

Multidisciplinary care in haemoglobinopathies

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Abstract

While most complications are related to haemoglobinopathies and their treatment, it is also possible to observe substantial differences in comorbidities' onset and seriousness which depend also to the different HPs genotypes. These differences should be carefully considered when health authorities set up and manage adequate care systems and treatments plans. We describe services organisation in Italy including the availability of multispecialty care and tools, in the HPs units participating to the HTA-THAL Multiregional Registry, with the aim to derive the impact of the services and multispecialty care availability on the management of the disease and on the patients wellbeing. The high dispersion and heterogeneity of services demonstrated, exposes the Italian system to a high risk of: a) inappropriate use of economical and medical resources, b) limited access to multidisciplinary care of some patients with apparent inequality among different centres, and c) low patients satisfaction with the services provided. The identification of a 'standard for HPs services' is necessary not only at national but also at interventional level in order to implement collaborative research and the identification and networking of reference' centres worldwide. Following the big efforts provided in the last years here there is a new challenging mission for the TIF.

Introduction

Congenital haemoglobinopathies (HPs), including thalassaemia major (TM) and sickle cell disease (SCD), are preventable rare disorders

which represent the commonest cause of anaemia in the European Union (EU) and have great health, social and economic impact. Notwithstanding the relevant improvement in patients survival and quality of life (QoL) observed in the past decades derived from a careful disease management, all affected patients, if not adequately treated, may experience the onset of secondary diseases or complications, leading to life-threatening situations.

While most complications are related to haemoglobinopathies and their treatment, it is also possible to observe substantial differences in comorbidities' onset and seriousness depending to the different HPs genotypes. These differences should be carefully considered when health authorities set up and manage adequate care systems and treatments plans.

For many years these plans and systems have been oriented, especially in Europe, to address the patients population prevalent in each single geographic area. However, the growing migration flows characterising the last decades, have led to a global spread of many different HPs carriers and patients, so posing considerable new challenges to all the European Countries in terms of services and tools to be provided.

In addition, we should consider that complications also have a relevant impact on Health Care System sustainability and costs, in light of the urgent need to adopt adequate measures aimed to reduce the costs of all the public and private Health managers and payers in the world.

Complications affecting HPs patients

Complication by HPs type

In β -thalassaemia a variable spectrum of complications can be presented just based on the different genotypes, such as the type of β thalassaemia gene (ie, β^+ or β^0), the co-inheritance of an thalassaemia gene, the high level of Hb F, etc.

Based on this variability, currently two group of patients are identified: the 'transfusion dependent' (TDT) and the 'non-transfusion dependent' group (NTDT) which include a large spectrum of genetic variables having clinical similarities and sharing similar clinical outcomes. However it is now well clear that quantitative and qualitative differences in comorbidities in the two groups is not so high as expected and that non-transfusion dependent patients also develop serious complications and require the same careful monitoring and management than thalassaemia major.

In TM patients:

- Iron overload currently represents the principal reason for complicated disease, mainly affecting liver,¹ cardiac and endocrine system.² Noteworthy, cardiac complications represent the first cause of death in thalassaemia patients.³
- Blood transfusion can cause immunisation, allergic reactions, febrile haemolytic, haemolytic anaemia, transfusion-related acute lung injury and, above all, transmission of infectious agents, including bacteria and parasites,⁴ and in particular virus infections (hepatitis B and C, HIV, new viruses -HGV, TTV, SEN-V-, etc).

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There is large consensus on the fact that to date even if the incidence of new infections is significantly reduced after the discovery of the virus C1 and the related diagnostic tests, hepatitis B and C represent one of the main risks for the survival of thalassaemia patients.⁵

- Splenectomy may give rise to complications such as bleeding, atelectasis and subphrenic abscess, thrombosis and uncontrollable sepsis.

Finally other life-threatening complications more recently recognized include severe thromboembolic events, pulmonary hypertension, pseudoxanthoma elasticum⁶⁻⁹ and haepatocarcinoma (with well-established correlation to HCV infection).^{8,10,11}

In *NTDT patients* iron overload manifests independently by the transfusional iron intake.¹² Consequently liver fibrosis, cirrhosis, and potentially, hepatocellular carcinoma can affect NTDT patients while they are less likely to show iron deposits in the heart.¹³ In addition, iron overload contributes to several vascular disorders so that NTDT patients are considered at higher risk of thrombosis or cerebrovascular disease than normal individuals¹⁴ and silent brain infarcts can be detected by magnetic resonance angiography (MRA) and positron emission tomography-computed tomography (PET-CT). Noticeable these silent injuries are often followed by overt stroke and neurocognitive decline.¹⁵ Other complications of NTDT that occur at a relatively high frequency, especially compared with patients with TM and requiring special management, are PHT pulmonary hypertension¹⁶ and extramedullary hematopoietic pseudotumors.¹⁷

SCD patients present different clinical features and severity depending on the genetic type. Symptoms start early in infancy leading to relevant complications and organ dysfunctions.¹⁸

The main feature in SCD is pain affecting bones, joints, soft tissue with typical manifestations such dactylitis, acute joint necrosis, acute abdomen in children etc.¹⁹

Painful vaso-occlusive crisis (VOC) is the typical clinical manifestation of SCD at any age and the most serious vaso-occlusive event is stroke.²⁰ Early detection of 'silent stroke' through screening and brain imaging is of the utmost importance, since imaging can help prevent recurrences.

Pneumonia (also called acute chest syndrome) is a leading cause of death in infants and young children with SCD while other infections can include fulminant meningitis and septicaemia. However the role of antibiotics treatment and of vaccine prophylaxis is under debate.^{21,22} Pulmonary hypertension is also increasingly recognized as a serious complication being associated to a high mortality rate in adult patients. Children with pulmonary hypertension have lower mortality, but high morbidity.²³

In Table 1 a pictures of the more frequent or more relevant complications differentiated by HPs type is provided.

Other factors that influence complications are the following.

Age of patients and birth cohort

The relevance of the birth cohort on the incidence of complications, and consequently of mortality is well documented in thalassaemia patients where more data for many years have been collected and published. The change in different birth cohorts are well represented in the publication presented by Modell in the Journal of Cardiovascular Magnetic Resonance 2008²⁴ showing the variations in the single cause of death in a 5 year period. Anaemia disappears as iron overload prevails and the overall mortality is reduced significantly.

However in cohort born after 1970 the rate of complications is substantially reduced⁸ with an associated change in typology.²⁵ The number of patients affected by multiple complications increase by age and is higher in adults patients where cardiac and endocrine damages prevail.²⁶

Geographic area

In non-European (in development) countries some other factors should be considered as potentially affecting morbidity of patients. The main factor is the suboptimal iron overload treatment due to costs and availability of the drugs. In addition a suboptimal transfusion regimen and increased transfusion-related complications (presence of alloantibodies and autoantibodies) have been also reported by Bejaoui M and, Guirat N²⁷ in patients with TM living in Tunisia. However a high alloimmunization rate is reported also in other series including transfusion dependant thalassaemia patients of predominantly non-European origin.²⁸ Another difference regards the hepatitis virus prevalence. Worldwide from 0.3% to 5.7% of thalassaemia patients are hepatitis B (HBV) surface antigen (HBsAg)-positive and from 4.4% to 85.4% are positive for anti-hepatitis C (HCV) antibodies; however the prevalence of HBV chronic infection is higher in Asia and Southeast Asia countries, whereas HCV chronic infection is equally widespread throughout the world.⁵

Aim of the presentation

All these evidences highlight the importance to cover the patients' needs at every age for any group of disease and to make available diagnostic and therapeutic tools to reduce the complications incidence and seriousness. Overall, the multi-organ involvement seen in thalassaemia and other haemoglobinopathies 'to a great degree dictate the multidisciplinary care organization' to cover these complex disease manifestation.¹⁴ The provision of multidisciplinary care to patients affected by thalassaemia and other HPs, has become a mandate for

Table 1. Complications frequently observed in TDT/NTDT and SCD.

Complications	TDT	NTDT	SCD
Acute chest syndrome			x
Anaemia	x		x
Acute (haemolytic) anaemia			x
Bone disease			
Osteoporosis	x	x	
Osteonecrosis			x
Cardiac complications	xx	x	x
Cerebrovascular disease		x	xx
Deep Vein Thrombosis			xx
Endocrine disease	xx	x	
Extramedullary haematopoiesis		x	
Gallstones		x	x
Infection			
Viral	xx	x	x
Bacterial	x	x	xx
Leg Ulcers		x	x
Liver disease	xx	x	x
Lung injury			xx
Maxillary deformities	x		
Pain "Episode"			xx
Pulmonary hypertension	x	x	xx
Pseudoxanthoma	x		
Retinopathy			x
Splenic sequestration			xx
Stroke			xx
Thromboembolic complications	x	x	xx

health professionals and patients associations which contribution has been of paramount relevance in advancing treatments and increasing survival and wellbeing. However these efforts need to be combined with appropriate health care settings and planning. This claims for a full commitment of health care administrators, health care providers and policy makers, in order to provide comprehensive and quality care to assure the best possible outcomes for patients.

The existing surveys and publication, mainly derived by the extraordinary efforts made by TIF with EUNERCA demonstrate that a large heterogeneity in the service organisation exists with anticipated effects on patients' expectancies and wellbeing also showing that few Countries in Europe, characterised by endemic HPs and well developed health services systems, have in place dedicated specialised HPs service. In Europe this is the case of Greece, Cyprus, Italy and UK.²⁹

However at today, few studies are available describing the HPs centres organisation and competences, including the availability of service aimed at covering patients' needs at the national or local setting.

We describe the organisation and competences provided by the Italian Thalassaemia/HPs centres adhering to the Multiregional Thalassaemia Registry Network set up in 2008 and partially co-funded by the Minister of Health and Fondazione Giambone. Services organisation and tools availability will be described with the aim to derive its impact on the management of the disease and on the patients wellbeing.

Materials and Methods

Data were collected on 60 centres and 1.899 patients

Data collected for each centre include:

- a) Centre dimension by number of patients in care;
- b) Availability of clinical diagnostic and monitoring services including:
 1. transfusion services, standard laboratory tests, ferritin assessment and standard medication;
 2. specialised visits/consultancy and laboratories (hepatology, cardiology, endocrinology, etc.);

3. iron overload monitoring facilities including hepatic Superconducting quantum interference device (SQUID) or liver and cardiac Magnetic Resonance Imaging (MRI).

Data collected on patients include:

1. Demographic data;
2. Clinical status and complications;
3. Specialised services accessed in the last calendar year (including visits and laboratory);
4. Iron overload monitoring procedures (liver biopsy, SQUID, liver MRI, cardiac MRI);
5. Patients satisfaction with the services and Quality of Life (QoL).

Results

Centres

Data collection has included 60 Italian Centres on a total of 182 identified through the entire national territory, so representing the 30% of the existing centres which have in care a total of 1889 thalassaemia patients (almost 30% of the estimated TN patients in Italy).

Distribution of both all the Italian centres and the centres participating to this study is reported in Table 2. It demonstrated that while globally in the north of Italy there is a higher number of clinical care centres, most of the centres adhering to the registry are in the south of Italy or in the islands.

Centres' dimension

The size of the centres based on the patients number, is strongly different, varying from small centres with less than 10 patients to very large centres with ≥ 80 patients. Three centres registered only one patient, while the largest one registered 150 patients. With reference to the patients' distribution according to the centre dimension our data demonstrated that while the majority of patients (almost 50%) refer to large centres, the majority of centres (66,3%) have in care less than 30 patients.

Table 2. Italian clinical care centres for thalassaemic patients distributed by Region and patients in the Registry (April 2011).

Italian Region		Centres identified in Italy	Centres in the HTA-THAL Registry	Number of Patients in the HTA-THAL Registry
North	Emilia Romagna	13	4	48 (2.5%)
	Friuli	6	1	1 (0.1%)
	Liguria	3	0	0
	Lombardia	20	9	95 (5%)
	Piemonte	12	2	14 (0.7%)
	Val d'Aosta	1	0	0
	Veneto	17	4	55 (2.9%)
	Trentino	3	1	3 (0.2)
	Centre	Lazio	10	5
Marche		4	1	1 (0.1%)
Toscana		11	1	23 (1.2%)
Umbria		1	1	3 (0.2%)
South	Abruzzo	2	0	0
	Basilicata	3	3	60 (3.2%)
	Calabria	9	3	134 (7.1%)
	Campania	10	2	153 (8.1%)
	Molise	1	0	0
	Puglia	13	4	225 (11.9%)
Islands	Sardegna	18	5	164 (8.7%)
	Sicilia	25	14	764 (40.4%)
TOTAL		182	60	1889 (100%)

Age of patients

On a total of 1873 TM patients, n=889 (47.5%) were male and n=984 female (52.5%), 259 patients are paediatric (13.8%) of whom 81% are under 12 years. N= 108 (5.8%) were aged > 45 (68,5% women). The mean age is 30.21 ± 11,04 years, with the youngest patient being 50 years-old and the oldest 65 years-old.

The age distribution of the patient population in the adult and paediatric units was not homogeneous. On a total of 407 patients referred from paediatric units only 120 (29,5%) are paediatric while the remaining 279 (70,5%) are adults. In contrast, the majority of paediatric patients (n°139=53,7 %) are treated in adults units (Figure 1).

Comorbidities

Clinical status evaluation is available in a cohort of 250 patients, balanced by age, sex and iron chelation treatment, followed for a 24 months in the context of a QoL/cost evaluation study. Results at baseline demonstrated that 226 patients (83%) have presented a total of 600 comorbidities, 165 patients have presented less than 3 complications, 107 had more than 3 complications. Musculoskeletal diseases have been the mostly represented complications (n=123 patients, 45%), hepatic, endocrine and sexual development diseases (41%, 33% and 30% of patients, respectively), 16.5% patients have had cardiac complications (Figure 2). Among patients with hepatic diseases, 100 have been identified as having HCV infection. 15 patients have reported blood disease (6 thrombocytosis and 5 secondary thrombocytosis).

The number of patients presenting more than 3 complications increase in older patients from 16% among young patients, to 51% among patients aged 26-40 years, up to 86% of patients aged >40 years (p<0.001).

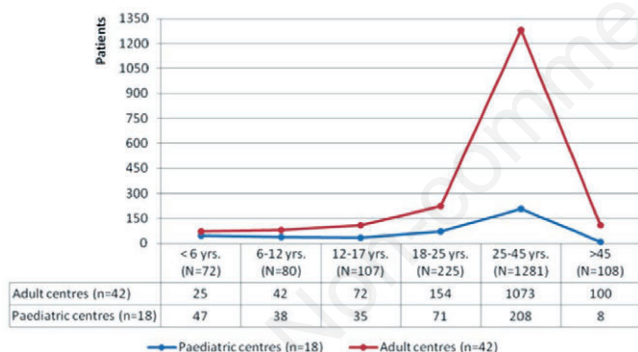


Figure 1. Patients' distribution in paediatric/no paediatric centres.

Our data also demonstrate a valuable increase of costs according to the number and seriousness of complications. The increased costs affect mainly liver disease and this measure is destined to further increase when (if) the use of the newly included sofosbuvir in the National Formulary in Italy become 'standard of care' (Table 3).

Comorbidities result also correlated to a worsened QoL (measured with SF-36 questionnaires in adults). Both physical and mental component summary scores of SF-36 (PCS and MCS) are statistically lower in patients with more than 3 complications.

Availability of equipment and services

A total of 19 centres (30%) declared not being able to perform all the specialized visits and lab tests requested for special patients' needs. In particular patients are referred to other specialised centres to perform endocrinology (11 out 19 centres), cardiology, fibroscan for bone densitometry examination (6 out 19 centres). In addition 40 centres (66,7%), declared not to be equipped to perform hepatic iron overload (39) while 42 centres (70%) are not able to perform cardiac MRI on site.

The availability of services is not dependent on centres dimension or type of patients in care (paediatric/adults) even if paediatric centres demonstrated to have a higher percentage of procedures coverage on site.

Using a patient's focussed questionnaire we also investigated the tests and the monitoring procedures received by each patients during the previous calendar year.

Our data demonstrated that 1,082 (58.8%) (patients not receiving iron chelation treatment (n=21) were excluded) out of 1,878 patients, patients have been monitored for liver iron overload in the last calendar year, using one or more monitoring procedures among biopsy, SQUID and MRI, and 1,035 patients (55.9%) were monitored with cardiac MRI.

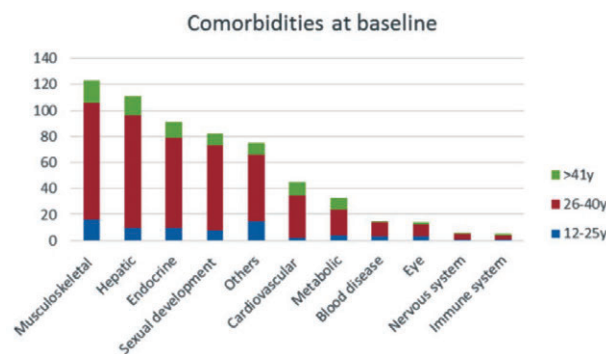


Figure 2. Comorbidities classified according to IC-10 disease categories: total number, age and percentage.

Table 3. Cost of the care and hepatitis C.

	With hepatitis C (n= 100 pts)	Mean annual cost per patient		P
		Without hepatitis C (n= 172 pts)	Total (n= 272 pts)	
Transfusion services	5612.4±1439.1	5718.5±1324.9	5679.5±1366.3	0.77
ICT	10300.3±8716.0	9732.5±8770.6	9938.2±8738.6	0.54
Additional visit /lab	2962.3±3184.5	3162.4±3667.0	3088.8±3492.0	0.68
Additional Drug	1099.4±2170.0	400.4±549.7	690.8±1496.4	<0.001
New clinical events	1076.6±2395.7	521.4 ±1479.0	736.2±1900.9	0.03
Total	20055.5±10190.3	18854.0±9668.2	19295.7±9861.7	0.33

Table 4 indicates that an increasing percentage of patients are evaluated with MRI as age increase ($p < 0.001$ when older groups are compared with younger). However MRI examinations have been used also in younger patients (under 6 year of age) in a significant percentage.

Patients satisfaction and needs

Patients refer that only 27% of the centres in the sample offer a comprehensive approach to the patients care, while in 73% of the cases patients are requested to move in other centres for receiving both specialist visits/laboratory and cardiac and liver MRI \pm SQUID (82%).

In terms of services integration at local level (social, home care, psychological care, etc) patients report an insufficient level of satisfaction and an highly variable regional situation. The involvement of patients associations to the centres' activities has been judged positive (Table 5).

Discussion and Conclusions

Centres for the treatment of thalassaemia in Italy are many and extremely heterogeneous in terms of age of patients (adult vs paediatric with no standardized transition from paediatric to adults settings), typology (clinical settings versus transfusion settings), size (from very small to very large centres) provision of services (medical expertise, laboratory and iron overload monitoring tools are different), models of the specialized care (hospital-based and only rarely home-based). This heterogeneity is the consequence of the fact that, notwithstanding the existence of a National Law (the Ministry Decree No. 279 of 18 May 2001) claiming for the creation of a National Network of centres for rare diseases (including thalassaemia), no organizational standards exist to guide the 'best services plan' in all the Italian Regions.

The high dispersion and heterogeneity of services exposes the Italian system to an high risk of: a) inappropriate use of economical and medical resources, b) limited access to the cure of some patients with apparent inequality among different centres, and c) low patients satisfaction with the services provided.

The Italian Association of Paediatric Hematology Oncology (AIEOP) with reference to the services provided to SCD patients has recently described a similar situation.³⁰ In its recent paper experts from AIOP underlined that the current situation is not optimal since:

- Regulation of health care provided by regional health care systems presents regional differences and disparities in health care facilities and resources across the country
- Specialized care are delivered on a hospital-based model and not on a medical home-based model
- Care for sickle cell patients is mainly delivered in paediatric hematology oncology centres and is characterized by:

- lack of teams dedicated to sickle cell patients
- management of pain crisis only possible in the emergency room
- lack of paediatric trans cranial Doppler services at the SCD centres

The need of standardized dedicated services to cover patients' needs in Italy appears to be of paramount importance and require a strong commitment of the National and local Authorities. In fact the urgency to adopt an evidence based national plan is more and more evident in consideration of:

The epidemiological change. Due to the growing migration flow, TM is not more the only prevalent HPs in Italy. The number of SCD is increasing together with other HPs genetic forms until now very rare in our country. In addition, despite the numerous efforts made in terms of prevention, due to the change in reproductive approach of many carriers, in Italy an important part of the thalassaemia population (as much as 13.8%) is currently below 18 years of age and 8.1% is under 12 years.

The high percentage of comorbidities. Patients in our observational study demonstrated a large incidence of complications that claims for a more intensive approach to patients. Considering that the management of these complex patients requires multidisciplinary and collaborative interventions, it is very urgent to identify the right dimension of specialized centres based both on the number of afferent patients and on the specific clinical and therapeutic needs they have. A greater concentration of competences in a limited number of centres (reference centres) together with the implementation of a networking process among reference's and peripheral centres could represent an interesting solution. This kind of organization is ongoing in UK following the NHS 'Specialized Services for Haemoglobinopathy Care' plan.³¹

The increasing costs of the disease. There are many reasons justifying an increased costs: the use of MRI as standard therapy, the high rate of migration claiming for expanding the rights to health care to migrants, the epidemiological change requiring that services and competencies are reassessed to be tailored on the new HPs population; the advancement in therapy including innovative new drugs and gene/cellular therapy. Of particular concern is the very high number of HCV positive patients among HPs people that is creating unsustainable increase of the public health expenditures.

Faced with these economical emergencies, Health Authorities have an urgent need to identify the local/national requirements and to plan and implement cost-effective measures covering all the mentioned dimensions. Our study provide a valid support in term of services, competences and diagnostic tools needed to cover a real patients population. However the identification of a standard for 'Specialized Services for Haemoglobinopathy Care' should be done not only at a national but also at the international level. The aim is to permit that centres belong-

Table 4. Instrumental Iron Overload monitoring by age.

Iron monitoring	Patients age						Total (N=1852)	P
	< 6 yrs. (N=51)	6-12 yrs. (N=80)	12-17 yrs. (N=107)	18-25 yrs. (N=225)	25-45 yrs. (N=1281)	>45 yrs. (N=108)		
Hepatic MRI	7 (13.7%)	20 (25.0%)	52 (48.6%)	131 (58.2%)	737 (57.5%)	56 (51.9%)	1003 (54.2%)	<0.001
Hepatic SQUID	6 (11.8%)	20 (25.0%)	13 (12.1%)	13 (5.8%)	55 (4.3%)	5 (4.6%)	112 (6%)	<0.001
Cardiac MRI	6 (11.8%)	25 (31.3%)	56 (52.3%)	137 (60.9%)	756 (58.5%)	55 (50.9%)	1035 (55.9%)	<0.001
Hepatic and cardiac MRI	6 (11.8%)	18 (22.5%)	49 (45.8%)	128 (56.9%)	716 (55.9%)	53 (49.1%)	970 (52.4%)	<0.001

Table 5. Patients' satisfaction with services.

Patient Satisfaction	Yes	No
Comprehensive approach at centres level	27%	73%
Services integration at local level		
Nursing	40%	60%
Medical	18%	82%
Social	42%	58%
Patients associations integration	40%	20%
New therapies informations	34%	26%
Research funds	25%	35%

ing to very different geographic and socio-cultural contest, work together in view of both:

- set up at international level large collaborative research potentially fundable by the EU or other funding Agencies or other sponsors requiring that high ethic and methodological standards are guaranteed;
- be able to Networking the existing Reference Centres offering the same diagnostic and therapeutic high level standard everywhere in the world.

We conduct a very preliminary survey in the context of countries participating to DEEP project here participating centres are requested to provide a) 'multidisciplinary care' according to 2 international study protocols, approved by the PDCO-EMA, that include all the current and innovative procedures to cover HPs patients' needs; and b) full compliance to stringent GCP ethic and methodological rules. (DEEP is a FP7 funded project, encompassing EU and no-EU countries, aimed to conduct two registrative trials and one additional observational study on Deferiprone, All congenital HPs are included in the study and all the paediatric ages (1 month to 18 years) are covered.)

Our data demonstrates that a large heterogeneity exists among the participating centres as well as a lack of a generally acknowledged 'standard of services and procedures' (See in DEEP WP4 deliverables available at <http://www.deepproject.eu/>). Faced with the difficulties we are encountering in term of timing and resources consuming but also well aware that positive results overcame the concerns, we conclude that the main lesson from the project is a strong motivation to implement common standard and to multiply collaborative research.

Following the big efforts provided in the last years here there is also a new challenging mission for the TIF.

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