Neglected Tropical Diseases (NTDs) and related infections in hematopoietic cellular therapy (HCT) in adults and children: a survey from the Infectious Diseases Working Party (IDWP) of the European Society of Blood and Marrow Transplantation (EBMT)

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Neglected tropical diseases (NTDs) are a diverse group of conditions (see footnote) defined by the World Health Organisation (WHO)[1] that are mainly prevalent in tropical areas, where they mostly affect impoverished communities and disproportionately affect woman and children. These diseases cause devastating health, social and economic consequences. According to the WHO website, NTDs "affect more than 1 billion people, while the number of people requiring NTD interventions (both preventive and curative) is 1.495 billion". The epidemiology of NTDs is complex and often related to environmental conditions. Many of them are vector-borne, have animal reservoirs and are associated with complex life cycles. All these factors make their wider public-health control challenging in endemic countries.

Our understanding of the NTDs in the setting of hematopoietic cellular therapy (HCT) in adults and children is limited. In addition, there are other commoner endemic or regionally limited diseases that are not in the current WHO NTDs list, but similar consideration is supported by recent publications[2-7]. Although transplant activity is not high in many Low- or Middle-Income Countries (LMIC) and tropical countries, we increasingly live in a world of travellers and displaced people who may have undergone or require HCT and chimeric antigen receptor T-cells therapy (CAR-T), and there will be a unique range of issues pre -, peri- and post-transplant in imported NTDs. Moreover, there is an increasing impact of climate change in changing the endemicity of some diseases.

In line with the mission, vision and values of the European Society of Blood and Marrow Transplantation (EBMT), the Infectious Diseases Working Party (IDWP) has developed a programme of investigation to scope and further characterize the diagnosis, treatment and impact of NTDs and related diseases in patients undergoing HCT. An initial search of the EBMT registry for NTDs and related diseases showed limited reported numbers, suggesting under-reporting via routine registry routes, and justifying a more targeted survey to scope the types of disease and estimate their frequency across EBMT as an initial exercise and basis

for potential further studies. We therefore undertook a directed scoping survey of all full EBMT members centres, for which data submission on all cases is mandated, irrespective of location. The primary objective was to perform a centre-level survey to collect the type and numbers of NTDs and related diseases in patients undergoing autologous (auto-) and allogeneic (allo-) HCT from 2003, and CAR-T from 2017 (when first EBMT registrations began) to 2023. Secondary objectives of the survey included identifying potential ~~cases~~diseases for more detailed retrospective analysis of NTDs and related diseases in HCT settings to be performed, either for specific diseases or broader disease groups, depending on numbers.

The survey, using Survey Monkey, and data collection were performed by the IDWP Study Unit in Leiden according to EBMT guidelines following formal review and approval by the IDWP. Analyses were descriptive. All centres could respond even if they had no experience of NTDs. The total numbers of HCT patients (as per autologous, allogeneic and CAR-T) treated over the stated time periods were obtained from the EBMT Registry and used as denominators to estimate frequency. Otherwise, formal statistical analysis was not undertaken because of the small numbers and the nature of this scoping exercise.

682 EBMT member centres were invited to participate in an online questionnaire-based survey identifying 32 pre-determined tropical infectious diseases, incorporating the WHO-defined NTDs* plus other infections considered to be potentially relevant to HCT** (see footnote). We excluded snakebite envenoming, ectoparasitoses, podoconiosis (i.e. non-infectious types of disease), and 'mycetoma' as there was confusion with 'typical' fungal infections in some centres. Tuberculosis was not included as there has been a recent publication of an EBMT registry analysis[8].

Overall, 149 (21.8%) EBMT centres from 36 countries in 3 continents (120 Europe, 26 Asia, 3 South America) participated in the survey. Twenty-six transplant centres (17 Europe, 5 Asia, 3 South America) from 15 countries reported diagnoses of NTDs: 17 EBMT centres from the

following 9 European countries reported as follows: Belgium (n=1), Czech Republic (n=1), France (n=2), Italy (n=2), Netherlands (n=1), Portugal (n=2), Romania (n=1), Spain (n=5), UK (n=2). Eight EBMT centres from the following 6 non-European countries reported as follows: Chile (n=1), Colombia (n=2), India (n=1), Saudi Arabia (n=2), Singapore (n=1), Turkey (n=1). The total number of patients at risk in participating transplant centres was: 67,626 allo-HCTs (data from 131 centres), 77,837 auto-HCTs (data from 131 centres), and 1736 CAR-Ts (data from 77 centres).

The survey responses are summarized in Table 1. Overall, 211 patients (98 allo-HCT, 113 auto-HCT) had NTDs and related infections recorded, including 61 patients with viral infections, 63 patients with bacterial infections, and 87 patients with parasitic infections. The relative frequency (%) of reported infections based on number of allogeneic and autologous HCT recipients at risk during the reporting period (2003-23) in European and non-European locations is described in the Table 1, with 171/211 (81%) patients with NTDs and related infections recorded in 8 non-European centres (5.4% of 149 responding centres overall): 137 patients from 5 Asian centres, 34 patients from 3 South American centres. For context, there are 16 South American EBMT centres, of which 3 responded (18.8%), and 121 Asian EBMT centres of which 26 responded (21.5%). No NTDs or related infections were reported among CAR-T recipients during the more limited time period (2017-23). Breakdown of diagnoses are summarised in table 1 with brucellosis, dengue, human T-lymphotropic virus (HTLV-1), strongyloidiasis and leptospirosis being the five most frequently reported infections.

Discussion

EBMT's mission, vision and values are based upon a global agenda with inclusive, equitable access to healthcare across the diversity of the clinical and patient community. Diagnostics and therapeutics of NTDs and related diseases vary widely depending on centre location, but by definition, these aspects are generally 'neglected' and under-resourced in endemic regions

and may therefore impact upon provision and outcomes in HCT. However, as a starting point our survey aimed to scope the scale of the issues as a means for greater understanding of the field for ultimate patient benefit.

Based on this EBMT-wide survey, which may have limitations being dependent on voluntary reporting and potential bias from the 21% responding centres, NTDs and related tropical infections appear to be rare in HCT patients managed in individual European centres, and the majority are encountered with much higher frequency in non-European member centres, and, outside Europe, seemingly greater in frequency in South American centres than in centres across Asia. The incidence of NTDs is probably related to the underlying prevalence in the community, reflected by European centres having a higher incidence of HTLV-1 and Asian centres a higher incidence of bacterial and parasitic infections while South American centres have a higher incidence of diseases such as Chagas disease. No NTD or related infections were reported among CAR-T recipients, possibly due to the more recent start of CAR-T programs and smaller patient cohort, although this may not entirely explain the absence of NTDs in this cohort. Overall numbers from European centres suggest that imported cases as a result of migration and return travellers may be an increasingly important cohort to consider, potentially alongside the context of evolving endemicity of NTDs because of climate change.

Ultimately, the HCT community will benefit from greater evidence-based recommendations in this area. Education and awareness may help HCT patients where these diseases are relevant. Further studies are warranted to establish the more detailed demographics, diagnosis, management and outcomes of individual diseases in HCT patients in both endemic and non-endemic settings. Wider prevalence data for each of the NTDs or related diseases in the population or from hospital-based data will be useful for evaluating the frequency in the context of the HCT population. Screening of donors for relevant infections should also be considered according to region with consideration of pre-travel advice and relevant

vaccination. This will include more detailed clinically-orientated focus on discrete disease areas and further demographic data including determining paediatric versus adult preponderance and delineating endemic cases versus imported cases. Our plan is to conduct further focussed studies in major pathogens and closely related groups, e.g. viral/protozoan/bacterial. A wider reach is being through partner organisations, including the WBMT and potentially other regional societies, where NTDs and related diseases may be more common. As it will be outside the EBMT, this will require additional consideration of other registries and data protection issues.

In conclusion, this centre-level survey aimed to scope NTDs and related diseases in HCT recipients across various geographical regions. Although, as expected, NTDs and related tropical diseases have been predominantly reported by EBMT centres in endemic regions, the report provides valuable information for future disease-specific studies and publications from the EBMT and associated groups to provide a greater understanding of this field to address unmet needs for patient benefit.

Footnote

**As of December 2023; NTDs include: Buruli ulcer; Chagas disease; dengue and chikungunya; dracunculiasis; echinococcosis; foodborne trematodiases; human African trypanosomiasis; leishmaniasis; leprosy; lymphatic filariasis; mycetoma, chromoblastomycosis and other deep mycoses; noma; onchocerciasis; rabies; scabies and other ectoparasitoses; schistosomiasis; soil-transmitted helminthiases; snakebite envenoming; taeniasis/cysticercosis; trachoma; and yaws. We excluded ectoparasitoses and snakebite envenoming and podoconiosis, and later mycetoma (based on confusion with 'typical' fungal infections in some centres).*

***Other infections (non-NTDs) included malaria (any species), brucellosis, leptospirosis, Burkholderia species-associated disease (excluding Burkholderia cepacia),Strongyloidiasis, Yellow fever, Zika virus and HTLV-1 infections.*

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TABLE 1. Summary of responses from participating centres

NTDs and related infections	Total	European centres, n= 120 (centres with reported cases: 17)	Non-European centres n=29 (centres with reported cases: 8)	Non-European centres: Asian centres n=26 (centres with reported cases: 5)	Non-European centres: South American centres n=3 (centres with reported cases:3)
TOTAL INFECTIONS REPORTED	211	40	171	137	34
Frequency*					
Allo-HCT	0.0017%	0.060%	0.571%	0.440%	18.519%
Auto-HCT	0.0014%	0.0086%	1.363%	1.151%	9.406%
Viral	61	21	40	38	2
Dengue	34	0	34	34	0
HTLV-1	23	21	2	0	2
Chikungunya fever	4	0	4	4	0
Bacterial	63	0	63	61	2
Brucellosis	28	0	28	28	0
Burkholderia species[+]	17	0	17	15	2
Leptospirosis	18	0	18	18	0
Parasitic	87	19	68	38	30
Strongyloidiasis	19	5	14	4	10
Leishmaniasis	13	8	5	5	0
Ascariasis	12	0	12	6	6
Hookworm infection	11	0	11	1	10
Malaria	11	3	8	8	0
Schistosomiasis	9	0	9	9	0
Chagas disease[++]	4	0	4	0	4
Taeniasis	4	3	1	1	0
Echinococcosis	3	0	3	3	0
Lymphatic filariasis	1	0	1	1	0

NTDs = Neglected Tropical Diseases
Allo-HCT = Allogeneic Haemopoietic Transplantation
Auto-HCT = Autologous Haemopoietic Transplantation
HTLV-1 = Human T-lymphotropic virus-1

* Estimated from total numbers of patients at risk during reporting period (see text). No NTD or related infections were reported among CAR-T recipients, possibly due to the more recent start of CAR-T programs and relatively smaller patient cohort

[+] *Burkholderia* species-associated disease (excluding *Burkholderia cepacia*)

[++] Includes cases also acquired before HCT

AUTHOR CONTRIBUTIONS

JAS, VP, TDS, NK (Data Coordinator to IDWP), DA and RC (Chairs of the IDWP) and JS and MM (Secretaries of the IDWP) led on designing the study protocol, with statistical support from GT and active strategic input from AS (EBMT) and DN and MA (WBMT). NK coordinated distribution of the survey from the EBMT Leiden Office and collated results. All authors reviewed and interpreted the data, contributed to draft versions of the manuscript and approved the final version of manuscript. The study was approved by the IDWP, conducted according to EBMT policies and procedures and all authors agree to be accountable.