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Review

Challenges of blood transfusions in β-thalassemia

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ABSTRACT

Patients with β-thalassemia major (BTM) require regular blood transfusions, supported by appropriate iron chelation therapy (ICT), throughout their life. β-thalassemia is a global disease that is most highly prevalent in Southeast Asia, Africa, and Mediterranean countries. However, the global distribution of patients with β-thalassemia is changing due to population migration, and Northern European countries now have significant thalassemia populations.

Globally, many patients with BTM have limited access to regular and safe blood transfusions. A lack of voluntary nonremunerated blood donors, poor awareness of thalassemia, a lack of national blood policies, and fragmented blood services contribute to a significant gap between the timely supply of, and demand for, safe blood. In many centers, there is inadequate provision of antigen testing, even for common red cell antigens such as CcEe and Kell. Policies to raise awareness and increase the use of red blood cell antigen testing and requesting of compatible blood in transfusion centers are needed to reduce alloimmunization (the development of antibodies to red blood cell antigens), which limits the effectiveness of transfusions and the potential availability of blood. Patients with BTM are also at risk of transfusion-transmitted infections unless appropriate blood screening and safety practices are in place. Hence, many patients are not transfused or are undertransfused, resulting in decreased health and quality-of-life outcomes. Hemovigilance, leukoreduction, and the ability to thoroughly investigate transfusion reactions are often lacking, especially in resource-poor countries. ICT is essential to prevent cardiac failure and other complications due to iron accumulation. Despite the availability of potentially inexpensive oral ICT, a high proportion of patients suffer complications of iron overload and die each year due to a lack of, or inadequate, ICT.

Increased awareness, training, and resources are required to improve and standardize adequate blood transfusion services and ICT among the worldwide population of patients with BTM. ICT needs to be available, affordable, and correctly prescribed. Effective, safe, and affordable new treatments that reduce the blood transfusion burden in patients with β-thalassemia remain an unmet need.

1. Introduction

The β-thalassemias are hereditary disorders of hemoglobin (Hb) production characterized by defective Hb synthesis, which leads to shortened survival of red blood cells (RBCs) through hemolysis, and the premature death of RBC precursors within the bone marrow (i.e., ineffective erythropoiesis) [1]. These conditions result in chronic severe anemia and bone marrow expansion [2,3]. Untreated, β-thalassemia leads to hepatosplenomegaly, bone deformities due to bone marrow expansion, and heart failure due to severe anemia [4,5]. Based on patients' clinical and genetic background, β-thalassemia can be classified as either β-thalassemia major (BTM), β-thalassemia intermedia (BTI), or β-thalassemia minor (carriers). Patients with BTM require lifelong regular blood transfusions, usually starting before the age of 2 years, and die in the first or second decade of life if untreated [6,7]. Patients with BTI may need only sporadic or no blood transfusions during the first two decades of life, although their transfusion requirement may increase later in life [6]. In clinical practice, β-thalassemia has been categorized as either transfusion-dependent β-thalassemia (TDT) or non-transfusion-dependent β-thalassemia (NTDT).

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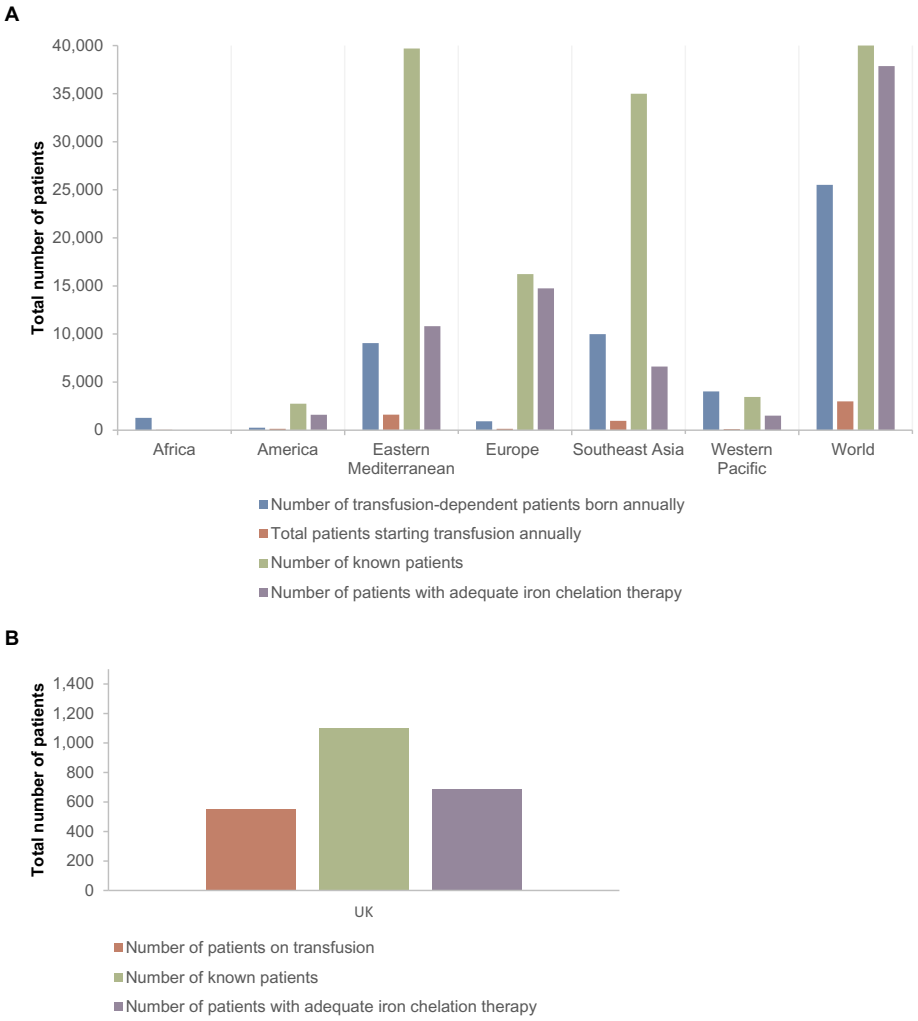

Fig. 1. Estimated distribution of β-thalassemia treatment worldwide (A) and in the UK (B). Data from Modell et al. [10] and NHR annual report 2016/17 [16].

However, TDT and NTDT are fluid categories and patients may shift between them during their lives [7]. The major problems associated with blood transfusions are iron overload, transfusion-transmitted infections (TTIs), and antibody formation (alloimmunization) [8,9]. Iron chelation therapy (ICT) to remove excess iron from the body is needed, usually within a year of starting regular blood transfusions, and is essential to extend life expectancy and prevent morbidity associated with iron overload [4,6,7].

Approximately 26,000 patients with TDT are born annually, and up to 90% of these births occur in low- or middle-income countries (Fig. 1) [7,10]. Hemoglobinopathies are endemic in Asia, Africa, the Middle East, the Indian subcontinent, and the Mediterranean region [10–13] and are currently the most common rare inherited genetic diseases in Europe [14]. Due to migration, hemoglobinopathies are increasingly common in parts of North America and Northern and Western Europe, where they are not indigenous, and in their indigenous countries of Southern Europe [12,15]. The UK has a longstanding tradition of immigration from areas endemic for hemoglobinopathies, which has led to an increase in the prevalence of β-thalassemia [14]. Approximately 800 patients with thalassemia are registered in the UK National Haemoglobinopathy Registry, with around 500 patients undergoing regular blood transfusions [16]. Between 2001 and 2007, the number of affected births increased overall by 15%, but 65% of this increase was to foreign-born mothers, coming mainly from β-thalassemia-prevalent countries [17]. Each year, 20–30 babies with clinically significant thalassemias are born in the UK [16], even with antenatal screening programs in England [18], Wales, and Scotland in place [7]. More than 100,000 UK inhabitants with a nonindigenous ethnic background are carriers of β-thalassemia [12], which is consistent with epidemiological data from Germany and Italy [19,20]. An economic modeling study predicted that the total UK healthcare expenditure per patient attributable to managing BTM is GBP 483,454 (USD 720,201) over 50 years [21]. Costs were attributed mainly to blood transfusions (47% of total costs) and ICT (43% of total costs). Koren et al. estimated the cost of treating a patient with β-thalassemia for a life expectancy of 50 years in Israel at USD 1,971,380, taking into account the costs of diagnosis, monitoring, treatment, complications, and social support [22]. However, none of these studies took hematopoietic stem cell transplantation (HSCT) into account. A Chinese study found that HSCT is an efficient and highly cost-effective treatment for eligible patients with BTM, with undiscounted mean costs for a 55-year lifetime estimated at USD 74,602 for HSCT versus USD 1,198,323 for conventional treatment [23].

2. Blood transfusion: essential, lifesaving therapy in β-thalassemia

Blood transfusions compensate for chronic anemia, prevent bone deformities, facilitate normal growth and activity levels, and allow patients to have a good quality of life (QoL) [6,7]. Transfusions provide fresh, normal RBCs that correct anemia and suppress ineffective erythropoiesis, which helps to prevent hepatosplenomegaly and limit bone

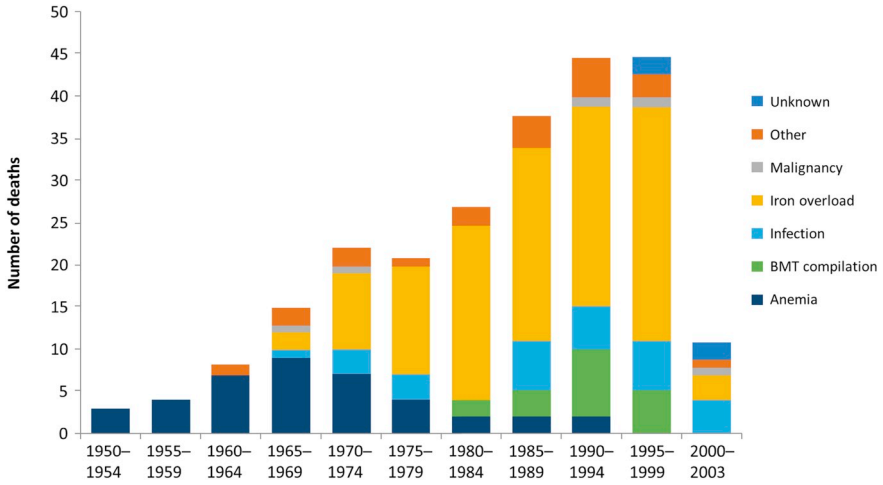

Fig. 2. Change in cause of death among patients with β-thalassemia major in the UK. Reproduced from Modell et al. [29]. BMT, bone marrow transplantation.

marrow hyperplasia [6,7,24].

Life expectancy for patients with β-thalassemia has improved dramatically since the development of ICT [25]. In Greece, patients' median age has increased from 10.5 years in 1983 to 34.5 years in 2008 [26]. In Palestine, the average patient age has increased from 7–8 years in 1996 to 19–20 years in 2015 [27]. In Taiwan, BTM mortality rates have decreased from 2.9% in 2007 to 0.7% in 2011, and 5-year survival rates have improved from 89.6% for patients born before 1995 to 94.3% for those born after 1995 [28]. In the UK, all-cause mortality rates have decreased significantly, from 12.7 per 1000 patients per year in 1990–1999 to 4.3 in 2000–2003 (a 62% decrease), mainly due to a reduction in deaths caused by iron overload (Fig. 2) [29]. Factors that improved survival included better awareness of BTM and its management among healthcare providers and patients, guidelines for safe processing of blood and blood products, better techniques for assessing iron overload, the availability of oral ICT, and compliance with ICT [4,30].

3. Guidelines on blood transfusion in thalassemia

Hb levels above 120 g/L for adult women and 130 g/L for adult men are considered normal [31]. General transfusion guidelines recommend initiating transfusions at an Hb threshold of 60–100 g/L, depending on the presence and severity of comorbidity [32]; however, these guidelines focus mainly on correcting anemia rather than suppressing ineffective erythropoiesis and may not be applicable to patients with β-thalassemia [33]. Guidelines for the management of β-thalassemia are available, including international guidelines by the Thalassaemia International Federation (TIF) [6] and several national guidelines [7,24,34,35]. There is a general consensus regarding most aspects of management, with some differences in iron overload assessment strategies and recommendations for ICT [36].

Patients with β-thalassemia should receive leukoreduced packed RBCs with a total Hb content of at least 40 g [6]. The blood should be obtained from voluntary nonremunerated donors and collected, processed, tested, stored, and distributed by high-quality blood transfusion centers. The decision to start blood transfusions should be based on the presence of anemia and/or clinical symptoms, such as failure to thrive (identified as reduced growth velocity and delayed developmental milestones), decreased QoL, and comorbidities such as organ dysfunction and extramedullary hematopoiesis [6,7,24,34]. TIF, UK, and US guidelines recommend initiating blood transfusions at an Hb threshold of 70 g/L (measured on two occasions approximately 2 weeks apart, excluding other causes for the anemia), or the presence of clinical complications irrespective of Hb level [6,7,24,34].

The blood volume received during transfusion is determined by pretransfusion Hb levels. In patients with TDT, pretransfusion Hb levels should be 90–105 g/L, and post-transfusion Hb levels should not exceed 140–150 g/L [6,7,24,34]. This strategy has been shown to facilitate normal growth and activity levels while minimizing iron overload [6]. Higher target pretransfusion Hb levels of 100–120 g/L [24] or 110–120 g/L [6] are recommended for patients with cardiac dysfunction or worsening/symptomatic extramedullary hematopoiesis. The British Society for Haematology recommends the following calculation to determine transfusion volume (mL) in pediatric patients: (Desired Hb [g/L] – Actual Hb [g/L] × Weight [kg] × Factor)/10, in which the factor ranges between 3 and 5 depending on the clinical situation [37]. However, this calculation is based on a UK standard unit of packed RBCs, which has an average hematocrit level of 0.5–0.6 [37]. Adult patients with BTM usually receive 2–4 donor units of blood every 3–4 weeks, but it may be prudent to use the pediatric calculations in very small adults (i.e., less than 40 kg). The volume and frequency of blood transfusions are adapted to patients' age and body weight and are often advised on the premise that the patient is getting a plasma- and leukoreduced-packed RBC unit.

Patients with BTI typically require few or no blood transfusions. They may receive sporadic transfusions at times of illness (e.g., sepsis) or for short periods (e.g., during pregnancy). For patients with BTI who become transfusion dependent, the transfusion regimen is similar to that used in patients with BTM.

4. Healthcare burden of β-thalassemia

In countries where hemoglobinopathies are endemic, β-thalassemia places a considerable strain on local healthcare resources and blood supplies. Between 1997 and 2010, the 4506 patients with hemoglobinopathies (including β-thalassemia) in the Greek national registry consumed 18% of the nation's total RBC supply [38]. Similarly, patients with BTM in Hong Kong used 9.5% of the national blood supply in 2009 [39], and this figure is expected to increase to 31.7% in 2024 [40]. In 2004, a UK modeling study predicted a 20% increase in the national demand for blood products relative to the supply within 20 years [41]. However, thanks to the development of national policies on the use of blood products, a more recent forecast estimates a slow decline in RBC demand between 2019 and 2022 [42].

5. National blood transfusion policies: the international picture

The World Health Organization (WHO) reported that, in 2013, 68% of 180 WHO member states had a national policy for establishing and managing blood transfusion services [43]. Whole-blood donation rates varied widely by region (0.3–56 donations per 1000 population per

year) and are not expected to meet blood demand in some countries. Examples include Greece and Italy, where β-thalassemia is prevalent: these countries rely on regional and international imports to overcome shortfalls in blood supply [44–46]. National blood policies are becoming more common in regions where β-thalassemia is endemic, such as South Asia [47]. WHO provides documentation and guidance for blood transfusions that can be used to develop and improve systems in resource-poor countries [48,49]. In 2003, the European Union created the European Blood Directive, which established quality and safety standards for the collection, processing, and distribution of human blood and blood components [50]. The European Committee on Blood Transfusion reported that most of the 45 countries evaluated had a nationally coordinated blood program (85%), but 22.5% of countries, including many countries with a high prevalence of hemoglobinopathies, could not meet their national need for blood supplies [51]. In 2004, eight Southeast European countries started a successful project to develop national policies on blood safety and increase the availability of safe and sustainable blood supplies from voluntary nonremunerated donors [52]. Many challenges remain for these blood services, including a lack of national authority, adequate financing, infrastructure, quality systems, information technology support, and hemovigilance policies.

While centralized blood transfusion policies may be present in well-resourced nations where β-thalassemia is endemic [12], many patients in resource-poor countries with a high prevalence of β-thalassemia do not have access to safe blood transfusions [53]. Barriers include fragmented and inefficient services, varying quality standards, and a lack of infrastructure and political support [53]. Many countries seek blood donations from family members or paid donors to meet demand. In Nigeria, 25% of blood donations are from paid donors [54], and even in European countries such as Italy, where there are national policies and specialized services in place, substantial variability exists between clinics [55].

Internal and external quality assessments are important components of blood transfusion services. WHO promotes the establishment of national quality-assessment programs, especially for TTI screening [56]. Laboratories that follow these quality controls have shown an improvement in quality and safety of blood transfusion [57,58].

6. Timely blood supply for patients

6.1. Blood donations and availability

In 1998, WHO established the Global Database on Blood Safety (GDBS) to compile and analyze data on blood and blood product safety to improve blood transfusion services worldwide [43]. Data from the GDBS indicate significant regional differences in blood donation levels, which range from 0.3 to 56 donations per 1000 population per year. Donation rates were highest in Europe, North America, and Australia and lowest in Africa and Southeast Asia, where β-thalassemia is endemic. From 2008 to 2013, the total number of blood donations increased by 20%. The largest increases were seen in Africa (from 2.95 million to 4.34 million, a 47% increase) and Southeast Asia (from 10.52 million to 14.86 million, a 41% increase), with a similar trend in the number of voluntary nonremunerated donations (in Africa, a 37% increase from 2.13 million to 2.92 million; in Southeast Asia, a 75% increase from 7.09 million to 12.44 million). Most (83.3%) of the 88.2 million whole-blood donations came from voluntary nonremunerated donors, while 16.4% were from family replacement donors (i.e., family members asked by the hospital to replace the blood supply used by the patient) and 0.3% from paid donors. Family replacement donors provided more than 50% of all donations in 71 of the 180 countries sampled. The proportion of voluntary nonremunerated donors was lowest in low-income countries. However, blood supplies in low-income countries remain too low to meet demand, leaving blood services no choice but to seek family replacement or paid donors.

Another signification complication is that a substantial proportion of all donated blood was discarded before transfusion [43]. Median blood discard rates were highest in low-income countries (9.0%, range 0.6–20.0%) and lower-middle-income countries (10.9%, range 0.5–26.4%). The most common reasons for discarding blood were the presence of infectious agents and exceeding the expiration date for blood products. While it is believed that transfusion of fresher blood may be beneficial to patients [7], studies remain inconclusive [59,60]. The debate has led to variations in the recommended time that blood can be stored prior to transfusion [61].

6.2. Variations in the availability and practices of blood transfusion services

Globally, more than 22,500 deaths occur annually because TDT patients do not receive adequate transfusions [10]. A WHO survey reported that the proportion of patients with TDT who receive blood transfusions ranges from less than 3% in African and Western Pacific regions to 52.4% in the Americas [10]. Due to blood shortages and high costs, patients with TDT in resource-poor countries often have inadequate transfusion and Hb levels below recommended levels [53,62].

In South Asia, a 38% regional shortfall in blood supplies has been reported [47]. Although seven countries in South Asia have national blood policies, fragmented blood transfusion services without sufficient regulatory control are prevalent. Other reasons for inadequate blood supplies include a lack of a proper reporting system and unauthorized blood collections and transfusions in nonregulated sectors [47]. Recently, wealthier nations have also been affected by insufficient blood supplies. In Northeastern Germany, whole-blood donations decreased by 18% between 2005 and 2015 [63]. In Taiwan, where β-thalassemia is prevalent, the numbers of young and repeat blood donors have decreased since 2000 [64].

6.3. Donor motivation

One reason for low blood supply in many countries is a lack of voluntary nonremunerated blood donors. Barriers to voluntary blood donation may include misinformation in the donor population. A Nigerian study among 542 blood donors showed that 52% of donors believed they could get human immunodeficiency virus (HIV) and/or hepatitis from blood donation, and 47% were afraid of side effects, including weight loss (24%), sexual failure (6%), and sudden death (3%) [65]. In a study in Saudi Arabia, the main reasons for not donating blood were lack of time, inability to access the blood donation center, fear of anemia, and family discouragement [66]. More research into donor motivation would be beneficial to national blood donor recruitment programs.

International organizations, such as WHO and the Red Cross, discourage paid blood donation, as offering money may attract unhealthy donors, lead to anemia due to frequent donations, and drive altruistic donors away, resulting in fewer donors overall [67]. However, this practice is still widespread in many countries. In Pakistan, which struggles to maintain adequate blood supplies, only 10% of blood donations are from voluntary unpaid donors; the remainder are from replacement donors (75%) or paid donors (15%) [53]. A Nigerian survey reported that donors prefer incentives such as certificates (41%) or money (14%), and fewer than 3% of respondents would donate for free [65]. However, 92% of 316 non-donating students reported that they would donate if a relative or friend needed blood. A Saudi Arabian study of 517 blood donors showed that 91% of donors objected to monetary compensation, although 63% would accept a token gift [68].

6.4. Successful strategies to improve rates of blood donation

Several countries in which β-thalassemia is endemic have implemented strategies to improve blood donations and blood transfusion services. In Turkey, a successful program to increase the number of

Table 1
Frequency of medical complications related to blood transfusions in patients with β-thalassemia.

Complication	Prevalence, % (n/N)	Incidence, per 100,000 person-years	Country	Reference, year
Iron overload				
Inadequate iron chelation	61.2 (59,764/97,630)		World	Modell et al. [10], 2008
	~60 (NR/1744)		23 countries (EPIC study)	Viprakasit et al. [86], 2013
	98 (140/142)		India	Shah et al. [87], 2010
	66.1 (199/301)		Tunisia	Bejaoui and Guirat [88], 2013
Death due to iron overload		3.1	World	Modell et al. [10], 2008
Cardiac morbidity				
Cardiac disease (general)	20.5 (46/224)		Italy	Bonifazi et al. [89], 2017
	37 (36/97)		USA	Olivieri et al. [90], 1994
	19.8 (63/318)		Tunisia	Bejaoui and Guirat [88], 2013
Cardiac death		9.5 on DFO 2.5 on DFX 1.4 on combination ICT	Greece	Ladis et al. [91], 2010
	2.8 (10/359) on DFO 0 (0/157) on DFP		Italy	Borgna-Pignatti et al. [92], 2006
	39 (20/51)		Tunisia	Bejaoui and Guirat [88], 2013
	18.6 (18/97)		USA	Olivieri et al. [90], 1994
Heart failure	6.8 (49/720)		Italy	Borgna-Pignatti et al. [93], 2004
	53.9 (34/63)		Tunisia	Bejaoui and Guirat [88], 2013
	18.9 (86/454)		Taiwan	Wu et al. [28], 2017
Arrhythmias/atrial fibrillation	4.5 (10/224)		Italy	Bonifazi et al. [89], 2017
	17.6 (80/454)		Taiwan	Wu et al. [28], 2017
	5.7 (41/720)		Italy	Borgna-Pignatti et al. [93], 2004
	7.9 (5/63)		Tunisia	Bejaoui and Guirat [88], 2013
Endocrine dysfunction				
Endocrine disease (general)	25.0 (56/224)		Italy	Bonifazi et al. [89], 2017
Hypogonadism	54.7 (273/499)		Italy	Borgna-Pignatti et al. [93], 2004
	23.1 (105/454)		Taiwan	Wu et al. [28], 2017
Growth retardation	Low (NR)		Italy	Bonifazi et al. [89], 2017
	26.7 (64/239)		Tunisia	Bejaoui and Guirat [88], 2013
	72 (103/142)		India	Shah et al. [87], 2010
Delayed puberty	39.3 (88/224)		Italy	Bonifazi et al. [89], 2017
	51.1 (46/90)		Tunisia	Bejaoui and Guirat [88], 2013
	62 (13/21) in patients who started DFO after age 10 10 (2/19) in patients who started DFO before age 10		Canada	Bronspiegel-Weintrob et al. [94], 1990
Diabetes	6.4 (46/720)		Italy	Borgna-Pignatti et al. [93], 2004
	4.2 (13/309)		Tunisia	Bejaoui and Guirat [88], 2013
	21.2 (96/454)		Taiwan	Wu et al. [28], 2017
	3.5 (5/142)		India	Shah et al. [87] 2010
Hypothyroidism	10.8 (78/720)		Italy	Borgna-Pignatti et al. [93], 2004
	17.9 (40/224)		Italy	Bonifazi et al. [89], 2017
	6.8 (18/262)		Tunisia	Bejaoui and Guirat [88], 2013
	8.8 (40/454)		Taiwan	Wu et al. [28], 2017
Hypoparathyroidism	2.0 (9/454)		Taiwan	Wu et al. [28], 2017
Skeletal complications (osteoporosis, osteopenia, lordosis)	17.4 (79/454)		Taiwan	Wu et al. [28], 2017
	59.8 (134/224)		Italy	Bonifazi et al. [89], 2017
Liver disease				
Hepatic disease (general)	50.4 (113/224)		Italy	Bonifazi et al. [89], 2017
Cirrhosis	16.5 (75/454)		Taiwan	Wu et al. [28], 2017
Infections				
HIV	1.7 (12/720)		Italy	Borgna-Pignatti et al. [93], 2004
	0 (0/391)		Tunisia	Bejaoui and Guirat [88], 2013
	2 (3/142)		India	Shah et al. [87], 2010
		2.16	USA	Zou et al. [95], 2012
	0.18/1,000,000 donations		UK	SHOT [96], 2016
	0.5 (6/1253)		Pakistan	Ahmed Kiani et al. [97], 2016
	0.3 (NR/1321)		Greece	Politis [26], 2010

(*continued on next page*)

Table 1 (*continued*)

Complication	Prevalence, % (n/N)	Incidence, per 100,000 person-years	Country	Reference, year
HBV	2 (3/142)		India	Shah et al. [87], 2010
		2.62	USA	Zou et al. [95], 2012
	0.79/1,000,000 donations		UK	SHOT [96], 2016
	2.3 (9/391)		Tunisia	Bejaoui and Guirat [88], 2013
	3 (38/1253)		Pakistan	Ahmed Kiani et al. [97], 2016
	1.8 (NR/1321)		Greece	Politis [26], 2010
HCV	44.6 (100/224)		Italy	Bonifazi et al. [89], 2017
	45 (64/142)		India	Shah et al. [87], 2010
	6.1 (24/391)		Tunisia	Bejaoui and Guirat [88], 2013
	54 (NR/1321)		Greece	Politis [26], 2010
	21.7 (273/1253)		Pakistan	Ahmed Kiani et al. [97], 2016
	0.025/1,000,000 donations		UK	SHOT [96], 2016
		2.98	USA	Zou et al. [95], 2012
Syphilis	0		UK	JPAC [98], 2014
Alloimmunization				
Any (unspecified)	8.2 (26/316)		Tunisia	Bejaoui and Guirat [88], 2013
	3.1 (NR/1321)		Greece	Politis [26], 2010
	2.8 (NR/4506)		Greece	Politis [38], 2013
	7.98 (15/188)		Egypt	Abdelrazik et al. [99], 2016
	7.59 (6/75)		India	Mittal et al. [100], 2014
	16.5 (115/697)		USA	Thompson et al. [101], 2011
Anti-D	4.25 (8/188)		Egypt	Abdelrazik et al. [99], 2016
Anti-E	1.1 (2/188)		Egypt	Abdelrazik et al. [99], 2016
	1.3 (1/75)		India	Mittal et al. [100], 2014
Anti-C	1.6 (NR/1321)		Greece	Politis [26], 2010
	1.1 (2/188)		Egypt	Abdelrazik et al. [99], 2016
Anti-Kell	1.1 (2/188)		Egypt	Abdelrazik et al. [99], 2016
	5.3 (4/75)		India	Mittal et al. [100], 2014
Other acute complications				
Nonhematolytic febrile transfusion reactions	41 (NR/1321)		Greece	Politis [26], 2010
		89.9	Greece	Politis [38], 2013
	1			TIF [6], 2014
Allergic reactions	41 (NR/1321)		Greece	Politis [26], 2010
		87.6	Greece	Politis [38], 2013
	1			TIF [6], 2014
Transfusion-related acute lung injury		0.13	Greece	Politis [38], 2013
	1 in 10,000			TIF [6], 2014
Intravascular hemolysis	1 in 25,000			TIF [6], 2014
Other delayed complications				
Extravascular hemolysis	1 in 2500			TIF [6], 2014
Transfusion-related graft-versus-host disease	Rare			TIF [6], 2014
DHTR/DSTR		13.2	Greece	Politis [38], 2013

DFO, desferrioxamine; DFP, deferiprone; DFX, deferasirox; DHTR, delayed hemolytic transfusion reaction; DSTR, delayed serological transfusion reaction; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICT, iron chelation therapy; NR, not reported.

blood donors for patients with thalassemia was started in 1998, allowing donors to donate blood specifically for patients with thalassemia [69]. In the Maldives, the National Thalassemia Center maintains a blood bank specifically for patients with thalassemia; however, blood is mainly provided by family replacement donors [47]. In 1990, the Omani Ministry of Health started a national campaign with local blood drives and remuneration, which led to self-sufficiency in blood supplies within a year [70]. A public awareness campaign, including posters and an annual event to honor donors, was implemented to encourage voluntary nonremunerated donors [70]. A similar strategy was enacted in Iran, which established a national blood transfusion service, resulting in a 100% voluntary nonremunerated blood donation rate [53]. Since 2004, the US President's Emergency Plan For AIDS Relief (PEPFAR) has provided financial support to national blood transfusion services in 14 countries in the Caribbean and sub-Saharan Africa. PEPFAR support led to a 19% increase in blood collections between 2011 and 2014, but only four countries (Botswana, Guyana, Namibia, and South Africa) had blood donation levels above 10 units per 1000 population (1%), the WHO-recommended adequacy level [71].

In South Asia, the significant shortfall between the total annual blood demand (16 million units) and the amount of blood donated (10 million units) has led to several initiatives to improve practices across the region [47]. In Myanmar, a public awareness program effectively increased the proportion of voluntary nonremunerated donors, which is now approaching 85% [47,72]. In Taiwan, following a 13-year public health and awareness campaign to increase the proportion of voluntary nonremunerated blood donors, paid blood donation was prohibited in 1987. Since then, voluntary blood donation rates in the population have increased by 8.13% [64].

Improvements have also been observed in countries with more advanced blood transfusion services after national blood policies were changed. After a universal fresh-blood policy for adult patients with β-thalassemia was implemented in the UK, pretransfusion Hb was significantly higher (mean increase 0.5 g/L) and fresher blood was used (mean age 9.5 days vs. 18 days) [73]; however, the sample size was small (n = 9). Moreover, NHS Blood and Transplant has developed a plan to increase blood donations by 2020 through multiple activities and initiatives, such as improving donors' overall experience [74]. Australia's national blood service adopted a framework for planning and inventory management that has helped meet demand and reduce blood product wastage [75].

6.5. Health services for β-thalassemia in the UK

Among European countries where β-thalassemia is not endemic, only the UK and France have health service policies for hemoglobinopathies [12]. In the UK, regional networks consist of local hemoglobinopathy teams (LHTs) supported by a specialist hemoglobinopathy team (SHT). Development of Haemoglobinopathy Coordinating Centres is underway to support regional activity, training, and consultation. Best-practice clinical guidelines are updated regularly, particularly concerning ICT and the management of specific complications. Attention is given to psychosocial aspects and treatment concordance, as patients frequently report anxiety and depression, especially as adults [76,77]. Attention is also given to specific patient groups, including pediatric patients transitioning into adult care and patients who were previously receiving treatment outside the UK. Services are independently reviewed every 2–3 years for quality purposes, using the quality standards developed by the UK Forum on Haemoglobin Disorders together with the West Midlands Quality Review Service [78]. In 2008, the UK National Haemoglobinopathy Registry was launched with the aim of informing healthcare planning by collecting information regarding numbers of patients with thalassemia syndromes, rare anemias, and sickle cell disease, and recording aspects of their clinical care and outcomes [7].

7. Safety of chronic blood transfusion therapy

Without transfusions, patients with BTM usually die before adolescence [14]; with transfusions, patients can expect to lead healthy lives well into adulthood and have a near-normal life span [6]. However, regular blood transfusions may interfere with school, work, and social functioning [62]. Cumulatively, thalassemia and its management have a substantial adverse effect on patient QoL [79–85].

Adverse events associated with blood transfusion can be acute (e.g., hemolytic reactions, infective shock, and severe allergic reactions) or delayed (e.g., TTIs, alloimmunization, and diseases related to iron overload such as cardiac, hepatic, and endocrine dysfunction) [6,14,28] (Table 1) [86–101]. The total incidence of transfusion-related adverse reactions, both acute and delayed, was 250 in every 100,000 transfusions based on data from 1315 patients with thalassemias between 1997 and 2010 [38]. In a study of complications and costs of treatment in 272 patients with BTM aged 12–50 years, 82.3% of patients reported having one or more delayed transfusion-related complications, leading to total additional costs (compared with routine care) of EUR 1232 per patient [86]. It is therefore vital to continually improve blood safety and reduce transfusion requirements.

7.1. Iron overload in patients with thalassemia

7.1.1. Consequences

Transfused blood contains iron, which mostly cannot be excreted from the body. Patients with β-thalassemia on a typical blood transfusion schedule accumulate iron at a rate of 0.3–0.6 mg/kg of body weight per day [6,7]. Excess iron within the body is toxic at levels above 12–24 g of total body iron [6,7] and accumulates in the heart, liver, and endocrine system [6]. Excess iron can lead to cardiomyopathy, and untreated patients may die from heart failure before 20 years of age [6,7]. Iron overload also increases the risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma, even in the absence of chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections. Iron overload may also lead to endocrine disorders, including hypogonadism, growth retardation, delayed puberty, infertility, diabetes, hypothyroidism, and hypoparathyroidism [6]. A population-based cohort study in Taiwan reported that cardiac complications were the most common complications in patients with BTM; endocrine dysfunction (hypogonadism and diabetes) and liver cirrhosis were also common [28].

7.1.2. Iron chelation therapy

Removing excess iron is essential in preventing complications due to iron overload, and ICT should be started within a year of initiating regular blood transfusions [7]. ICT improves overall survival [90,92,102–104] and decreases the risk of complications related to iron overload, such as heart disease, short stature, and endocrine abnormalities [90,91,93,94,105]. The first iron chelator to become widely available was desferrioxamine, which is administered subcutaneously or intravenously over 8–24 hours, 5–7 nights per week [7]. Desferrioxamine is therefore unpopular and leads to low treatment adherence, particularly in adolescents and young adults [7], which negatively affects survival [106,107]. Oral ICT (deferiprone and deferasirox) is now available and can be used alone or in combination with desferrioxamine [7]. Oral ICT has been shown to be more effective than desferrioxamine [108,109], with excellent compliance [109]. In the UK, most patients now receive ICT with either deferasirox or deferiprone monotherapy, or combination ICT (usually subcutaneous desferrioxamine and deferiprone), which has greatly impacted how thalassemia is perceived and experienced by patients and those around them [7]. Life expectancy in well-chelated patients with BTM has improved since 2000 [29,92,107].

7.1.3. Regional variation in ICT

ICT has led to notable improvements in survival in well-resourced countries; worldwide, however, fewer than 40% of patients with β-thalassemia receiving blood transfusions receive adequate ICT, resulting in approximately 3000 deaths each year [10]. An Indian study of 142 patients with BTM found that only 67% of eligible patients received any ICT, and just 2% of patients received adequate ICT [87]. Significant regional variation in myocardial and liver iron burden was highlighted by an analysis of data from CORDELIA, a randomized, phase 2 study that compared desferrioxamine with deferasirox in 925 patients with transfusion-dependent anemia (99% with β-thalassemia) from 11 countries worldwide [110]. In a Tunisian study of 391 patients with BTM, moderate iron overload (ferritin 1501–2500 ng/mL) was found in 61 patients (15.6%), while 81 patients (26.9%) had a ferritin level greater than 2500 ng/mL and 21 patients (6.9%) had a ferritin level greater than 5000 ng/mL [88]. Mortality rates due to insufficient iron chelation were highest in Southeast Asia and in the Eastern Mediterranean region, which together report approximately 2900 deaths each year due to iron overload (approximately 90% of worldwide deaths from iron toxicity) [10]. In a report from a Greek national registry that included 4506 patients with hemoglobinopathies, heart disease (52.3%) and liver carcinoma (13.8%) were the most common causes of death in patients with β-thalassemia [46]. A retrospective Italian study of 284 patients with BTM showed that since the introduction of ICT, the life expectancy of patients with BTM has increased and approaches that of patients with BTI [104]. In this study, the most common cause of death in patients with BTM was cardiac complications (40.0%), whereas cancer (38.5%) and infections (23.1%) were the most common causes of death in patients with BTI.

7.1.4. Impact of ICT on QoL

While some reports suggest that ICT negatively affects patient QoL [81,83], oral ICT may have a more favorable effect than desferrioxamine [81,82,84]. In an Iranian study of 528 patients with BTM, health utility scores were significantly higher for patients receiving oral ICT than for those receiving injectable ICT [82]. In a study of adolescents (aged 13–17 years) in Iraq, the best QoL scores were observed in patients given deferasirox, followed by desferrioxamine, and combination therapy; in younger patients (aged 2–12 years), the type of ICT did not influence QoL significantly [84]. Since ICT is a clinical necessity in TDT, it is important to provide patients with an effective and manageable ICT regimen.

7.1.5. Economic costs of ICT

Even though prices may be negotiated locally, ICT is a major cost

driver in β-thalassemia [111]. A retrospective Greek study of 331 patients (87.6% with β-thalassemia) estimated that the mean overall cost per patient was EUR 35,928 for deferasirox treatment, EUR 34,035 for combination therapy (desferrioxamine plus deferiprone), EUR 31,637 for desferrioxamine, and EUR 17,208 for deferiprone [111]. Overall, 31% of patients received deferasirox (33%), 23% received combination therapy, 97% received deferiprone, and 5.1% received desferrioxamine.

Cost-effectiveness analyses in the UK and Italy have shown that deferiprone is more cost-effective than desferrioxamine and deferasirox for managing chronic iron overload in patients with β-thalassemia [112,113]. A UK economic study compared the lifetime cost utility of deferasirox and desferrioxamine and found the higher acquisition costs of deferasirox were offset by the high costs of infusion-related equipment for desferrioxamine [114]. A subsequent analysis found that deferiprone was more cost-effective than all ICT comparators, at a willingness-to-pay threshold of GBP 20,000 [112]. In Italy, deferiprone was also found to be the most cost-effective ICT; deferasirox was associated with a greater gain in quality-adjusted life years (QALYs) but at a significantly higher overall cost [113].

In a Thai study, deferiprone was associated with lifetime cost savings of USD 91,117 compared with desferrioxamine, while deferasirox was not found to be cost-effective [115]. In contrast, an Iranian study reported that deferasirox was more cost-effective than subcutaneous or intravenous desferrioxamine [116]. In international dollars ($Int; used to compare countries' purchasing power), the estimated total lifetime costs per patient treated with deferasirox were $Int 47,029 and estimated total discounted QALYs per person were 12.28, compared with $Int 143,522 and 7.76 QALYs for desferrioxamine. In summary, the patchy results of ICT cost-utility analyses may be related to the fact that the pharma industry has been directly or indirectly involved in the published studies.

7.2. Transfusion-transmitted infections

TTIs, including viral, bacterial, and parasitic infections, are a major risk associated with regular blood transfusion [6,14]. WHO and the TIF recommend screening all donated blood for HIV, HBV, HCV, and syphilis [6,43,56]. The incidences of these four main TTIs are summarized in Table 1. In certain countries, screening for other local infectious diseases such as human T lymphotrophic virus (HTLV1 and 2) and Chagas disease is also advised [6,43,56]. Emergent pathogens, such as the Zika virus, variant Creutzfeldt-Jakob disease, and hepatitis E, have led to additional screening recommendations in some areas [117–119]. Strict donor blood screening and quality-control measures have increased blood safety significantly over the past decades, resulting in a very low risk of TTIs in countries with well-regulated blood supplies [32,120]. In the USA, the risk of TTIs among donors is below one in 1 million donations for HIV, HCV, and HTLV, and one in 300,000 for HBV [95]. The incidence of transfusion-transmitted syphilis infections in the USA and Australia has been so low in recent decades that it has sparked debate regarding the continued need to test blood donors for syphilis [121,122].

In low-income countries, it is estimated that approximately 2.3% of all blood donations are infected with HIV, compared with 0.001% in high-income countries [123]. The latest WHO report on blood safety reported that 13 countries are currently unable to screen 100% of blood donations for one or more of the four key TTIs (HIV, HBV, HCV, and syphilis) [43]. Thirty-five countries reported that they had run out of testing kits for TTIs either nationally or regionally, at least once during the reporting period [43]. In Nigeria, the high prevalence of TTIs in the general population (HIV, 18%; HBV, 23%; HCV, 13%), a high reliance on paid blood donors, and lack of universal access to screening tools for TTIs, is likely to compromise the safety of donated blood [54]. Similarly, in Tanzania, 12.7% of blood donors, especially HIV-positive donors, were positive for syphilis antibodies [124]. A review in India demonstrated that although the prevalence of viral disease was 2% in blood donors, the prevalence of TTIs in patients with β-thalassemia was 45% due to ineffective blood screening and cumulative risk exposure [125]. In another Indian study of 142 patients with BTM, the prevalence of HCV, HBV, and HIV was 45%, 2%, and 2%, respectively; up to 15% of children born in or after 2002 were HCV positive despite blood screening for HCV [87]. Similarly, a cross-sectional study of 1253 Pakistani patients with BTM who had received multiple transfusions reported that 317 (25.3%) patients had TTIs (HCV, 21.7%; HBV, 3.0%; HIV, 0.5%) [97]. These data show that transfusion blood safety is still a concern, particularly in low- or middle-income nations, where the prevalence of TTIs in the general population is relatively high and donor blood screening may not meet international standards [43]. However, the risk of infection from transfusion is decreasing in both resource-poor and well-resourced countries, and this trend may accelerate with the introduction of pathogen inactivation systems for RBCs [126].

7.3. Alloimmunization

Alloimmunization, the development of antibodies against specific RBC antigens, occurs in 10–20% of transfusion-dependent patients with β-thalassemia [6,101,127,128] and causes difficulties in RBC cross-matching, shortened in vivo survival of donor blood, and an increased rate of iron accumulation [101,127]. The most common alloantibodies are anti-E, anti-C, and anti-Kell, and 5–10% of patients develop alloantibodies against other RBC antigens. To reduce the risk of alloimmunization, international and national guidelines recommend that all blood donations should be screened, and patients should be given antigen-compatible blood, including ABO, Rh (C, c, D, E, e), and Kell [6,7,24,34]. However, a 2011 survey of eight thalassemia centers in the USA revealed notable differences in the approach to antigen testing [129].

The reported prevalence of RBC alloantibodies varies among countries. In a study by the Thalassemia Clinical Research Network involving 697 patients with thalassemia (582 with β-thalassemia), 16.5% of patients developed alloantibodies, of which 19.0% were anti-E, 18.1% were anti-Kell, and 9.5% were anti-C [101]. Greek studies among patients with hemoglobinopathies reported alloimmunization in 2.8–3.1% of patients [26,38]. In Nigeria, the observed prevalence of RBC sensitization varied between 3.4% and 18.7% [54], and the prevalence of alloimmunization in India ranged from 3.8% to 9.8% [100]. An Egyptian study in 188 patients (147 with BTM) reported an alloimmunization prevalence of 7.98%, with anti-D being the most common alloantibody (4.25%) [99]. In a UK study, 11 of 105 transfusion-dependent patients with thalassemia (98 with BTM) had evidence of alloimmunization [130]. Alloimmunization occurs more frequently in patients who initiate blood transfusions after the age of 3 and in those who receive sporadic transfusions [99,100,131–133]. Higher rates of alloimmunization have also been observed in female patients, in patients with BTI (due to older age at initiation of transfusions), in splenectomized patients, and in Rh(D)-negative patients [99].

7.4. Other complications of blood transfusions

Acute complications of blood transfusions include febrile non-hemolytic transfusion reactions (occurring in 1% of transfusions), allergic reactions (1%), transfusion-related acute lung injury (0.01%), and intravascular acute hemolytic transfusion reactions (0.004%) [6]. Delayed adverse reactions to blood transfusions include extravascular delayed hemolytic transfusion reactions (occurring in 0.4% of transfusions) and transfusion-associated graft-versus-host disease, which is very rare [6]. Bone disease and osteoporosis have also been reported and have a multifactorial background [14,134].

8. Economic costs of blood transfusions

Blood transfusions are expensive [32]. In 2008, the mean direct cost of one unit of leukoreduced RBCs in the USA was estimated at USD 223 [135]. This increases to USD 761 when costs associated with acquisition and patient administration are also included [136]. A more recent US retrospective cohort study indicated that the mean total annual cost of treating a transfusion-dependent patient with β-thalassemia was USD 128,062, which was significantly higher than the cost of treating a matched control patient (USD 5438) [137]. ICT and RBC transfusions were the main cost drivers in this study with mean annual costs per patient of USD 61,974 and USD 39,723, respectively. These costs were higher than the costs identified by Paramore et al. in their analysis of a US administrative claims database from 2011 to 2016, which estimated the mean cost per patient at USD 52,718 for ICT and USD 22,748 for blood transfusions, respectively [138]. In Greece, where the national prevalence of BTM is approximately 8%, the mean annual cost per patient with β-thalassemia was EUR 32,064 for all treatment strategies in 2009–2011; the main cost drivers were medication including ICT (45.9%), and blood transfusions (38.1%) [111]. In Thailand, the annual average cost of β-thalassemia treatment was estimated at USD 950 in 2010, with a median annual cost of USD 109 directly related to blood transfusions [139]. Drugs for ICT contributed to 39% of total medical costs, but adequate iron chelation significantly reduced the burden and cost of complications from thalassemia and blood transfusions.

9. Consequences of undertransfusion

Of approximately 25,500 transfusion-dependent children born with β-thalassemia worldwide each year, only 3000 (11.7%) actually receive blood transfusions [10] (Fig. 1). As a direct consequence, at least 22,500 patients with β-thalassemia die each year. Southeast Asia and the Eastern Mediterranean region have the highest mortality rates, which WHO estimated in 2008 at 9021 and 7443 deaths each year, respectively [10]. A Thai study reported that most patients with BTM died from anemia and very few died due to heart failure, suggesting that a high proportion of patients received inadequate transfusion [140]. Indeed, the study reported that in Thailand, only 20% of patients with BTM survive until their fourth decade. Of 142 Indian patients with BTM receiving multiple blood transfusions, 76 (53.5%) were undertransfused [87].

Inadequate transfusions leave patients with β-thalassemia exposed to the progressive effects of chronic anemia, such as reduced QoL and long-term complications [6,7]. Anemia-related symptoms, such as fatigue, generalized weakness, and diminished mental alertness, may affect patients' QoL in many ways, and several studies have reported that patients with more severe anemia tend to have a worse QoL [81,85,141]. In a cross-sectional study of 315 Thai pediatric patients with thalassemia, lower pretransfusion Hb levels negatively affected QoL. Patients with pretransfusion Hb levels greater than 90 g/L had significantly higher total QoL scores, psychosocial health summary scores, and social and school functioning subscale scores on a pediatric QoL tool (PedsQL 4.0 Generic Core Scale) than patients with pretransfusion Hb levels of 70–90 g/L or less than 70 g/L [85]. Similarly, in a survey of Omani children, those with higher pretransfusion Hb levels and lower serum ferritin levels had better overall QoL scores, as reported by their parents and caregivers [141]. QoL in children can also be negatively affected by multiple factors including blood transfusion frequency [81] and the need for ICT [81,83,84]. In the Thalassemia Clinical Research Network's Thalassemia Longitudinal Cohort study, patients with more disease complications and side effects from chelation reported lower QoL scores than did patients with fewer complications and side effects [142].

In patients with β-thalassemia who receive insufficient blood transfusions, ineffective erythropoiesis is not fully inhibited and bone alterations are not fully prevented [6,143]. Iron absorption in the gastrointestinal tract increases to 3–5 mg/day or more (compared with iron absorption of 1–2 mg/day in healthy individuals), resulting in an additional 1–2 g of iron accumulation annually [6]. Although this accumulation is much lower than that seen in patients on a regular transfusion schedule, it can nevertheless lead to iron toxicity and organ complications over time. Possible reasons for the prevalence of undertransfusion in resource-poor nations include a lack of donor blood, limited access to transfusion and chelation treatments, heterogeneity in standards of care [55], and clinicians' insufficient understanding of the clinical impact of undertransfusion on patients [85]. While desferrioxamine is available in resource-poor nations, infrastructural challenges often block patients' timely access to these drugs. Deferasirox is fully reimbursed in more than 40 countries, with some form of government or private funding in more than 20 additional countries.

10. Alternatives to blood transfusions in the treatment of β-thalassemia

Alternatives to blood transfusions include splenectomy, HSCT, and hydroxyurea [13]. Splenectomy can increase Hb levels and improve growth and QoL and was used historically as an alternative for blood transfusion therapy. However, splenectomy is associated with an increased risk of sepsis and thrombosis, and, for most patients, its disadvantages outweigh the potential benefits [6,13]. Today, with adequate blood transfusions, the need for splenectomy is decreased in most transfusion-dependent patients with β-thalassemia [144].

HSCT is a curative and cost-effective treatment option for children with BTM and can significantly improve overall survival and QoL [6,13,23]. However, HSCT is not available to many patients due to their age, a lack of matched donors, high initial costs, and a significant risk of morbidity and mortality [6,13].

Hydroxyurea increases fetal Hb levels and is approved for reducing the need for blood transfusions in patients with sickle cell disease [13]. Studies of hydroxyurea in patients with β-thalassemia have reported inconsistent results [145], and a Cochrane review found no conclusive evidence that hydroxyurea reduces transfusion requirements in patients with BTI [146]. Current guidelines suggest that hydroxyurea may be considered to treat specific patients with β-thalassemia, such as patients who are alloimmunized and patients with BTI who are homozygous for the *Xmnl* polymorphism or have pulmonary hypertension or leg ulcers [147]. However, patients receiving hydroxyurea should be monitored closely for response, and in the absence of response, considered for alternative treatments. Other fetal Hb inducers that have been tested in humans include 5-azacytidine, decitabine, short-chain fatty acids, and thalidomide [6,145,147]. New fetal Hb inducers can now be screened by efficient ex vivo systems, driving clinical development [148]. Clinical evidence for making recommendations on the use of these treatments is lacking.

A better understanding of the disease and its pathology has led to the development of new treatment approaches for β-thalassemia. Initial phase 2 clinical trial results indicate that luspatercept, an investigational first-in-class erythroid maturation agent, ameliorates anemia, decreases the need for blood transfusions, and reduces complications associated with the disease and blood transfusions [149]. In BELIEVE, a recent phase 3 study of adult patients with β-thalassemia, 21.4% of luspatercept-treated patients reached the primary endpoint of a ≥ 33% reduction in transfusion burden (with a reduction of ≥ 2 RBC units) versus 4.5% of patients who received a placebo [150]. Preclinical trials have shown that novel treatments that increase hepcidin levels and improve iron dysregulation, such as hepcidin mimetics and TMPRSS6 inhibitors, can reduce ineffective erythropoiesis, anemia, and iron overload, and represent potential new therapeutic options for β-thalassemia [151–153]. Synthetic hepcidin is now in phase 2 clinical development [154]. Finally, gene therapy, or gene editing, may offer a potential cure for β-thalassemia. However, this approach may be too expensive for many, especially those living in lower-income countries,

where β-thalassemia is most prevalent [155]. Lentiglobin products have shown positive preliminary results in transfusion-dependent patients [156]. Phase 3 trials (NCT03207009, NCT02906202) are ongoing to determine gene therapy's potential in treating β-thalassemia, and gene editing approaches are currently in full preclinical development, as they are deemed very promising for β-thalassemia. Different approaches are under investigation, including correcting specific β gene mutations, suppressing the whole mutated β gene, or suppressing the *BCL11A* gene or others involved in postnatal γ-gene inactivation [155].

11. Conclusions

RBC transfusion offers an essential lifesaving treatment for patients with severe β-thalassemia. Worldwide blood supplies are limited, particularly in (but not limited to) resource-poor nations, and the safety of transfused blood cannot be guaranteed in many countries due to their blood-screening and antigen-matching practices and general lack of donors. Many patients who receive regular transfusions for thalassemia do not receive adequate ICT to prevent complications arising from iron accumulation. As a result, blood transfusions for β-thalassemia are associated with medical complications and may place a significant burden on healthcare systems, especially in low- and middle-income nations that can least afford it. The disease does not significantly affect the finances of most countries where it is rare. Undertransfusion also results in poorer patient outcomes, such as shorter life expectancy and reduced QoL.

12. Future considerations

Governments of countries where β-thalassemia is prevalent recognize it as an important public health issue, though there is an unmet need for safe, effective, and affordable new treatments that reduce the blood transfusion burden in β-thalassemia. However, there is no "one-size-fits-all" approach, since β-thalassemia is an umbrella term for a variety of genetic conditions, and treatments affect patients differently. Nevertheless, new promising treatment strategies, such as erythroid maturation agents, hepcidin mimetics, and gene therapies are currently being explored and clinically tested.

In the meantime, it is important to increase awareness of β-thalassemia and improve access to safe, timely, and affordable treatments in countries where the disease poses a substantial burden, thereby preventing unnecessary morbidity and mortality.

Practice points

- Patients with BTM require regular RBC transfusions to suppress ineffective erythropoiesis and correct anemia. Without transfusions, patients usually die before reaching adolescence. The blood should be collected, processed, tested, stored, and distributed by high-quality blood transfusion centers.
- TTIs are a major risk associated with regular RBC transfusions, especially in countries with limited resources. Guidelines recommend screening all donated blood for HIV, HBV, HCV, and syphilis.
- Alloimmunization develops in 10–20% of transfusion-dependent patients with β-thalassemia. To reduce this risk, guidelines recommend that all patients should be given antigen-compatible blood.
- To avoid damage to major organs due to iron overload, lifelong daily ICT should be started within a year of initiating regular RBC transfusions. Oral ICT has been shown to be more effective than injectable ICT, with excellent compliance.
- HSCT is the only potentially curative therapy for β-thalassemia, but is not available to many patients due to their age, a lack of matched donors, high initial costs, and safety concerns.

Research agenda

- New treatment strategies that can reduce the economic and social burden of regular RBC transfusions are currently being explored and clinically tested.
- Luspatercept, an investigational first-in-class erythroid maturation agent, has been shown to ameliorate anemia and decrease the need for RBC transfusions in phase 2 and phase 3 trials.
- Preclinical trials have shown that hepcidin mimetics and TMPRSS6 inhibitors can reduce ineffective erythropoiesis, anemia, and iron overload. Moreover, synthetic hepcidin is now in phase 2 clinical development.
- Phase 3 trials are ongoing to determine the potential of gene therapy in treating β-thalassemia, and gene editing approaches are currently in full preclinical development.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Authors' contributions

F.T.S. selected the literature and designed the review. All authors participated in reviewing and editing the draft and approved the final manuscript.

Declaration of Competing Interest

F.T.S. has served on a steering committee for Celgene Corporation, a speakers' bureau for Novartis, and advisory boards for Celgene Corporation, La Jolla, Novartis, Silence Therapeutics, and Roche. F.S. has received research funding from Celgene Corporation. S.T. has served as a principal/chief investigator for research trials and on an advisory board for Novartis, and received research funding from Novartis. E.D. has served on speakers' bureaus for Novartis. A.P. has received research funding from Acceleron, Celgene Corporation, bluebird bio, and La Jolla.

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