a plausible explanation of thrombocytosis that can be observed in severe ID. In the therapeutic field, novel schedules of oral iron administration at alternate day suggest optimal efficacy with less side effects, at least in ID[19]; indications to intravenous iron both in absolute and functional ID are increasing.[20]

Plans for the future

- It is urgent to clarify how ID affects tissues other than erythropoiesis in animal models.
- In particular, it is important to investigate how kidneys reabsorb iron and whether this participates to systemic homeostasis and to explore the contribution to iron balance of local hepcidin produced by different tissues. The value of soluble transferrin receptor, serum hepcidin levels, and reticulocyte hemoglobin content should be better explored in the diagnosis of complex cases of ID; the standardization of these parameters would further facilitate clinical use.
- There is a need for identification and validation of functional markers of ID beyond hemoglobin.

Future research should address:

- The physiological role of gut microbiome and its crosstalk with the intestinal machinery of iron absorption. It is relevant to define whether and how gut microbiota modulate iron absorption, the role of microbiota in ID, its potential interference with pharmacological iron absorption and its role—if any—in the side effects caused by oral iron supplementation.

There is room for optimizing and personalizing ID treatment modalities:

- clear schedules should be established for oral iron treatment in IDA, criteria for oral versus intravenous iron should be defined under different conditions and according to disease severity;
- guidelines to replace total iron needs with single/double infusion(s) of intravenous iron should be drawn;
- iron supplementation strategies based on individual genetic susceptibility to ID should be considered;
- long-term complications of intravenous therapy not addressed in clinical trials should be explored;

- novel therapies for functional ID that counteract hepcidin function or promote EPO production and iron mobilization await clinical introduction.

Iron overload disorders

Where we are now

Disorders of systemic iron overload are a heterogeneous group of diseases classified into several subtypes based on the underlying genetic or acquired cause. These include (1) primary genetic defects in proteins controlling iron homeostasis; (2) erythroid maturation defects resulting in secondary iron overload; and (3) very rare genetic conditions that include disorders of iron transport, such as hypotransferrinemia, aceruloplasminemia, and DMT1 deficiency. Most frequently, misregulation of the hepcidin-ferroportin regulatory axis is responsible for iron overload. In most subtypes of hemochromatosis, reduced hepcidin activity explains increased iron uptake mediated by the iron exporter ferroportin, while mutations in ferroportin hallmark ferroportin disease. In iron loading hematological diseases, including thalassemias, congenital hemolytic diseases, sideroblastic anemias, congenital dyserythropoietic anemias, myelodysplastic syndromes, and aplastic anemia, inefficient erythropoiesis explains some degree of iron overload, which is severely aggravated by regular blood transfusions to treat anemia.

In the past 20 years, novel genes with critical roles in the generation of iron overload disorders were discovered and the subsequent development of experimental disease models had a tremendous impact on our understanding of the mechanisms that maintain cellular and systemic iron metabolism. Not only they explained the pathogenesis of hemochromatosis and other primary disorders of the hepcidin-ferroportin axis they also generated new insights into mechanisms underlying iron accumulation in iron loading anemias. This knowledge enabled the development of novel treatment options for iron overload diseases. Additionally, it laid the basis for research on the impact of iron in common acquired diseases, such as chronic liver disease, diabetes, neurodegeneration, atherosclerosis, or cardiovascular disease, where moderate elevations of tissue iron levels may exacerbate the underlying pathologies.

A major advance was the identification of erythroferrone (ERFE), a long-sought erythroid regulator of hepcidin synthesis and iron homeostasis,[21] and the recognition of its mechanism of action.[22] An ERFE immunoassay was developed for human studies of normal and disordered erythropoiesis and its effect on iron homeostasis.[23] Mechanisms of iron-induced oxidative stress sensing in the liver were clarified with the demonstration that BMP6 production in sinusoidal endothelial cells[24] is under the control of the transcription factor NRF2 in conditions of hepatic iron loading.[25] Novel iron overload disease models revealed the importance of tissue-specific iron homeostasis and the impact of iron accumulation in different organs such as retina,[26] lungs,[27] heart,[28] or the cardiovascular system.[29] The role of TFR2 on the mutual control of iron homeostasis and erythropoiesis was revealed, opening a new door to potential novel therapeutic targets in iron-loading anemias.[30] This was also the era when novel targeted drugs such as hepcidin replacement therapy or hepcidin agonists were tested as novel approaches for treating iron overload under a variety of conditions, including iron-loading anemias.[31] In addition, ferroportin inhibitors were first developed for therapeutic purposes.[32] The role of the iron status of the mother on child's health was assessed in a preclinical study showing that maternal hepcidin, through regulation of maternal plasma iron concentrations, determines the amount of iron taken up by the placenta and protects the fetus from iron excess even when the mother is iron overloaded.[33]

Plans for the future

We need basic research into mechanisms that maintain iron homeostasis under iron overload conditions and an increased demand for erythropoiesis. We further need to understand how iron accumulation in the BM affects early steps of hematopoiesis and the damage that occurs in diseases such as thalassemia, myelodysplasia, or leukemia.

- It is of interest to learn how specific organs handle iron or heme released during hemolysis, and the role of ferritin secretion on tissue iron redistribution.
- We need to investigate the role of the iron status of the mother on child's health.
- Research is required to identify the role of proteins involved in iron regulation on different cell types, for example, of the immune system or in the brain.
- Definitely estimate the hemochromatosis prevalence in Europe, describe its natural history and clarify the genetic and environmental determinants of its penetrance. European registries promoted by EuroBloodNet are a critical requirement to fill this gap and for future implementation of preventive strategies.
- Epidemiological and prospective cohort studies are required to substantiate knowledge on how perturbations of iron homeostasis are linked to disease progression and development of comorbid complications in acquired disorders, such as cancer, cardiovascular, liver, kidney, bone, or neurological diseases. This research may justify the implementation of clinical trials with the novel targeted therapies to reduce systemic iron levels.
- Research needs to support the initiative by the WHO to define adequate world-wide Hb values and its close link to iron availability.

Hemolytic anemias, including membrane and enzyme defects

Where we are now

Hemolytic anemias (HAs) are a heterogeneous group of hereditary and acquired disorders. The former includes defects of the red cell membrane and metabolism, and the latter warm autoimmune hemolytic anemia (wAIHA) and cold agglutinin disease (CAD). In the past 5 years, substantial improvement has been made with regard to dehydrated hereditary stomatocytosis (DHS) or hereditary xerocytosis (HX), familial pseudohyperkalemia (FP), pyruvate kinase deficiency (PKD), CAD, and wAIHA.

Regarding DHS, during the last 5 years, the second causative locus, *KCNN4* gene encodes for the Gardos channel, was identified.[34–37] Senicapoc, a Gardos channel antagonist, previously proposed for use in sickle cell anemia, showed efficacy in preventing RBC K+ loss and dehydration in both *PIEZO1* and *KCNN4* mutated cells.[38–40] Moreover, two large retrospective cohort studies have been recently described comprising overall 249 patients with several forms of membrane defects due to altered transport function.[41,42] These studies highlighted that *PIEZO1* was the most frequent mutated gene under these conditions and that the major complication is the severe hepatic iron overload. A recent study demonstrated the role of PIEZO1 in the liver by regulation of hepcidin expression through increased phosphorylation of ERK1/2 and inhibition of the BMP-SMADs pathway. This was the first demonstration of a direct link between PIEZO1 and iron metabolism, which defines the channel as a new hepatic iron metabolism regulator and as a possible therapeutic target of iron overload in DHS and other iron-loading anemias.[43] Furthermore, two recent studies have elucidated the role of PIEZO1 during erythroid

differentiation. PIEZO1 activation delays erythroid differentiation of normal and DHS1-derived human progenitor cells.[44] Patients carrying PIEZO1 mutations showed reduced reticulocyte count respect to patients with *KCNN4 mutations*, despite the similar Hb levels. Indeed, it has been demonstrated that PIEZO1 gain-of-function (GoF) mutations delay reticulocyte maturation in DHS.[45,46] PIEZO1 GoF mutations are also associated to resistance of *Plasmodium* infection in mice and human. As matter of fact, a novel human GoF PIEZO1 allele, E756del, is present in a third of the African population (Figure 2).[47]

Regarding FP, it was demonstrated that the ABCB6 missense mutations cause elevated potassium ion efflux in RBCs.[48] Of note, FP individuals are present in the blood donor population.[48,49]

Moreover, a genetic mutation in ATP11C, one of the major flippase of RBCs, was identified in a male affected by congenital hemolytic anemia inherited as an X-linked recessive trait.[50]

The widespread of NGS has revolutionized the field of diagnostic and research of new causative genes in these anemias. Indeed, the NGS targeted panels were routinely introduced in the diagnostic practice facilitating not only the diagnosis, but also the prognostic evaluation of these patients.[51–53]

Regarding PKD, recommendations for the diagnosis, including pros and cons of enzymatic and molecular testing, have been published.[54,55] Moreover, a large retrospective/prospective global registry of 254 patients has been activated, enabling a more precise definition of clinical and molecular features of the disease. In particular, treatments, complications, and their monitoring and management have been described.[56,57] The most important therapeutic improvement regards mitapivat, a small molecule, an oral activator of red cell PK, which was administered in 52 nontransfused patients with PKD, obtaining a maximal hemoglobin increase >1 g/dL in half of the patients (median 3.5 g/dL), with an acceptable safety profile.[58]

Regarding CAD, a large retrospective multicenter study including 232 patients has better defined the clinical characteristics and response to the few available treatments (rituximab alone or in combination with bendamustine or fludarabine).[59,60] Consistently, a pivotal study with the complement inhibitor sutimlimab (a humanized anti-C1s monoclonal antibody) has shown a mean hemoglobin increase of 2.6 g/dL, with 20/24 (83.3%) patients displaying hemoglobin increase ≥1 g/dL, along with a meaningful improvement of quality of life.[61] Finally, several experts' opinions and an International Consensus meeting have provided recommendations for the diagnosis and treatment of wAIHA and CAD (Figure 3).[62,63]

Plans for the future

In the next years, regarding the RBCs membrane defects it will be important:

- to further understand the pathogenic mechanism of anemia in DHS also by the use of the mouse model with PIEZO1 GoF mutations;
- the mechanism of hepatic iron overload in DHS needs further deeply dissection.
- to identify new causative genes for the cases still lacking a genetic base that are about 10%–15%.
- to find new therapeutic treatments.

The study of pathogenic mechanism will be useful for the identification and development of therapeutic treatments also in the field of gene therapy. Senicapoc seems to be a good promising drug to treat dehydration in DHS. A future clinical trial on the use of this drug in DHS could confirm its efficacy also in vivo. Regarding FP, could be useful to further dissect the role of ABCB6 and its correlation to blood transfusion.

- In the next years, ongoing long-term follow-up of mitapivat-treated PKD patients will determine whether the rise in hemoglobin will also be associated with a decreased incidence of complications. Ongoing studies in transfusion-dependent patients will confirm its efficacy in more severe settings (ClinicalTrials.gov NCT03559699).
- Following preclinical studies using a lentiviral vector in myeloablated PK-deficient mice, a clinical trial on gene therapy is close to start in humans (ClinicalTrials.gov NCT04105166). This promising new therapeutic approach will dramatically change the prognosis of severe PKD, unresponsive to splenectomy and mitapivat, also considering the uncertain results with BM transplant.[64]
- Regarding wAIHA and CAD, several target therapies are under development, including inhibitors of complement (at different levels of the cascade), tyrosine kinases, proteasome, and neonatal Fc-receptor (Figure 3) (ClinicalTrials.gov NCT03538041, NCT03226678, NCT03075878, NCT04256148, NCT04119050, NCT02612558, NCT03764618, NCT04083014, NCT02389231).

In the next years, this expanded therapeutic armamentarium will help in defining the best choice, sequence and combination of drugs aimed at "cure" the disease.[65]

Congenital BM failure, aplastic anemias, PNH

Where we are now

BM failures (BMFs) are a heterogeneous group of diseases characterized by a quantitative deficiency in one or more blood cell lineages. Inherited BMFs are rare and include different entities such as Fanconi's anemia (FA, which is due to impaired DNA repair and cytokine hypersensitivity),[66] Dyskeratosis Congenita (DKC), Diamond Blackfan Anemia (DBA), and Shwachman-Diamond Syndrome (SDS) (all associated with impaired ribosomal or telomere function). Acquired forms of BMF are more frequent; the most typical form is idiopathic aplastic anemia (IAA), characterized by a severe pancytopenia due to an immune-mediated attack of hematopoiesis. PNH is a less common form, where the underlying BM disorder is associated with the expansion of an abnormal, nonmalignant, blood cell population which is deficient in the expression of glycosyl-phosphatidyl-inositol (GPI)-linked proteins due to a somatic *PIG-A* mutation. Since lacking GPI-linked proteins include the complement regulators CD55 and CD59, the clinical phenotype of PNH is characterized by complement-mediated, intravascular, hemolytic anemia, variously embedded with thromboembolisms and cytopenia.

The improved understanding of all BMFs has led to better patient management in Europe; the Severe Aplastic Anemia Working Party (*SAAWP*) of the EBMT historically has contributed greatly to improved clinical outcome in this field, pioneering the therapeutic use of antithymocyte globulin (ATG) in IAA, as well as the use of HSCT in patients with FA and other inherited forms. The database of the SAAWP of the EBMT contains data on >16,000 patients with different subtypes of BMFs, thereby providing a unique opportunity for investigating many different critical aspects of these diseases. The SAAWP of the EBMT continues to run a multinational database to collect data from all European BMFs, aiming to perform robust retrospective studies. At the same time, the SAAWP is now fully equipped for academic prospective trials: the RACE study, the largest clinical trial performed in IAA, has just been completed.

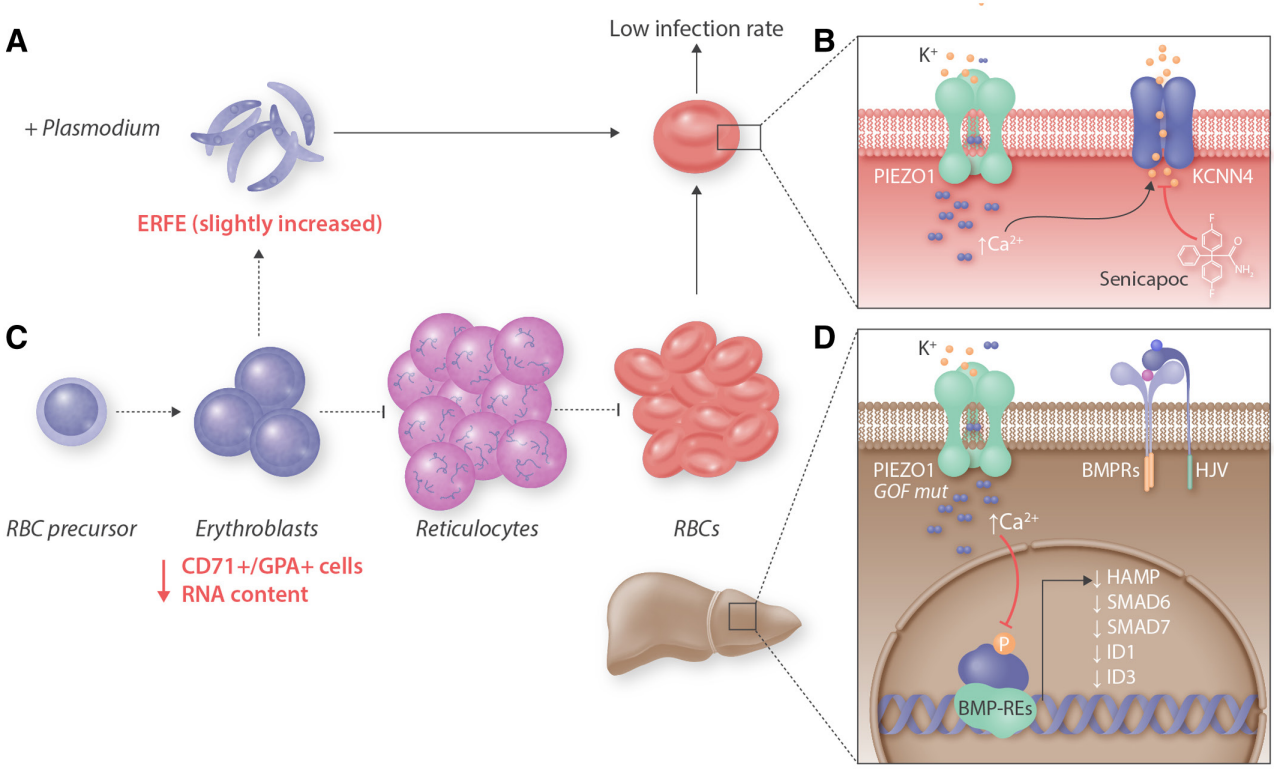

Figure 2. Schematic representation of pathogenic mechanism of DHS and new discovery on Plasmodium infection. (A) Recent study demonstrated that RBCs of DHS patients with PIEZO1 gain-of-function (GOF) mutations show a low rate of infection by *Plasmodium falciparum*. (B) RBCs of DHS patients show dehydration that is caused by the increased potassium efflux and increased calcium influx of PIEZO1 GoF mutations or KCNN4/Gardos GoF mutations. Senicapoc, a Gardos antagonist, is able to restore the hydration status in both PIEZO1 and KCNN4 mutants. (C) RBCs of DHS patients with GoF mutations in PIEZO1 show delayed terminal differentiation and reticulocytes maturation. (D) At the hepatic level, PIEZO1 GoF mutations in DHS result in increased intracellular Ca^{2+} concentrations. The hyperactivation of the mechanoreceptor leads to amplification of the phosphorylation of ERK1/2, which acts in turn by inhibiting the BMP/SMADs pathway. The lack of phosphorylation of SMAD1/5/8 inactivates *HAMP* transcription.

Plans for the future

Patients suffering from BMFs continue to represent a challenge for the medical community, for their poor prognosis when the underlying disease is not controlled. Additional efforts are needed to offer the most appropriate treatment to all European patients, and to improve current standards of care. The SAAWP of the EBMT is dedicated to this goal through different research lines.

Improvements in HSCT for inherited and acquired forms of BMF. HSCT remains a key treatment option for all BMF patients, with the actual indication depending on the phase/severity of the disease and on the availability of alternative treatments. The SAAWP is actively working to improve the outcome of HSCT in all these conditions, mostly through high-quality registry retrospective studies, implementing:

- Disease-specific, patient-tailored, conditioning regimen as well as post-HSCT immunosuppressive treatments;
- Development of novel HSCT protocols in the setting of alternative donor, including not only HSCT from unrelated donors, but also HSCT from familiar haploidentical donors;
- Demonstration of more effective treatment algorithm for individual forms of acquired or inherited BMFs.
- Improvement of nontransplant treatment for acquired IAA. After years of failures trying to develop more aggressive immunosuppressive regimens, the treatment of IAA has been improved by the addition the thrombopoietin-mimetic agent eltrombopag on the 'scaffold' of standard immunosuppression. After the initial results coming from the United States,[67] the SAAWP has just announced the results of a pivotal randomized trial which has demonstrated the superiority of horse antithymocyte globulin (ATG) + cyclosporine (CsA) +Eltrombopag (the "triple therapy") as compared with standard horse-ATG+CsA.
- Improvement of management of PNH. The introduction of the anti-complement agent eculizumab led to the control of most disease manifestations and to improved survival in PNH. The SAAWP is currently looking at unmet clinical needs in PNH, as well as to improve the mechanistic understanding of anticomplement treatment in vivo, paving the way for the development of more effective treatments.[68] Pivotal clinical trials are ongoing, and preliminary data already anticipate the a novel scenario in the field of anticomplement treatment for PNH.

The management of BMFs still represents a challenge for the medical community. European efforts aiming to investigate in the real-life the actual impact of these disorders is essential to improve the management of all BMFs. Considering the rarity of these conditions, as well as the growing cost of available therapies, these research studies are essential not only to develop better treatments, but also to optimize the financial resources.

Thalassemia and congenital hemoglobinopathies

Where we are now

A better understanding of the pathophysiology of β-thalassemia in addition to key developments in optimizing transfusion programs and iron-chelation therapy has led to an

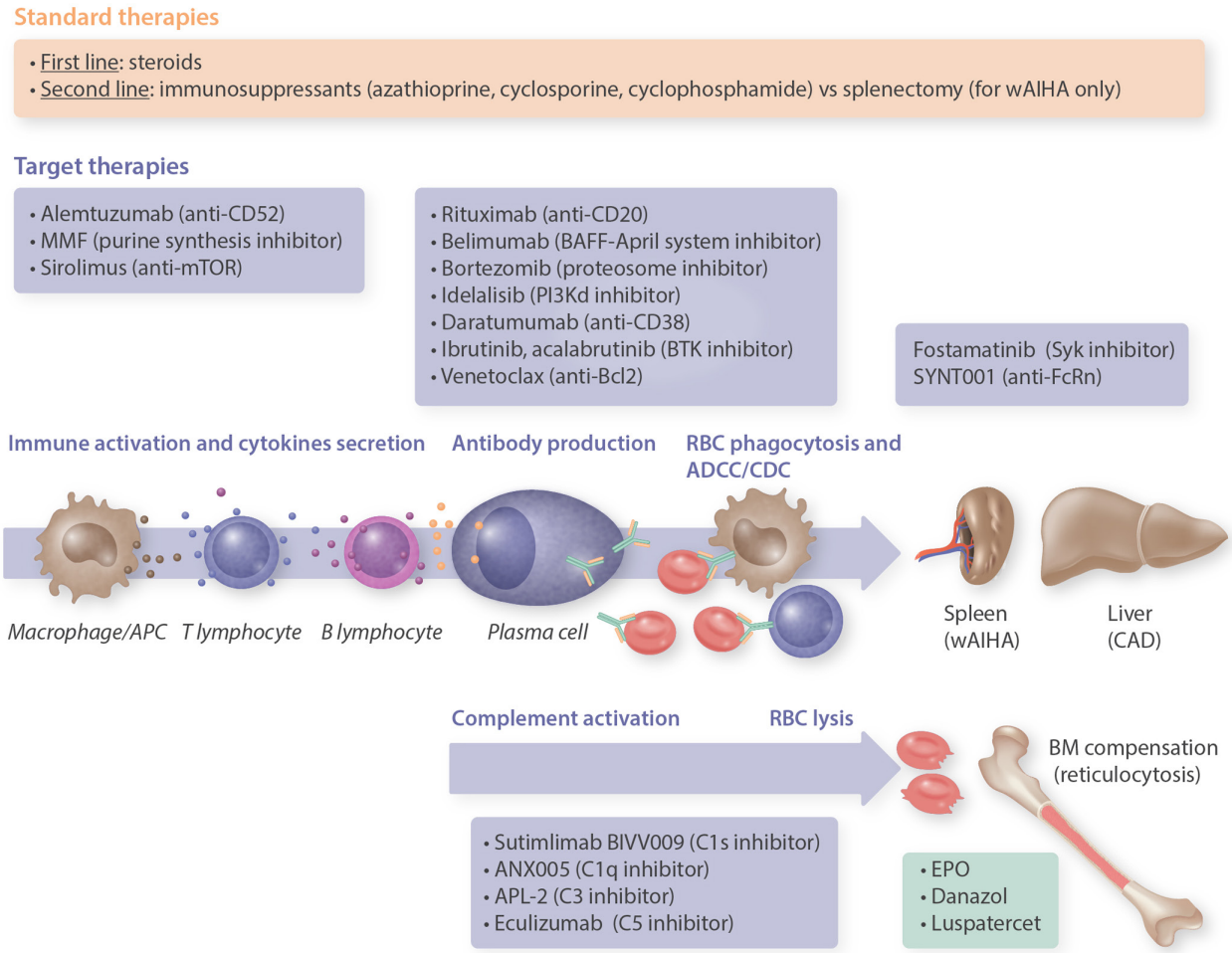

Figure 3. Standard and target therapies for warm autoimmune hemolytic anemia (wAIHA) and cold agglutinin disease (CAD). The figure shows the several immunologic mechanisms involved in pathogenesis, including macrophages, T and B lymphocytes, cytokines, activation of the complement cascade, antibody-dependent cellular cytotoxicity (ADCC) in the spleen and/or complement-dependent cytotoxicity (CDC) in the liver, and possible inadequate bone marrow compensation. Standard therapies include steroids and immunosuppressors that act not specifically on the various mechanisms, and splenectomy. Target therapies are directed against specific immunological mechanisms either inhibiting the immune attack or stimulating bone marrow compensation. APC = antigen presenting cell; BAFF = B-cell activating factor; BM = bone marrow; BTK = Bruton tyrosine kinase; CAD = cold agglutinin disease; EPO = erythropoietin; FcRn = neonatal Fc receptor; MMF = mycophenolate mofetil; PI3K = phosphoinositide 3-kinase; Syk = spleen tyrosine kinase.

increase in the life span of thalassemia patients and paved the way for novel therapeutic strategies.[69,70] The latest advancement and breakthrough in the thalassemia realm during the past years is the FDA and EMA approval of luspatercept for the treatment of transfusion-dependent thalassemia (TDT) patients at a starting dose of 1 mg/kg once every 3 weeks by subcutaneous injection. Luspatercept or ACE-536 is a recombinant fusion protein that acts as a trap for activin receptors. The approval was based on the results of the BELIEVE trial, a phase 3, randomized, double-blind, placebo-controlled trial that was conducted in 65 sites across 15 countries, enrolling a total of 336 adult TDT patients (>18 years) randomized in a 2:1 ratio to receive luspatercept or placebo subcutaneously every 21 days for at least 48 weeks.[71] The percentage of patients who had a reduction in the transfusion burden of at least 33% from baseline during weeks 13 through 24 plus a reduction of at least 2 red-cell units over this 12-week interval was significantly greater in the luspatercept group than in the placebo group (21.4% versus 4.5%, $P < 0.001$).[71] During any 12-week interval, the percentage of patients who had a reduction in transfusion burden of at least 33% was greater in the luspatercept group than in the placebo group (70.5% versus 29.5%). Similarly, the percentage of those who had a reduction of at least 50% was also greater in the luspatercept group, compared to placebo (40.2% versus 6.3%). AEs included bone pain, arthralgia, dizziness, hypertension, and hyperuricemia. These were more commonly seen in patients on luspatercept than those on placebo. A greater percentage of patients in the luspatercept group than in the placebo group had at least one AE of grade 3 or higher during the treatment period. Treatment discontinuation due to an AE was reported in 12 patients (5.4%) in the luspatercept group and in 1 patient (0.9%) in the placebo group. No deaths related to luspatercept or placebo were reported.[71]

Plans for the future

Ongoing clinical trials are currently underway looking at the use of luspatercept in different settings:

- A phase 2a study is currently ongoing to evaluate the safety and pharmacokinetics of luspatercept in pediatric patients with TDT (ClinicalTrials.gov number NCT04143724).
- The BEYOND trial is another ongoing phase 2 trial looking at the efficacy and safety of luspatercept in patients

with nontransfusion-dependent thalassemia (NTDT) (ClinicalTrials.gov number NCT03342404).
- Several other clinical trials are investigating the safety and efficacy of gene therapy and genome editing to restore Hb synthesis in β-thalassemia.
- Clinical trials investigating the use of novel therapeutic agents targeting iron dysregulation are also currently underway and details of these trials have been summarized in recent publications. These agents stimulate hepcidin expression and activity and/or target the hepcidin-ferroportin axis and include minihepcidins, ferroportin inhibitors, and TMPRSS6 inhibitors. They have already been investigated in preclinical studies on animal models, demonstrating a beneficial activity.[32,72–74] Several other agents are in evaluation for a similar effect in these patients. These agents directly target iron dysregulation (VIT-2763 and TMPRSS6- LRx)[32,75] or ineffective erythropoiesis (mitapivat [AG-348]) to ameliorate anemia and prevent iron overload, which are strictly related. Combinations of these agents may be useful to control or reverse the disease process in β-thalassemia.[76]

As we await the data from all these trials, we believe that long-term, head-to-head, and comparison trials using these novel therapies will be necessary in the future to determine their optimal use. Moreover, whether these novel therapies will be used on their own or in combination with other conventional therapies, such as iron chelators are yet to be determined.

Sickle cell disease

Where we are now

SCD is the commonest severe monogenic disease in the world.[77] It is caused by a point mutation in the β-globin gene, resulting in the synthesis of pathological hemoglobin S (HbS). The term SCD includes different genotypes that cause the characteristic clinical syndrome (SS, SC, $S\beta^{+/0}$ thalassemia). SCD causes chronic morbidity and high mortality related to the severity of both acute and chronic organ damage. In the last 2 decades, due to immigration, the number of patients with SCD has dramatically increased across Europe. The prevalence of SCD newborns and SCD carriers in EU is approximately 1–5/10,000 and 1/150, respectively, and is set to increase in the near future. The years lived with disability (YLDs) for hemoglobinopathies and SCD is estimated to be 10,197, which is a very significant, considering that the YLDs for cardiovascular disorders is 21,985. In high-income countries, nearly all children with SCD are expected to survive to adulthood, although mortality increases in adulthood and median survival is reduced by >20 years.[78] In low-income countries, the majority of patients with SCD still die in childhood. SCD was first described by James Herrick in 1910, and understanding has increased steadily since then, including recognition that polymerization of deoxygenated HbS is the primary event, and that a cascade of pathological problems, including: red cell dehydration, vaso-occlusion, hemolysis, anemia, inflammation, hypercoagulability, and aberrant expression of adhesion molecules.[79,80] Past achievements in Europe include defining the structure of HbS polymers, identification of embryonic hemoglobins, evaluation of hydroxyurea, the development of comprehensive sickle cell centers, the development of HSCT, and the first clinical trials of gene therapy in SCD.[81,82] In addition, European research contributed to the development of the first transgenic mouse model for SCD-related organ damage, and understanding of the control of HbF expression.

Plans for the future

Although significant progress has been made in the clinical management of patients with SCD, the treatment of SCD is still unsatisfactory, with few effective treatments. More therapeutic approaches are starting to emerge as gene therapy. There are ongoing clinical trials assessing the efficacy and safety of gene therapy in SCD patients, but the results are not yet available. The ongoing clinical trials are assessing the efficacy in different types of SCD based on the types of mutations and types of vectors available. Moreover, genome editing technology has made it possible to repair the β-globin mutation in patient HSCs or target genetic loci associated with reactivation of endogenous γ-globin expression.[83]

The roadmap for research on SCD in Europe includes:

- the development of multinational collaborative studies across Europe to establish biobanks to identify genetic and other biomarkers predicting outcomes in SCD, which will be useful in clinical care and therapeutic trials. This will include collection of detailed phenotypes;
- selection of new therapeutic targets using both in vitro and animal models for SCD;
- development of novel imaging techniques for both clinical and research purposes;
- establishment of network of SCD clinical trials units to assess and develop the new treatments, including stem cell therapies, small molecules and supportive care. In addition, the recent COVID-19 pandemic has highlighted the importance of EU action to support and intensively treat fragile patients such as SCD subjects.[84]

The proposed research roadmap will help develop:

- progress in the knowledge of disease progression;
- new therapeutic molecules for management of SCD;
- new profiling of disease severity for personalized medicine;
- optimization of SCD patient care;
- clinical trials addressing basic aspects of clinical cares.

These will improve:

- patient health and quality of life;
- national and European Health systems by reductions of hospitalization length and of care costs;
- national and European Welfare spending due to the reduction in disabilities of SCD patients and in the level of sickness absence from jobs.

These advances would benefit patients in the United States, and low- and middle-income countries, including many African countries, India, and Brazil. This research will also stimulate collaboration with commercial companies.

Dyserythropoietic and hyporegenerative anemias

Where we are now

Dyserythropoietic and hyporegenerative anemias comprise a heterogeneous group of disorders that affect the normal differentiation–proliferation pathways at the different steps through the erythroid lineage, and that mainly result in monolinear cytopenia.[85]

The congenital dyserythropoietic anemias (CDAs) are a group of disorders characterized by anemia caused by ineffective erythropoiesis, erythroid hyperplasia with distinct morphological features in BM late erythroblasts, and often associated with secondary iron overload. Based on BM morphology, the CDAs are classically divided into 3 types (CDA I, II, and III), a classification that is now supported by the identification of different genes mutated in each type.[86] Mutations in erythroid-specific transcription factors genes *GATA1* and *KLF1* (designated CDA type IV) have been described in few such patients. Dyserythropoietic changes were described in several disorders

with additional clinical features like sideroblastic anemia, Majeed syndrome (*LPIN2* mutations), epileptic encephalopathy (*CAD*), pancreatic insufficiency (*COX4I2*), and mevalonate kinase deficiency (*MVK*) and thus add to diagnostic confusion.[87]

It has been shown recently that the nonspecific clinical picture and light microscopy BM findings cause diagnostic difficulties with delay diagnosis and appropriate therapy. Indeed, a genetic-based NGS diagnostic led to modification of original clinical diagnosis in 10%–40% of patients.[51,52,88] For example, a recent case series showed that among patients originally classified with CDAs, 45% had anemia caused by enzymatic defects, most commonly pyruvate kinase deficiency with mutations in the *PKLR* gene.[52]

Regarding the pathogenesis of the CDAs, proteins encoded by involved genes are ubiquitous expressed and their role in erythropoiesis is still unknown. CDA I is caused by mutations in *CDAN1* or in *CDIN1* (previously known as *C15orf41*) genes. It has been recently found that the protein encodes by CDAN1 tightly binds to C15orf41 and sequester C15orf41 and Asf1 in the cytoplasm pointing to involvement in chromatin assembly processes.[89,90] CDA II is the most common CDA subtype and results from mutations in *SEC23B* (>80% of cases). Recently, a recurrent low-frequency variant in the *ERFE* gene, encoding the erythroferrone, was identified in 12.5% of CDA II patients with severe phenotypes. This variant results in increased levels of ERFE, with subsequent marked impairment of iron regulation pathways at the hepatic level.[91]

Diamond Blackfan anemia (DBA) patients classically show severe macrocytic anemia in the first year of life. The BM is characterized by a paucity of erythroid precursors. Approximately, 30% of DBA patients also have physical anomalies (eg, craniofacial, thumb, and cardiac malformations). The risk of solid tumors, myelodysplastic syndrome, or leukemia is elevated in DBA and was calculated to be 20% by age 46 years.[92] Following the first year of life, the anemia is treated with corticosteroids. Patients who do not respond to steroids or require high doses with unacceptable toxicities or infants in the first year of life receive chronic RBC transfusions.[93] Those patients often develop substantial iron overload and require careful detection of iron overload, as well as, iron chelation therapy.

Stem cell transplantation is an alternative to chronic transfusions. Excellent results of stem cell transplantation have recently been observed (91% overall survival) in young children with DBA using matched sibling donors and matched unrelated donors.[94]

DBA is caused by mutations in least 20 genes encoding ribosomal proteins (RPs) resulting in ribosomal haploinsufficiency. Mutations in ribosomal genes account for 60%–70% of DBA cases. "DBA-like" disorders with congenital red cell aplasia and intact ribosomal function were described, including biallelic pathogenic mutations in *CECR1* gene coding for adenosine deaminase 2 (ADA2) and in the erythropoietin (*EPO*) gene.[95,96]

Regarding the pathogenesis of DBA, the effect of decreased ribosomal activity in vivo and in a tissue-specific manner is unknown; p53 activation has been observed in BM from DBA patients, after depletion of RPs. Recently, it has been shown that rarely mutations in the *GATA1* gene can cause DBA. Subsequently, an elegant study suggested that impaired translation of GATA1 mRNA (as a consequence of RP haploinsufficiency) is an important factor in mediating the erythroid defect observed in DBA. It has further been suggested that GATA1 has a complex 5′ UTR that predicts poor translation initiation rates, and such mRNAs are more sensitive to ribosome deficiency as found in DBA.[97] Two recent articles suggested that a decrease of GATA1 full-length protein resulting from RP haploinsufficiency and deficiency of HSP70 can disturb the balance of globin-heme and lead to the accumulation of free cytoplasmic heme in erythroid progenitors, which increase the P53-dependent apoptosis of DBA erythroid cells.[98] An alternative model suggests that both RP and GATA1 mutant cells showed reduced proliferation and delayed erythroid differentiation.

Plans for the future

There is a need for wide implementation of NGS programs to improve diagnosis, for more basic research to better understand the role of the proteins involved normal and affected erythropoiesis, and for programs to identify new potential drugs and therapeutic options for patients with these rare disorders.

- Improving CDA and DBA European Registries by harmonization and collaboration among the existing national registries to create a unique European database.
- Continued wide implementation of NGS molecular diagnosis to achieve a correct diagnosis and to further identify new candidate genes.
- Continued efforts for unraveling the pathogenesis of both disorders and the role of the involved proteins in erythropoiesis which eventually may lead to discovery of new therapeutic targets. The existence of appropriate erythroid models like induced pluripotent stem cell (iPSC cells) and human erythroblasts cell lines capable of terminal erythroid maturation may facilitate this effort.
- Clinical trials of novel drugs: Results of clinical trial of L-leucine in DBA are awaited (ClinicalTrials.gov NCT01362595). TGF-β ligand modifiers correct anemia by promoting the late-stage erythropoiesis. Sotatercept was administered to DBA patients (ClinicalTrials.gov NCT01464164) and results are still pending, and Luspatercept was recently approved (by Celgene) for CDA II patients.
- Gene therapy and gene editing for patients with DBA is an attractive potential therapy. The feasibility of gene therapy to cure RPS19-deficient DBA mouse model using lentivirus vectors have been shown.[99] Future studies in transduced human CD34 cells and clinical trials are awaited. The fast-moving CRISPR/Cas9-mediated genome editing may offer BM cure without the use of an integrating viral vector.

Anemia in the elderly

Where we are now

The recent years have witnessed an increased awareness on the huge prevalence of anemia in the elderly (AE), and its negative prognostic impact.[100,101] In 2018, nearly on fifth of the EU population (estimated at 512 million) was aged >65 years, with projections towards a continuously increasing proportion, especially for the "oldest old" (ie, those aged >85 years; https://ec.europa.eu/eurostat/statisticsexplained/index.php/Population_structure_and_ageing#Past_and_future_population_ageing_trends_in_the_EU). Anemia reveals a prevalence ranging from 12% in community living up to 47% in nursing home residents.[102] Remarkably AE is independently associated with impaired patient-reported outcomes,[103] and a number of adverse outcomes including hospitalizations, frailty, and even mortality. Thus, AE clearly represents a forthcoming EU major public health problem. Traditionally, AE has been attributed by one third to nutritional deficiency (primarily ID), one-third to chronic inflammation (AI) and/or other comorbidities (eg, CKD),[104] while the remaining third has been considered "unexplained." However, recent advances suggest that: (1) at variance with anemia in younger persons where a single cause is the rule, AE is near invariably multifactorial[100,101]; (ii) absolute ID is underrecognized in the elderly, due to the frequent absence of microcytosis,[101] as well as the unawareness of the need of considering upper ferritin

thresholds than those commonly used in the young[105]; (iii) hepcidin upregulation leading to functional ID is relatively common in elderly, due not only to comorbidities (including CKD and chronic heart failure [CHF]),[106] but also to reduced levels of sexual hormones and to a low-grade inflammatory process linked to age and immunosenescence termed "inflammaging"[107]; indeed, patients with AI reveal pronounced restrictions in health-related quality of life (HRQoL) as compared with other forms of anemia; and (4) besides unrecognized ID, a proportion of "unexplained" AE is associated to age-related clonal hematopoiesis of indeterminate potential,[108] a process driven by acquired somatic mutations in certain genes (eg, TET2, DNMT3A, and JAK2) also predisposing to myelodysplastic syndromes (MDS) and other hematological malignancies. When CHIP is associated to isolated anemia without fulfillment of other MDS diagnostic criteria, the condition is named "isolated cytopenia of undetermined significance (ICUS) with anemia (ICUS-A), regarded as a possible prototype of "unexplained" AE.[100] Noteworthy, CHIP has been consistently associated with increased mortality due to cardiovascular rather than hematological complications, likely through a CHIP-induced proinflammatory state.[109]

In summary, it is clear that AE, even mild, can no longer be considered as a mere consequence of aging, but should be always taken seriously. A precise definition of the cause(s) in the individual patient, which is instrumental to anemia correction, is far from easy and can be demanding for either patients or physicians.

Plan for the future

Despite the remarkable progress outlined above, a number of critical issues should be addressed in the coming years:

- Hb thresholds for AE are still incompletely defined, especially in the oldest old. Studies enrolling adequate number of elderlies without significant comorbidities ("wellderly" subjects)[110] may be the key for resolving this long-debated issue.
- Specific guidelines or recommendations on AE diagnosis and management are scarcely available. Multidisciplinary efforts in this sense should be promoted, for example, regarding the appropriateness and cost-effectiveness of searching intensively the cause, particularly in vulnerable and frail patients.
- Nutritional AE is in principle effectively correctable with relative safe and inexpensive supplementations, but needs an accurate diagnosis. Future studies should clarify the appropriate cutoff levels of old and new laboratory tests, not only for ID,[20] but also for B12 and folate deficiency.
- The independent association of AE with major adverse outcomes including mortality is highly suggestive but does not represent a definite proof of causality of anemia per se, or of a distinct additive effect beyond that of comorbidities. Such proofs may derive by showing improved outcomes with anemia correction. Encouraging results already established for some specific conditions very common in the elderly (eg, CHF)[106] cannot be generalized to all AE. Nonetheless, with the increasing availability of novel antianemic drugs,[111] future studies in this sense should be promoted.
- Patient-reported outcomes including HRQoL with focus on physical functioning and fatigue should be included in initial assessment and evaluation of treatment response.
- So far, only a few studies have addressed the relative contribution of CHIP to AE.[112,113] This should be further investigated, as well as the reciprocal influences between CHIP and inflammaging, which can elicit a detrimental loop.[114] This would be of particular interest considering the results of a recent proof-of-concept analysis on the beneficial effects of anticytokine agents on AE.[115]

Summary box: Main research & policy priorities

1. Genetic variability will likely influence the efficacy of gene therapy and gene editing trials for the cure of β-thalassemia and sickle cell disease (SCD). For this reason, we recommend the use of next-generation technologies to assess the role of genetic makeup of the patients leading to personalized treatment for each individual.
2. Future research in the field of iron deficiency (ID) should address the physiological role of gut microbiome and its crosstalk with the intestinal machinery of iron absorption. It is relevant to define whether and how gut microbiota modulate iron absorption, the role of microbiota in ID, its potential interference with pharmacological iron absorption, and its role—if any—in the side effects caused by oral iron supplementation.
3. We need to understand how iron overload in the bone marrow (BM) affects early steps of hematopoiesis; to learn how specific organs handle iron; and to investigate the role of the iron status of the mother on child's health. This research may justify the implementation of clinical trials with the novel targeted therapies to reduce systemic iron levels.
4. In the field of the red blood cell membrane defects, it will be important to further understand the pathogenic mechanism of anemia in dehydrate hereditary stomatocytosis by the use of the mouse model with PIEZO1 GoF mutations. Moreover, the mechanism of hepatic iron overload in DHS needs further deeply dissection. These studies led to the identification and development of therapeutic treatments in the field of gene therapy.
5. In the next years, ongoing long-term follow-up of mitapivat-treated PKD patients will determine whether the rise in hemoglobin was associated with a decreased incidence of complications. This promising new therapeutic approach will dramatically change the prognosis of severe PKD, unresponsive to splenectomy and mitapivat, also considering the uncertain results with BM transplant.
6. In the field of congenital BM failure, aplastic anemias, and paroxysmal nocturnal hemoglobinuria (PNH), it will be crucial to improve hematopoietic stem cell transplantation (HSCT) for both inherited and acquired forms; to improve the nontransplant treatment for acquired idiopathic aplastic anemia; and to improve the management of PNH.
7. In the next years, data from the ongoing clinical trials in patients with dyserythropoietic and hyporegenerative anemias are awaited: (a) L-leucine and Sotatercept for DBA patients and (b) Luspatercept for CDA II patients.
8. In the field of anemia in the elderly, there is the need to define Hb thresholds for adverse event (AE), to obtain specific guidelines or recommendations for the AE diagnosis and management, and to perform studies to establish the appropriate cutoff levels of nutritional deficiencies.

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