

A clinician survey for management of the secondary immunodeficiency caused by hematological malignancies in China

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Abstract

Unlike Western countries, there are still few clinical immunology specialists in China, and the optimal care for secondary immunodeficiency caused by hematological malignancies is unknown. Therefore, we initiated this clinician survey study to describe the current situation of the care for malignancy patients with hypogammaglobulinemia in China.

We adapted a previously published online questionnaire of current clinical practices regarding the management of secondary immunodeficiency caused by hematological malignancies and then distributed the questionnaire to 52 hematologists in China via WeChat mobile software; the survey collected demographic details, starting dosage, target immunoglobulin (Ig) level, monitoring, criteria for stopping Ig replacement, vaccination use, and oral antibiotic prophylaxis for hypogammaglobulinemia patients.

Forty-eight hematologists responded. 28(58.33%) respondents had more than 10 years of experience. Nevertheless, 40(83.33%) respondents reported that they did not use any specific criteria for prophylactic Ig replacement in hypogammaglobulinemia patients. However, 27(56.25%) respondents reported that they had used intravenous immunoglobulin (IVIg); however, the starting dose, frequency, and target Ig level were significantly varied. Additionally, the criteria for stopping Ig replacement were significantly varied. Only one respondent (2.08%) used subcutaneous immunoglobulin (SCIg). Moreover, 35(72.92%) respondents reported no vaccination prior to Ig replacement, and 47(97.92%) respondents reported that they had not used antibiotic prophylaxis in secondary hypogammaglobulinemia patients.

Official guideline for the care for secondary immunodeficiency (SID) of the hematological malignancies patients should be issued in China, and significant attention of the hematologists should be paid to the use of prophylactic antibiotics and Ig replacement for the care of patients with hypogammaglobulinemia caused by hematological malignancies, as these agents could significantly reduce the infection rate in China.

Abbreviations: CLL = chronic lymphocytic leukemia, Ig = immunoglobulin, IVIg = intravenous immunoglobulin, MM = multiple myeloma, NHL = indolent non-Hodgkin lymphoma, PJP = Pneumocystis jiroveci pneumonia, SCIg = subcutaneous immunoglobulin, SID = secondary immunodeficiency.

Keywords: China, clinician survey, Ig replacement, secondary immunodeficiency

1. Introduction

Primary immunodeficiency (PID) is caused by genetic factors, while secondary immunodeficiency (SID) is mainly a consequence of a variety of diseases or a side effect of a range of medical treatments.^[1] In the clinic, SID is more common than PID,

especially for hematological malignancy patients who have received chemotherapy or immunosuppressive drugs, which could severely destroy the immune system.^[2] These SID patients, characterized by low immunoglobulin (Ig) levels, always suffer from recurrent or severe infections, which is the leading cause of

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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morbidity and mortality.^[3] Multiple myeloma (MM), chronic lymphocytic leukemia (CLL), indolent non-Hodgkin lymphoma (NHL), and other relevant B-cell malignancies are the most common diseases underlying hypogammaglobulinemia in the hematological clinics,^[1,4–6] and multiple factors can cause SID.^[7–9]

Until now, only intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG) administration has been indicated as an effective therapy for SID patients; immunoglobulin administration has been shown to significantly reduce the risk of infection, hospital admission, and the use of antibiotics.^[3,10] Over the last 40 years, guidelines that have assessed the safety and efficacy of IVIG or SCIG products have been issued and revised in Western countries, such as the UK, US, or Australia.^[11–14] Nevertheless, unlike Western countries, the number of immunology specialists is still limited in China. To the best of our knowledge, clinical immunology services became available in Hong Kong in 2016, and there were no immunology specialist services for adult immunodeficiency patients in the mainland. General consciousness for the care of these patients is still lagging behind in China.^[15]

Moreover, Ig is a costly and limited resource, and Ig replacement is not as common as in Western countries.^[15] Therefore, in this study, we used a questionnaire previously published in Austria and New Zealand and made minor revisions according to our health system and used this adapted instrument to survey front line hematologists about their Ig replacement practices for patients with hypogammaglobulinemia caused by hematological malignancy,^[16] then describe the real-world status of care for hematological malignancy patients with hypogammaglobulinemia in China.

2. Methods

We adapted a previously published questionnaire with minor revisions according to our health system.^[16] In this study, a 34-item online questionnaire was designed and distributed via WeChat software to 52 hematologists in April 2020 in China (see questionnaire, Supplemental Digital Content includes 34-items, <http://links.lww.com/MD/F472>). This study was approved by the ethics committee of Zhejiang Province People's Hospital (N: 2020QT135).

Questions 1 to 5 referred to the characteristics of the respondents, including position, practicing years, location, and practice type (see questionnaire, Supplemental Digital Content, which illustrates respondent demographics, <http://links.lww.com/MD/F472>). Questions 6 to 10 were aimed at investigating secondary hypogammaglobulinemia patients in terms of CLL and MM patients and how they are managed (see questionnaire, Supplemental Digital Content, which illustrates preventive strategies of infections in patients with secondary hypogammaglobulinemia, <http://links.lww.com/MD/F472>). Questions 11 to 24 were formulated to assess Ig replacement, including starting dose and Ig replacement monitoring practices (see questionnaire, Supplemental Digital Content, which illustrates the current situation about specific criteria or guidelines of hypogammaglobulinemia patients' selection, and the administration of IVIG including starting dosage, target Ig level, monitoring practices, <http://links.lww.com/MD/F472>). Questions 25 to 34 were focused on the use vaccination or oral antibiotic prophylaxis for secondary hypogammaglobulinemia (see questionnaire, Supplemental Digital Content, which illustrates the use of prophylactic vaccination and prophylactic antibiotics in second-

ary hypogammaglobulinemia patients before Ig replacement, <http://links.lww.com/MD/F472>). Several items regarding IVIG treatment, such as starting dose, frequency and target Ig level, were open-ended, thus allowing for a full range of responses. Data were collected anonymously. Analysis of this survey focused on descriptive summaries for each question, including the characteristics of the respondents, the management of CLL and MM patients with hypogammaglobulinemia, Ig replacement, and vaccination and oral antibiotic prophylaxis. The percentage and absolute numbers of participants for each question were calculated.

3. Results

3.1. 28(58.33%) respondents had practiced more than 10 years and worked in tertiary public hospitals

Fifty-two questionnaires were distributed via WeChat software, 48 were returned, and the response rate was 92.5%. These data were collected from 8 provinces in mainland China, including Zhejiang, Shandong, Hebei, Heilongjiang, Hainan, Henan, Jiangsu, and Jiangxi Provinces (Table 1); 26(54.17%) hematologists came from Zhejiang Province. Among them, 28(58.33%) respondents had practiced more than 10 years in a hematology department, 20(41.67%) were professors of hematology or the hematologist-in-charge. Forty-seven (97.72%) respondents were currently working in public hospitals (Table 1).

3.2. Prevention of infection in secondary hypogammaglobulinemia was low in this study

For the question “When would you typically monitor IgG levels in a patient with CLL?,” 22(45.83%) respondents

Table 1

Characteristics of respondents.

| Characteristics | N (%) |
|---------------------------------|------------|
| Position | |
| Professor of hematologist | 20 (41.67) |
| Hematologist-in-charge | 23 (47.92) |
| Hematologist | 4 (8.33) |
| Trainee in hematology | 0 (0) |
| Clinical fellow in hematology | 0 (0) |
| Specialist nurse | 0 (0) |
| Other specialty or role | 1 (2.08) |
| Practicing years | |
| Less than 10 years | 20 (41.67) |
| 11–20 years | 25 (52.08) |
| 21–30 years | 2 (4.17) |
| More than 30 years | 1 (2.08) |
| Location | |
| Zhejiang Province | 26 (54.17) |
| Shandong Province | 9 (18.75) |
| Hebei Province | 7 (14.58) |
| Heilongjiang Province | 2 (4.17) |
| Hainan Province | 1 (2.08) |
| Henan Province | 1 (2.08) |
| Jiangsu Province | 1 (2.08) |
| Jiangxi Province | 1 (2.08) |
| Practice type | |
| Mainly public | 47 (97.72) |
| Mainly private | 1 (2.08) |
| Evenly split public and private | 0 (0) |

Table 2**Answers refer to the time and frequency of IgG levels monitor, and management for the hypogammaglobulinemia patients.**

| Question | Answers | N (%) |
|--|--|------------|
| When would you typically check IgG levels in a patient with CLL? | At diagnosis | 18 (37.50) |
| | At treatment initiation | 3 (6.25) |
| | Regularly (e.g., every 3 months or annually) | 22 (45.83) |
| | If an infectious complication arises | 1 (2.08) |
| | Never or rarely | 1 (2.08) |
| | I do not manage patients with CLL | 1 (2.08) |
| | Other (please specify) | 2 (4.17) |
| Do you routinely check uninvolved immunoglobulin subtypes in your patients with myeloma to look for hypogammaglobulinemia? | Routinely, on a regular basis (e.g., every 3 months or annually) | 33 (68.75) |
| | Routinely, at diagnosis only | 3 (6.25) |
| | Only in the event of an infectious complication | 2 (4.17) |
| | Never or rarely | 6 (12.50) |
| | I do not manage patients with myeloma | 1 (2.08) |
| | Other (please specify) | 1 (2.08) |
| What treatments do you use to prevent infections in secondary hypogammaglobulinemia? (check all that apply) | Intravenous immunoglobulin replacement | 34 (70.83) |
| | Subcutaneous immunoglobulin replacement | 1 (2.08) |
| | Pneumococcal vaccination | 1 (2.08) |
| | Prophylactic antibiotics | 5 (10.42) |
| | None | 10 (20.83) |
| | Other (please specify) | 0 (0) |

CLL = chronic lymphocytic leukemia.

indicated that they regularly monitored IgG levels, such as every 3 months or annually, but 18(37.50%) respondents only monitored IgG levels at diagnosis. Moreover, 33(68.75%) respondents reported that they routinely monitored uninvolved Ig subtypes in patients with myeloma to care for hypogammaglobulinemia. In the UK guidelines, vaccination and oral antibiotic prophylaxis were strongly recommended before Ig replacement therapy.^[11] Nevertheless, according to the results of our survey, 34(70.83%) respondents used IVIG to prevent infections, only 1(2.08%) respondent chose SCIG, 1(2.08%) respondent chose pneumococcal vaccination and 5(10.42%) respondents chose prophylactic antibiotics. Surprisingly, 10(20.83%) respondents did nothing to prevent infections in secondary hypogammaglobulinemia patients (Table 2).

3.3. No specific criteria or guidelines were used to select hypogammaglobulinemia patients for Ig replacement in this study

Although these doctors were experienced, further questions showed that 40(83.33%) hematologists reported that fewer than 20 patients were currently receiving prophylactic Ig for secondary hypogammaglobulinemia at their hospitals (Table 3). Moreover, 26(54.17%) respondents reported that there was no policy for the use of Ig replacement in hematological malignancy patients. For the question “Do you have to apply to any of the following to access Ig replacement?,” 11(22.92%) respondents reported that they did not have to apply to any organization to access Ig replacement. Additionally, 40(83.33%) respondents reported that no specific criteria were used to select patients for prophylactic Ig replacement (Table 3).

3.4. The starting dosage, target Ig level, monitoring practices, and criteria for stopping IVIG were significantly varied in this study

For IVIG treatment decision making, 31(64.58%) respondents did not routinely start Ig replacement for patients with isolated low serum IgG levels without a history of severe or recurrent infections (Table 4). Only 27(56.25%) respondents stated that they had used IVIG, but the starting dose, frequency, and target Ig level were significantly varied, ranging from 0.4 g/kg/month to 10 g/week, or 5 g/day; roughly more than 30 different answers were collected for this question. Interestingly, for the question “What IgG level do you aim for in the IVIG treatment?,” approximately one-third of respondents reported that their target Ig level for IVIG replacement was higher than 15 g/L (Table 4). Furthermore, 44(91.67%) respondents did not use SCIG, though SCIG had used for more than 20 years in Western countries, and the advantages of SCIG were obvious when compared to the IVIG.^[12] Moreover, 42 (87.50%) respondents did not use IgG levels to adjust the Ig replacement dose, and 11(22.92%) respondents did not stop Ig replacement unless adverse events occurred (Table 4).

3.5. Prophylactic vaccination is rarely used before Ig replacement

In general, lower serum IgG concentrations in SID patients are associated with an increased risk of infection. However, serum IgG alone is not a definitive biomarker for evaluation. Patients with very low IgG levels may not suffer from infections.^[17] Therefore, evaluation of the response to the polysaccharide vaccine is critical before initiating Ig replacement.^[11,17] Nevertheless, in this clinician survey, 35(72.92%) respondents did not

Table 3**Answers refer to IVIG treatment policy and criteria.**

| Question | Answers | N (%) |
|--|---|------------|
| How many hematology patients in your hospital do you estimate are currently receiving prophylactic immunoglobulin for secondary hypogammaglobulinemia? | 0–20 | 40 (83.33) |
| | 21–50 | 7 (14.58) |
| | 51–100 | 1 (2.08) |
| | >100 | 0 (0) |
| Does your hospital have a policy for the use of immunoglobulin replacement in hematological malignancies? | Yes | 13 (27.08) |
| | No | 26 (54.17) |
| | I don't know | 7 (14.58) |
| | Other | 2 (4.17) |
| At your hospital, do you have to apply to any of the following to access Ig replacement? | Hospital or medical insurance | 25 (52.08) |
| | Department of pharmacy | 9 (18.75) |
| | Blood Service clinician | 2 (4.17) |
| | Multidisciplinary or departmental meeting | 4 (8.33) |
| | None of the above | 11 (22.92) |
| | I don't know | 7 (14.58) |
| | Other | 5 (10.42) |
| Which formal criteria do you use to select patients for prophylactic Ig replacement? | No specific criteria | 40 (83.33) |
| | Other | 8 (16.67) |

routinely vaccinate their patients with secondary hypogammaglobulinemia, let alone assess the antibody response to vaccination (Table 5).

3.6. Prophylactic antibiotics were rarely used

Antibiotic prophylaxis is strongly recommended for SID patients according to the UK guidelines.^[11] Nevertheless, in this study, 47

(97.92%) respondents did not use oral antibiotic prophylaxis in secondary hypogammaglobulinemia patients (Table 5). Moreover, 44(91.67%) respondents reported that they did not give a trial of oral antibiotic prophylaxis before commencing IVIG. More specifically, 34(70.83%) or 36(75%) hematologists stated that cotrimoxazole was not given to patients with CLL or MM, respectively, for *Pneumocystis jiroveci* prophylaxis (PJP) (Table 5).

Table 4**Answers refer to target Ig level, monitor, and stop of Ig replacement.**

| Question | Answers | N (%) |
|--|--|------------|
| Do you routinely start Ig replacement for patients with isolated low serum IgG level who do not have a history of recurrent or severe infection? | No | 31 (64.58) |
| | Yes, if IgG below lower limit of reference | 13 (27.08) |
| | Yes, only if total IgG < 4 g/L | 2 (4.17) |
| | Yes, in selected patients | 2 (4.17) |
| Do you use intravenous Ig replacement? | No, I do not use IVIG | 21 (43.75) |
| | Yes | 27 (56.25) |
| Do you use subcutaneous Ig replacement? | No, I do not use SCIG | 44 (91.67) |
| | Yes | 4 (8.33) |
| Do you monitor IgG levels during Ig replacement, and if so, how often? | No | 11 (22.92) |
| | Opportunistically (e.g., only if infections arise) | 16 (33.33) |
| | Every month (or more frequently) | 10 (20.83) |
| | Every 2–6 months | 6 (12.50) |
| | Annually | 0 (0) |
| | I don't know | 2 (4.17) |
| | Other | 3 (6.25) |
| What serum Ig level do you aim for, for IV Ig replacement? | I don't know | 9 (18.70) |
| | Lower than 6 g/L | 6 (12.50) |
| | 6–15 g/L | 9 (18.70) |
| | Higher than 15 g/L | 16 (33.30) |
| | Within normal reference range | 8 (16.70) |
| Do you use IgG levels to adjust the Ig replacement dose? | No | 42 (87.50) |
| | Yes | 6 (12.50) |
| When do you stop Ig replacement? | I do not stop Ig replacement unless adverse events occur | 11 (22.92) |
| | After a fixed duration of treatment | 30 (62.50) |
| | Other | 10 (20.83) |

Note: Ig = immunoglobulin, IVIG = intravenous immunoglobulin, SCIG = subcutaneous immunoglobulin.

Table 5
Answers on the usage of vaccination and oral antibiotic prophylaxis.

| Question | Yes | No |
|--|-------------|-------------|
| Do you routinely vaccinate patients with secondary hypogammaglobulinemia? | 13 (27.08%) | 35 (72.92%) |
| Do you use oral antibiotic prophylaxis in secondary hypogammaglobulinemia? | 1 (2.08%) | 47 (97.92%) |
| Do you give a trial of oral antibiotic prophylaxis before commencing intravenous immunoglobulin replacement? | 4 (8.34%) | 44 (91.67%) |
| Do you routinely give CLL patients cotrimoxazole for PJP prophylaxis? | 14 (29.17%) | 34 (70.83%) |
| Do you routinely give multiple myeloma patients cotrimoxazole for PJP prophylaxis? | 12 (25%) | 36 (75%) |

CLL = chronic lymphocytic leukaemia, PJP = Pneumocystis jiroveci pneumonia.

4. Discussion

To the best of our knowledge, this is the first study to describe Ig use for hypogammaglobulinemia patients in China via a questionnaire distributed among Chinese hematologists. In this Chinese survey, we highlight that methods for selecting patients for Ig replacement, including criteria, guidelines, awareness of IVIG, prophylactic antibiotic usage, and prophylactic vaccination, are severely lacking when compared to the previous study from which we adapted the questionnaire.^[16] Moreover, the hematologists we investigated are currently practicing in mainland China, and 28(58.33%) had practiced more than 10 years in public hospitals. They come from 8 provinces; 54.17% were from Zhejiang Province, which had a population of 58 million, and a GDP that ranked fourth in 2019 among the 31 provinces in China. To some extent, the hematologists we investigated may reflect the hematologists in a prosperous province.

Most hematologists at our hospital participated in this questionnaire. To avoid bias in this study, questionnaires were further distributed anonymously to hematologists in other provinces via WeChat software. Ultimately, 48 respondents from 8 provinces in southern and northern China completed the questionnaire, and 28(58.33%) respondents had practiced in public hospitals for more than 10 years. In the clinics, SID can occur due to the use of chemotherapeutic and immunosuppressive drugs that could severely impair the immune system, such as glucocorticoids, cyclophosphamide, vincristine, or methotrexate.^[18] In Western countries, to prevent infections in patients with secondary hypogammaglobulinemia, vaccination, and oral antibiotic prophylaxis were strongly recommended before Ig replacement therapy.^[11] Therefore, monitoring IgG levels is a critical component of monitoring hypogammaglobulinemia patients. Nevertheless, in this survey, 22(45.83%) respondents responded that they monitored IgG levels in CLL patients regularly, such as every 3 months or annually, and 18(37.50%) respondents only monitored IgG levels at diagnosis. Moreover, 33(68.75%) respondents reported that they routinely checked uninvolved Ig subtypes in MM patients to care for hypogammaglobulinemia. Therefore, more attention should be paid to monitoring the IgG concentration. In addition, only 1(2.08%) respondent chose pneumococcal vaccination, and 5(10.42%) respondents chose prophylactic antibiotics. Thirty-four (70.83%) respondents would use IVIG to prevent infections. Surprisingly, 10(20.83%) respondents did nothing to prevent infections in secondary hypogammaglobulinemia patients. Therefore, general awareness regarding Ig replacement therapy is still inadequate in China according to these answers, even though these IVIG treatments can significantly reduce the infection rate and improve the quality of life of SID patients.^[2]

Furthermore, hypogammaglobulinemia did not have enough priority to receive Ig replacement. A previous survey of UK immunology consultants showed that objective clinical indicators of frequency and severity of infection tended to take precedence over immunization studies in determining the start of Ig replacement.^[17] In this study, for IVIG decision making, 31 (64.58%) respondents reported that they did not routinely start Ig replacement for patients with isolated low serum IgG levels without a history of recurrent or severe infection. In contrast, 89% of hematologists in a survey conducted in Australia and New Zealand reported that they would only start Ig replacement in the setting of hypogammaglobulinemia if a history of recurrent or severe infection was also present.^[16]

Therapeutic Ig is a limited, expensive resource, and the Departments of Health in the UK and US have issued clinical guidance on the use of Ig replacements, which covers approved indications, recommended dosing and monitoring.^[11,14] However, 83.33% of respondents reported that fewer than 20 hematological patients were currently receiving prophylactic Ig for secondary hypogammaglobulinemia in this study. A total of 54.17% of respondents reported no policy for the use of Ig replacement, and 68.75% of respondents reported that they did not have to apply to any organization to access Ig replacement. Consistent with a previous study,^[19] these results revealed that no specific criteria were used to select patients for prophylactic Ig replacement in China. Furthermore, criteria and guidelines for Ig replacement differ between countries. In Canada, IVIG treatment is widely used for patients with SID.^[20] In EU countries, indications for IVIG are mandatory for SID patients.^[21–23] Moreover, according to UK guidelines for Ig replacement, the starting dose should generally be 0.4g/kg/month.^[11] However, this survey found that significant variation exists in the frequency and starting dose of IVIG, ranging from 0.4g/kg/month to 10g/week or 5g/day; roughly more than 30 different answers are collected, while in the Australia and New Zealand survey, from which we adapted the questionnaire, 76% of hematologists started with a dose of 4g/kg every 4 weeks.^[16] To some extent, the IVIG treatment in this study was random. For the criteria to select patients for prophylactic Ig replacement, recommended guidelines are shown in Table 6. In contrast, no specific guidelines on Ig use were available in China.^[19]

In the UK guidelines, Ig replacement was frequently targeted at achieving an IgG trough level of at least the lower limit of the serum IgG reference range.^[11] Interestingly, in this study, more than one-third of respondents reported that the target serum IgG level was more than 15g/L, reflecting that the expectations of some hematologists were high, although they did not frequently use Ig replacement. Moreover, 87.5% of respondents did not use IgG levels to adjust the Ig replacement dose, which was similar to

Table 6
Recommended guidelines on immunoglobulin use.

| Number | Country | Issue time | Organization | Guidelines |
|--------|-----------|------------|---|--|
| 1 | USA | 2008 | U.S. Department of Health and Human Services; Food and Drug Administration; Center for Biologics Evaluation and Research | Guidance for Industry Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency http://www.fda.gov/cber/gdlns/igivimmuno.htm . |
| 2 | UK | 2019 | Department of Health | Updated Commissioning Criteria for the use of therapeutic immunoglobulin (Ig) in immunology, haematology, neurology, and infectious diseases in England, November 2019 chrome-extension://cdonnmffkdaoajfknoeeecmchibpmkmg/static/pdf/web/viewer.html?file=http%3A%2F%2Figd.mdsas.com%2Fwp-content%2Fuploads%2FNHSE_Commissioning_Criteria_for_the_use_of_Ig_V1.4_November_2019.pdf |
| 3 | Australia | 2012 | National blood authority | Criteria for the clinical use of intravenous immunoglobulin in Australia https://www.blood.gov.au/system/files/documents/NBA_IVIgCriteria_Second |
| 4 | European | 2018 | European Medicines Agency | Guideline on core SmPC for normal human immunoglobulin for intravenous administration (IVIg) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/07/WC500252345.pdf |
| 5 | China | 2016 | Comment on the lack of guidelines in China and comparative study of clinical guidelines for intravenous immunoglobulin in western countries | http://d.wanfangdata.com.cn/periodical/zgxylycz201601013 (comparative study of clinical guidelines for intravenous immunoglobulin) |

the 86% hematologists who responded the same in the Australia and New Zealand study.^[16]

Prophylactic antibiotics were used by 85% of UK immunologists, and vaccinations were used to reduce the infection rate by most immunologists before IVIG.^[17] In the UK guidelines, a trial of oral antibiotic therapy for 3 months and a trial of serum antibody response to pneumococcal or other vaccines before IVIG was mandatory.^[11] However, guidelines for access to IVIG in other countries do not mandate a trial of oral antibiotics.^[13,14] In contrast, 97.92% of respondents described that they did not use oral antibiotic prophylaxis in secondary hypogammaglobulinemia patients, similar to the findings in the Australia and New Zealand survey.^[16] Moreover, in this survey, 72.92% of respondents reported that they did not routinely vaccinate patients with secondary hypogammaglobulinemia. Therefore, in this study, even the minority of hematologists had used Ig replacement for the SID patients, but they did not use it correctly.

More importantly, myeloma was associated with increased rate of infections, which was the main cause of death for myeloma patients.^[24] According to European myeloma network guidelines for the management of multiple myeloma-related complications, antibiotic prophylaxis was recommended for MM patients receiving immunomodulatory drugs, mainly during the first 3 months of therapy. Prophylactic acyclovir was recommended for patients receiving proteasome inhibitors, autologous, or allogeneic transplantation.^[24] In ESMO clinical practice guidelines for CLL, antiviral and antibiotic prophylaxis were recommended for patients with recurrent infections or patients with very high risk of developing infections.^[25] Additionally, primary antifungal prophylaxis was not recommended in MM and CLL patients due to low attack rate of fungal infection by European guidelines for primary antifungal prophylaxis in adult hematology patients.^[26]

Our study was limited by its small sample size (48 out of approximately 7000 hematologists in China according to the records of the 2019 hematology conference of the Chinese Medical Doctor Association). This survey could not be officially performed on behalf of the hematological society, this small survey was only designed to direct attention to the care of SID patients, especially those with hematological diseases in China. Additionally, lack of

statistical comparison with the western countries was another limitation in this clinician survey study. Our questionnaire only reported the descriptive data in a small group of Chinese hematologists.

In conclusion, prophylactic antibiotic or Ig replacement for the care of patients with hypogammaglobulinemia caused by hematological malignancies is rarely used in China, and relevant criteria and guidelines to select hypogammaglobulinemia patients are lacking. Therefore, official guideline for the care for secondary immunodeficiency of the hematological malignancies patients should be issued in China, and we highlighted that significant attention of the hematologists should be paid to prophylactic antibiotics or Ig replacement, which could significantly reduce the infection rate in China.

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Correction

At the request of the authors, the corresponding author has been updated from Sujie Zheng to Jinlin Liu.

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