A Japanese retrospective study of non-tuberculous mycobacterial infection in children, adolescents, and young adult patients with hematologic-oncologic diseases

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Supplemental Methods

Questionnaire

A detailed questionnaire on the clinical manifestations and demographic characteristics of NTM infection was administered, including age of onset, institutional diagnosis of primary disease, exposure to cytotoxic and/or immunosuppressive agents, transplantation outcomes, NTM antimicrobial agents, and survival outcomes. This questionnaire also included information on the NTM subspecies isolated. For patients with prior hematopoietic stem cell transplantation (HSCT), additional data on conditioning regimen, donor source, human leukocyte antigen identity, post-transplant immunosuppressive therapy, and transplant-related complications, particularly acute and chronic graft-versus-host disease (GVHD), were collected. The intensity of conditioning regimens for HSCT was classified as myeloablative and reduced intensity based on the definition of the Center for International Blood and Marrow Transplant Research (1).

Statistical methods and software libraries used for analysis and plotting

Statistical analyses were performed using EZR 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (2). Box and UpSet plots were created in Rstudio version 1.4.1103 using the packages “ggplot2” (https://ggplot2.tidyverse.org) and “ComplexUpset” (http://doi.org/10.5281/zenodo.3700590), respectively. The Wilcoxon rank-sum test was used to assess the difference between RGM and SGM at the time of infection, as noted in the box plot. For patients who underwent HSCT, the time to NTM onset was calculated from the date of transplantation. For IEI patients without HSCT, time to NTM onset was calculated from the date of birth, and for non-IEI patients without HSCT, including leukemia, time to NTM onset was calculated from the date of diagnosis of the underlying disease. All data analyses and plotting were performed using the statistical software package R Version 4.1.2, except for geographical analysis. The Python library "Geopandas" (https://github.com/geopandas/geopandas) was used to plot the geographic distribution.

References

1. Giralt S, Ballen K, Rizzo D. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. *Biol Blood Marrow Transplant.* 2009;15(3):367-9.

2. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant.* 2013;48(3):452-8.

Supplemental Tables

Supplemental Table 1. Details of the transplant setting and infection patterns for each hematopoietic stem cell transplant patient.

UPN	Age at NTM onset, y	Primary disease	R/UR	HLA matching	Source	Intensity	Conditioning	TBI, Gy	ATG	GVHD prophylaxis	Type of NTM	Subspecies	Infection sites	Outcome
12	12.3	ALL	R*	8/8	BM	MAC	CY + ETP	12	-	CSA + MTX	SGM	*M. avium*	L	Alive
13	12.0	ALL	R	4/8	PBSC	RIC	FLU + MEL + AraC + ETP	-	+	TAC + MTX	SGM	*M. intracellulare*	L	Alive
24	5.0	AML	UR	5/6	CB	MAC	BU4 + MEL	-	-	CSA + steroid	SGM	*M. intracellulare*	L	Alive
30	9.7	ALL	UR	7/8	BM	MAC	MEL	12	-	TAC + MTX	SGM	*M. gordonae*	L	Alive
10	16.8	ALL	UR	6/8	CB	MAC	CY + ETP	12	-	TAC + MTX	RGM	*M. abscessus*	L, B	Dead
01	19.8	AA	UR	7/8	BM	RIC	FLU + MEL	3	+	TAC + MMF	RGM	*M. abscessus*	L	Alive
26	21.0	ALL	UR	6/8	BM	RIC	FLU + MEL + AraC	-	-	TAC + MTX	RGM	*M. abscessus*	L	Dead
37	18.3	CGD	UR	8/8	BM	RIC	FLU + BU2	3	+	TAC + MTX	RGM	*M. abscessus*	L	Dead
02	13.7	ALL	R	6/8	BM	MAC	BU4 + CLO	-	-	TAC + MTX	RGM	*M. fortuitum*	L	Alive
15	15.8	AML	UR	7/8	BM	MAC	BU4 + FLU + MEL	-	+	TAC + MTX	RGM	*M. abscessus*	L	Alive
06	14.5	AA	R*	5/8	BM	RIC	FLU + MEL	3	+	TAC + MTX + steroid	RGM	*M. abscessus*	L	Alive
16	4.3	STAT1 GoF	R*	8/8	BM	RIC	FLU + MEL	3	+	CSA + MTX	RGM	*M. abscessus*	L	Alive
31	3.7	AML	R	5/8	BM	RIC	FLU + MEL	-	-	TAC + MTX	RGM	*M. chelonae*	C	Dead
19	3.0	DBA	UR	8/8	BM	MAC	FLU + BU4	-	+	TAC+ MTX	RGM	*M. mucogenicum*	B	Alive
05	24.3	ALL	UR	6/8	BM	MAC	CY + ETP	12	-	CSA + MTX	SGM	*M. kansasii*	S	Dead
35	13.7	ALL	R	6/8	PBSC	MAC	CY	12	-	TAC + steroid	SGM	*M. kansasii*	S*	Dead
33	17.8	IPEX	UR	8/8	BM	RIC	FLU + MEL	4	+	TAC	RGM	*M. chelonae*	S	Alive
04	21.6	GATA2	UR	7/8	BM	RIC	FLU + MEL + ETP	3	+	CSA + MTX	RGM	*M. chelonae*	S	Dead
36	21.0	XLP-2	UR	8/8	BM	RIC	FLU + MEL + ETP	3	+	TAC + MTX	RGM	*M. abscessus*	S, C	Alive
11	11.9	JMML	R	5/8	PBSC	MAC	FLU + BU4 + MEL	-	-	TAC + MTX	SGM	*M. avium* complex	BM	Alive
22	17.3	ALL	UR	7/8	BM	MAC	CY + ETP	12	-	TAC + MTX	SGM	*M. kansasii*	J, M	Dead

Abbreviations: AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AraC, cytarabine; ATG, antithymocyte globulin; B, bloodstream; BM, bone marrow; BU2, reduced dose of busulfan; BU4, myeloablative dose of busulfan; C, catheter-related bloodstream; CB, cord blood; CGD, chronic granulomatous disease; CLO, clofarabine; CSA, cyclosporine; CY, cyclophosphamide; DBA, Diamond–Blackfan anemia; ETP, etoposide; FLU, fludarabine; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; IPEX syndrome, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; J, joint; JMML, juvenile myelomonocytic leukemia; L, lung; M, muscle; MAC, myeloablative conditioning; MEL, melphalan; MMF, mycophenolate mofetil; MTX, methotrexate; NTM, nontuberculous mycobacterium; PBSC, peripheral blood stem cell; R, related donor; R*, sibling donor; RGM, rapid-growing mycobacteria; RIC, reduced intensity conditioning; S, skin; S*, subcutaneous insulin injection site; SGM, slow-growing mycobacteria; STAT1 GoF, *STAT1* gain-of-function mutation; TAC, tacrolimus; TBI, total body irradiation; UPN, unique patient number; UR, unrelated donor; XLP2, X-linked lymphoproliferative disease 2.

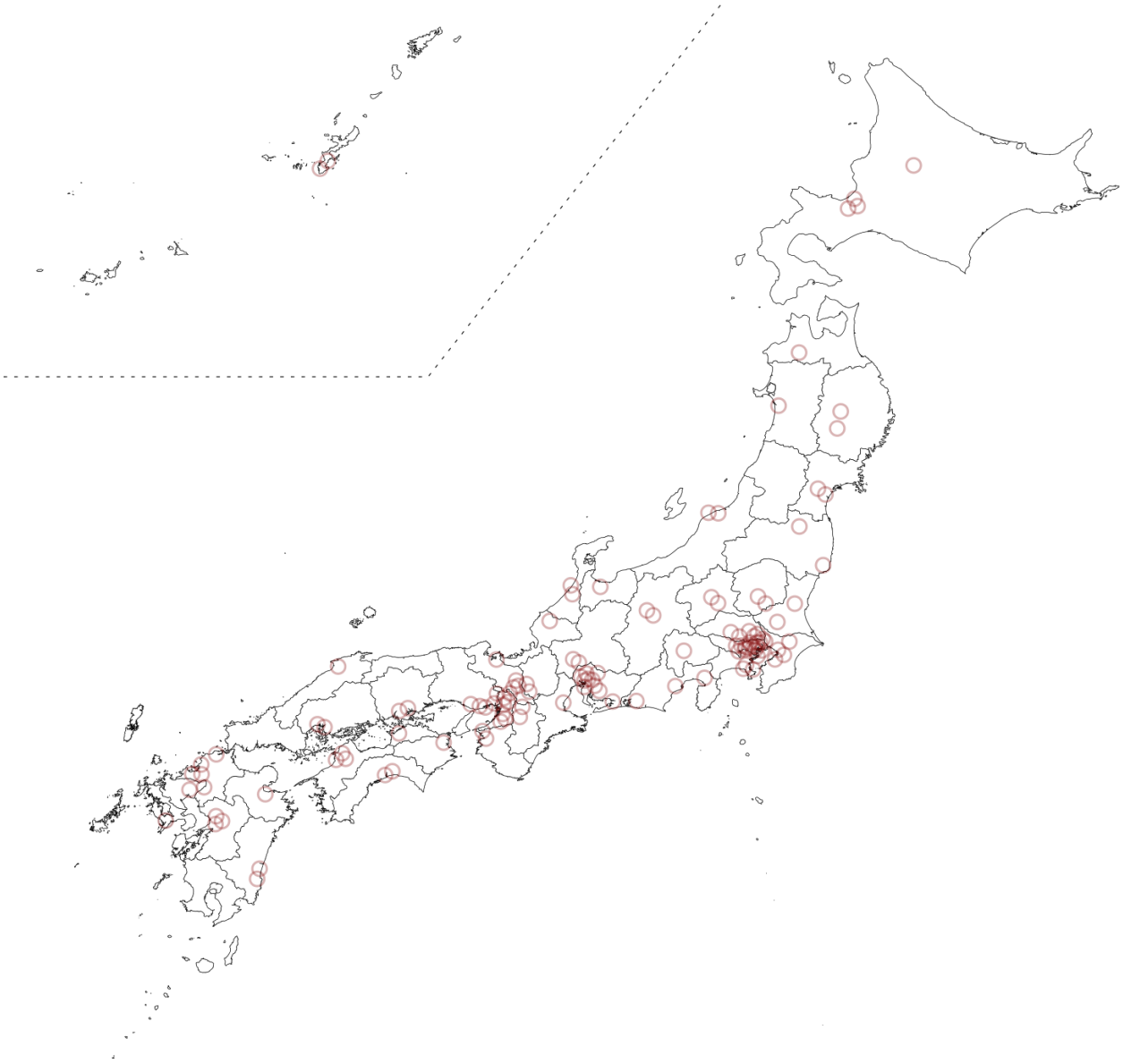
Supplemental Table 2. Estimated nontuberculous mycobacterial prevalence in the general pediatric population in Japan based on the Diagnosis and Procedure Combination database.

	Age group (years)	Study period (years)	Number of NTM cases	Denominator	Prevalence /100,000 inpatients)
General pediatric population	<20	April 2012–June 2022	5	Total number of pediatric inpatients (n = 741,962)	0.7

Because there are no epidemiological data on nontuberculous mycobacterial (NTM) infection in the general pediatric population in Japan, we estimated the prevalence using part of a nationwide inpatient administrative claims database called Diagnosis and Procedure Combination (DPC). DPC is a Ministry of Health, Labor and Welfare classification, introduced in 2002, to code the diagnosis and treatment of inpatients. It is linked to the healthcare subsidy system for hospitals, which benefit from revenue. Furthermore, most medium and large hospitals participate in this system. Our available regional DPC database covers over 90% of DPC hospitals in Aichi and Gifu prefectures, which comprise 7.6% of Japan's total population. We detected five distinct cases of NTM infection among hospitalized patients under 20 years of age between April 2012 and June 2022 in the database. We calculated the prevalence using the total number of hospitalized patients during the period as the denominator. Patients with NTM infection were identified if they had the NTM infection disease codes A310, A311, A318, A319, or B200 (International Classification of Diseases, 10th Revision) assigned to their principal diagnosis, most resource-intensive diagnosis, or diagnosis prompting hospitalization.

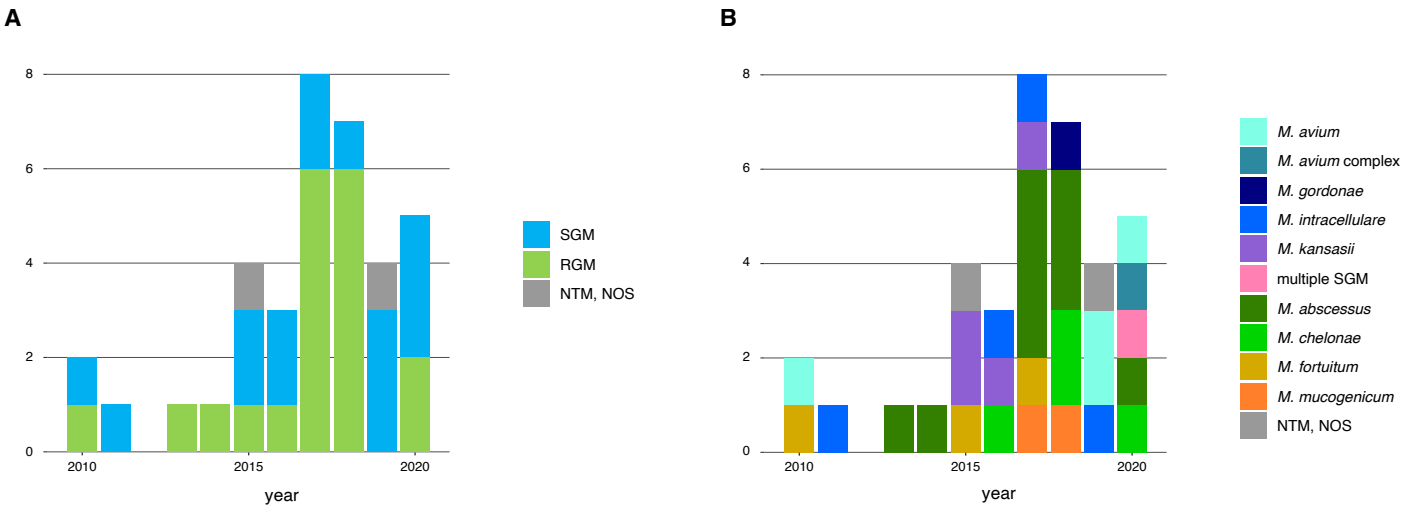
Supplemental Figures

Supplemental Figure 1. Geographic distribution of institutions participating in this study.



A total of 121 Japanese pediatric hematology/oncology institutions participated in this study. Red circles indicate the location of each participating institution.

Supplemental Figure 2. Number of newly diagnosed nontuberculous mycobacterial patients per year.

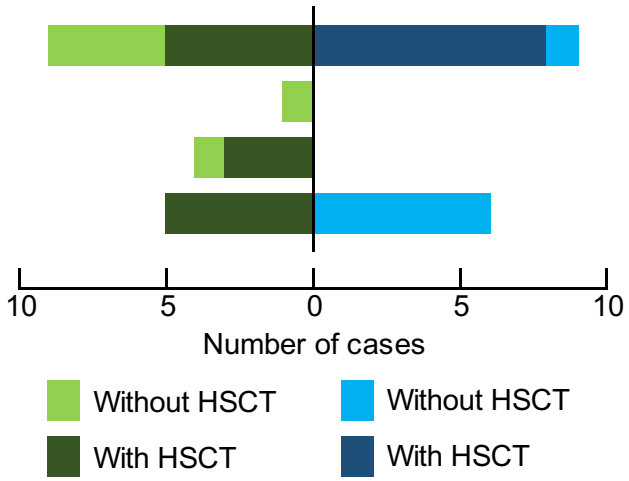


(A) Lime green bars, rapid-growing mycobacteria (RGM); light blue bars, slow-growing mycobacteria (SGM); gray bars, nontuberculous mycobacterial (NTM) not otherwise specified.

(B) Each colored bar indicates a different NTM species. Color codes are noted in the column to the right.

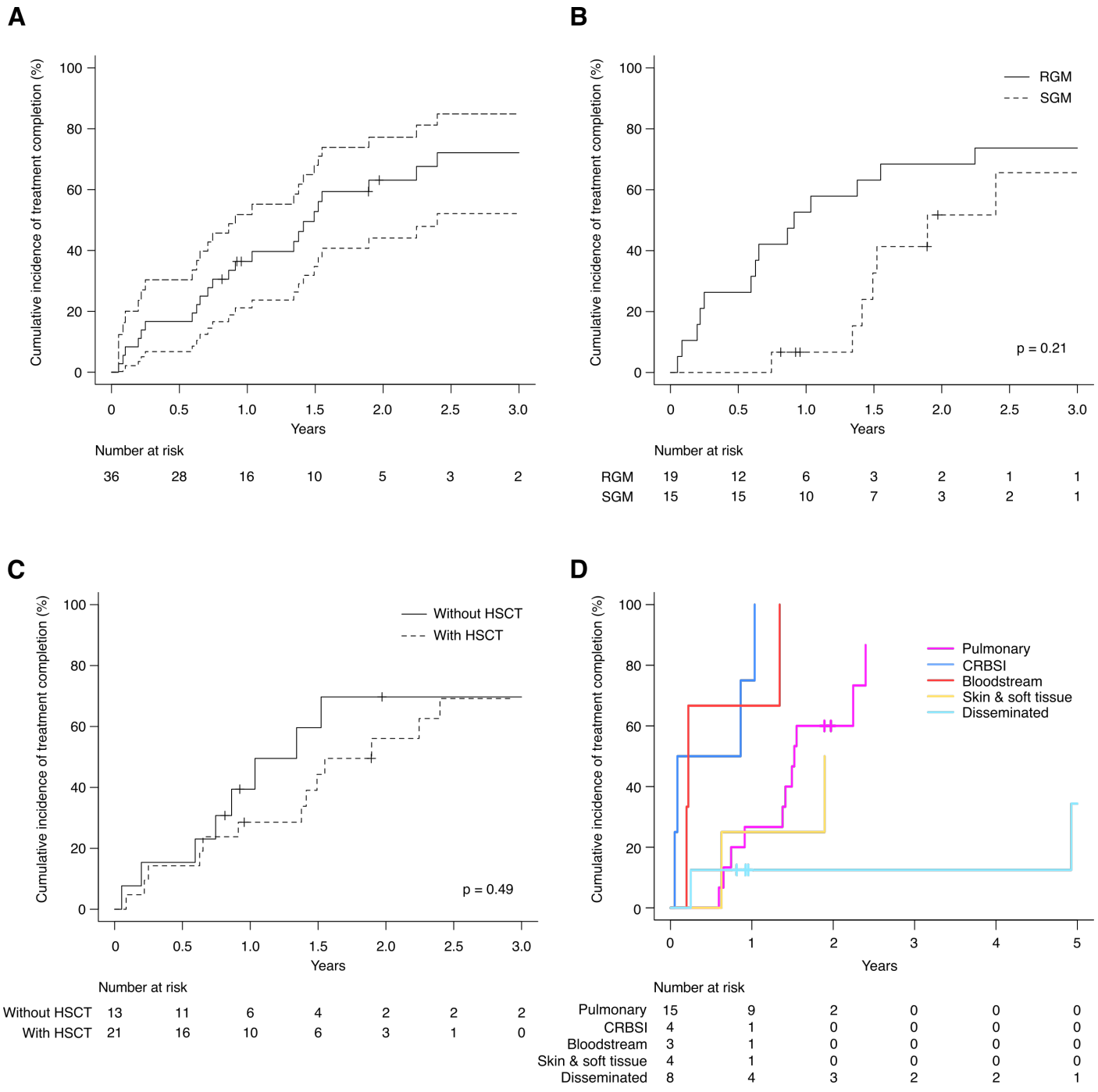
Supplemental Figure 3. Comparison of patient characteristics of RGM and SGM infections.

	RGM (n = 19)	SGM (n = 15)
Sex, male/female	8 / 11	9 / 6
Median age at NTM diagnosis, years (range)	14.6 (3.0–21.6)	12 (5.0–24.3)
Co-infecting pathogens with NTM, n (%)	4 (21)	1 (7)
Aspergillus species, n	3	-
Zygomycetes, n	1	-
S.epidermidis, n	-	1
Stem cell transplantation, n (%)	13 (68)	8 (53)
Primary diagnosis		
Hematologic malignancies		
Solid tumors		
Non-malignant hematological diseases		
Inborn error of immunity		



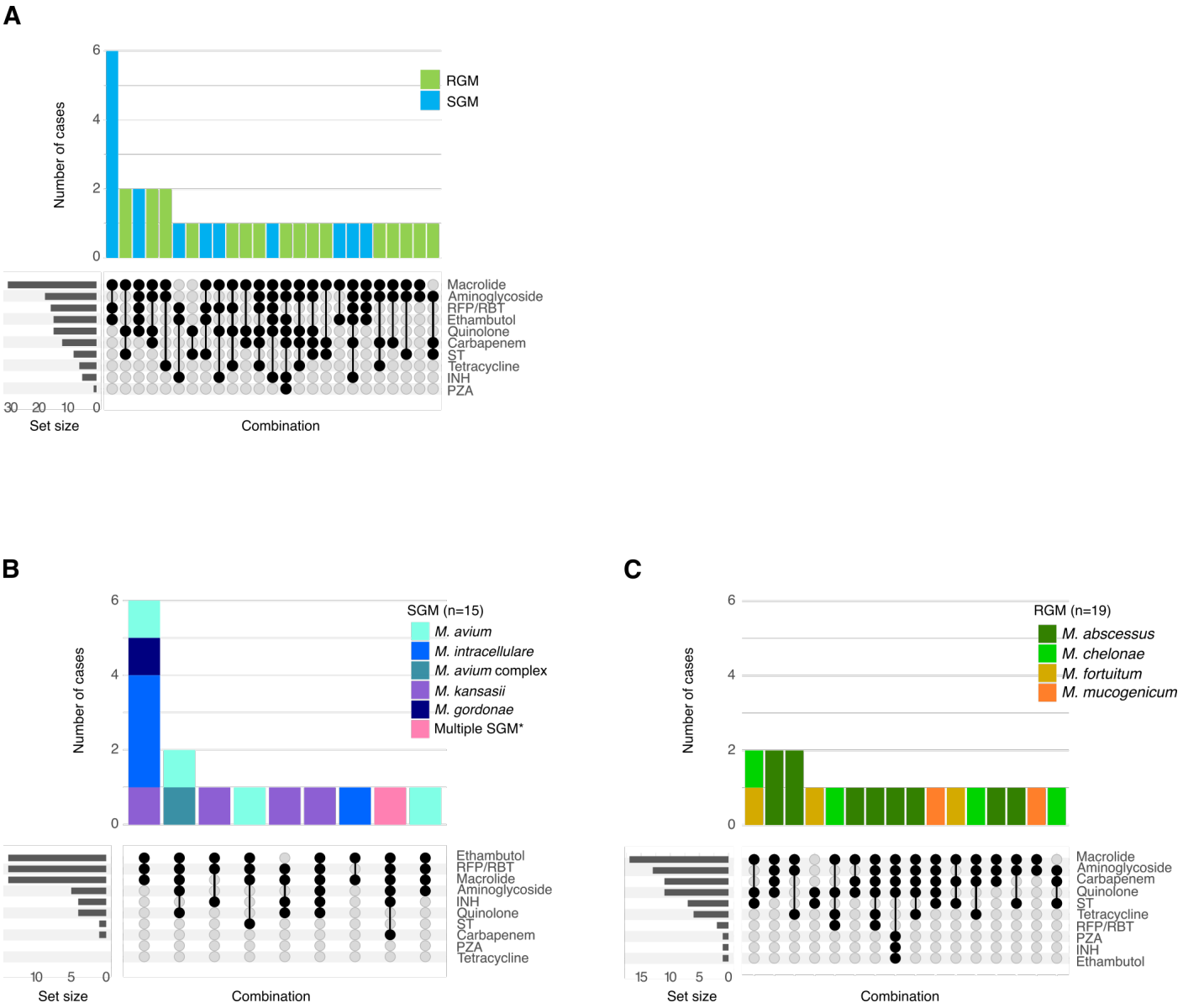
Green bars on the left indicate the number of rapid-growing mycobacterial (RGM) infections, and blue bars on the right indicate the number of slow-growing mycobacterial (SGM) infections. Light colors indicate cases without hematopoietic stem cell transplantation (HSCT), and dark colors indicate cases with HSCT. Patients were classified according to the type of nontuberculous mycobacterium (NTM) that first infected the patient.

Supplemental Figure 4. Outcomes of nontuberculous mycobacterial infection in pediatric hematology/oncology patients.



(A) Cumulative incidence of treatment completion in pediatric hematology/oncology patients with nontuberculous mycobacterial (NTM) infection. Cumulative incidence of treatment completion by: (B), classification of NTM growth rate; (C), presence of prior hematopoietic stem cell transplantation; (D), site of infection.
Abbreviations: CRBSI, catheter-related bloodstream infection; HSCT, hematopoietic stem cell transplantation; RGM, rapid-growing mycobacteria; SGM, slow-growing mycobacteria.

Supplemental Figure 5. Combinations of chemotherapeutic agents used in treating nontuberculous mycobacterial infections in pediatric hematology/oncology patients.



Antibiotic combinations used in treating nontuberculous mycobacterial (NTM) infections are summarized by UpSet plots. (A) Drug combinations used in the 34 pediatric hematology/oncology patients with identified NTM species. Lime green bars, rapid-growing mycobacteria (RGM); light blue bars, slow-growing mycobacteria (SGM). One case with unidentified NTM species was treated with three drugs (macrolide, aminoglycoside, and quinolone) and the other with two drugs (macrolide and quinolone) (data not shown). Panels B and C depict drug combinations used to treat slow-growing mycobacteria (SGM; n = 15) and rapid-growing mycobacteria (RGM; n = 19), respectively. Color codes are displayed in the right column of each panel.

Abbreviations: INH, isoniazid; PZA, pyrazinamide; RBT, rifabutin; RFP, rifampicin; ST, sulfamethoxazole-trimethoprim.

Supplemental Appendices

Supplemental Appendix 1. Participating institutions.

All of the following centers provide care for pediatric hematology/oncology patients and participated in this study: Aichi Medical University Hospital, Anjo Kosei Hospital, Asahikawa Medical University Hospital, Chiba Children's Hospital, Chiba University Hospital, Dokkyo Medical University Hospital, Ehime Prefectual Central Hospital, Ehime University Hospital, Fujita Health University Hospital, Fukuoka University Hospital, Fukushima Medical University Hospital, Gifu Municipal Hospital, Gifu University Hospital, Gunma Children's Medical Center, Gunma University Hospital, Hamamatsu University Hospital, Hirosaki University Hospital, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Hiroshima University Hospital, Hokkaido University Hospital, Hospital of the University of Occupational and Environmental Health , Hyogo Prefectural Amagasaki General Medical Center, Hyogo Prefectural Kobe Children's Hospital, Ibaraki Children's Hospital, Iwaki City Medical Center, Iwate Medical University Hospital, Iwate Prefectural Chubu Hospital, Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital, Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital, Japanese Red Cross Narita Hospital, Japanese Red Cross Otsu Hospital, Japanese Red Cross Wakayama Medical Center, Japanese Red Cross Wakayama Medical Center, Jichi Medical University Hospital, Juntendo University Hospital, Kanagawa Children's Medical Center, Kanazawa Medical University Hospital, Kanazawa University Hospital, Keio University Hospital, Kindai University Hospital, Kitano Hospital, The Tazuke Kofukai Medical Research Institute, Kobe City Nishi-Kobe Medical Center, Kobe University Hospital, Kochi Health Science Center, Kochi Medical School Hospital, Kumamoto Red Cross Hospital, Kumamoto University Hospital, Kurashiki Central Hospital, Kurume University Hospital, Kyorin University Hospital, Kyoto City Hospital, Kyoto University Hospital, Kyushu University Hospital, Matsuyama Red Cross Hospital, Mie University Hospital, Miyagi Children's Hospital, Miyazaki Prefectural Miyazaki Hospital, Nagano Children's Hospital, Nagasaki University Hospital, Nagoya City University Hospital, Nagoya Memorial Hospital, Nagoya University Hospital, Nakadori General Hospital, Nanbu Medical Center & Children's Medical Center, Nara City Hospital, Nara Medical University Hospital, National Center for Child Health and Development, National Center for Global Health and Medicine, National Defense Medical College Hospital, National Hospital Organization Kumamoto Medical Center, National Hospital Organization Kyushu Cancer Center, National Hospital Organization Maizuru Medical Center, National Hospital Organization Nagoya Medical Center, Nihon University Itabashi Hospital, Niigata Cancer Center Hospital, Niigata University Medical & Dental Hospital, Nippon Medical School Hospital, Oita University Hospital, Okayama University Hospital, Osaka City General Hospital, Osaka City University Hospital, Osaka Medical and Pharmaceutical University Hospital, Osaka University Hospital, Osaka Women's and Children's Hospital, Saga University Hospital, Saiseikai Yokohamashi Nanbu Hospital, Saitama Children's Medical Center, Saitama City Hospital, Saitama Medical University International Medical Center, Sapporo Hokuyu Hospital, Sapporo Medical University Hospital, Shiga University of Medical Science Hospital, Shikoku Medical Center for Children and Adults, Shimane University Hospital, Shinshu University Hospital, Shizuoka Cancer Center, Shizuoka Children's Hospital, St. Luke's International Hospital, St. Marianna University School of Medicine Hospital, Teikyo University Chiba Medical Center, Teikyo University Hospital, The Jikei University Hospital, The University of Tokyo Hospital, Toho University Omori Medical Center, Tohoku University Hospital, Tokai University Hospital, Tokushima University Hospital , Tokyo Medical And Dental University Medical Hospital, Tokyo Metropolitan Children's Medical Center, Toyama University Hospital, Toyohashi Municipal Hospital, Toyonaka Municipal Hospital, University Hospital, Kyoto Prefectural University of Medicine, University of Fukui Hospital, University of Miyazaki Hospital, University of the Ryukyu Hospital,

University of Tsukuba Hospital, University of Yamanashi Hospital, Wakayama Medical University Hospital, Yokohama City University Hospital.

Supplemental Appendix 2. Patient data contributors.

The following is a complete list of investigators who contributed by providing detailed patients data: Haruna Okuno, Gunma University Hospital; Makiko Mori, Yuichi Mitani, and Takuma Ohnishi, Saitama Children's Medical Center; Nao Yoshida, Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital; Shinya Osone, University Hospital, Kyoto Prefectural University of Medicine; Toshihiro Matsui, National Center for Child Health and Development; Chihaya Imai, Niigata University Medical & Dental Hospital; Hideki Sano, Fukushima Medical University Hospital; Hiroaki Kikuchi, Kochi Medical School Hospital; Hiroshi Yagasaki, Nihon University Itabashi Hospital; Katsutsugu Umeda, Kyoto University Hospital; Koji Suzuki, University of Fukui Hospital; Motohiro Matsui, Tokyo Metropolitan Children’s Medical Center; Naoki Sakata, Kindai University Hospital; Naoto Fujita, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital; Nobuyuki Yamamoto, Kobe University Hospital; Takako Miyamura, Osaka University Hospital; Takayuki Takachi, Shizuoka Children’s Hospital; Yuichi Taneyama, Chiba Children’s Hospital; Aiko Kozaki, Hyogo Prefectural Kobe Children's Hospital; Kimiyoshi Sakaguchi, Hamamatsu University Hospital.