






**BRIEF REPORT****TRANSFUSION****A global analysis of the use of immunoglobulin, shortages in supply, and mitigating measures: A survey of hospital providers (a BEST Collaborative study)**

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**Abstract**

**Background:** Immunoglobulin (IG) therapy is widely used to treat primary and secondary immune deficiencies and as immunomodulatory agent for various disorders. There is great concern that shortages of IG may rise, potentially affecting medical treatment options.

**Study Design and Methods:** An international survey was developed to study how intravenous immunoglobulins (IVIGs) are used and managed within hospitals in case of shortages. Study data were collected and managed using REDCap electronic data capture tools hosted by the Biomedical Excellence for Safer Transfusion (BEST) Collaborative. The survey was directed to hospital pharmacists and

**Abbreviations:** IG, immunoglobulin; IVIG, intravenous immunoglobulin; BEST, biomedical excellence for safer transfusion; CAR, chimeric antigen receptor; MMN, multifocal motor neuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; BIG, BEST immunoglobulin; IQR, interquartile range; mAb, monoclonal antibodies; SID, secondary immune deficiencies; BTC, blood transfusion committee; EBA, European Blood Alliance; EHA, European Hematology Association; IPFA, International Plasma and Fractionation Association; SUPPLY, strengthening voluntary non-remunerated plasma collection capacity.

\*Members listed at the end of the manuscript

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blood bank transfusion professionals and disseminated through members of the BEST Collaborative network.

**Results:** Survey respondents from institutions in the USA, Canada, Europe, Japan, and Australia ( $n = 13$ ) confirmed that the primary specialties utilizing IG are neurology, hematology, and immunology. More than 60% of respondents reported IG supply shortages, but mitigation strategies were not well developed.

**Discussion:** As IG is the leading driver in plasma demand, more studies are needed to understand current and future demand for IG from the clinical perspective. Necessity lies in establishing clinical guidance to address shortages.

#### KEYWORDS

immunoglobulins, shortages, strategies, usage

## 1 | INTRODUCTION

Immunoglobulins (IGs) are used for a wide range of disorders including primary immune deficiencies such as severe congenital immunodeficiency syndrome (SCID) and secondary immune deficiencies due to immunosuppressive therapies such as chimeric antigen receptor (CAR)-T cell therapy or rituximab that target subsets of B cells. IGs have also proved their efficacy as immunomodulatory agents in neuromuscular disorders such as multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyneuropathy (CIDP).<sup>1</sup> The indications for IG on- and off-label are growing, which puts a constraint on the IG supply and, consequently, the supply of plasma worldwide from which IG is manufactured. The Biomedical Excellence for Safer Transfusion (BEST) ImmunoGlobulin (BIG) Study group as part of the BEST Collaborative Clinical Transfusion Study Group collected data from hospital providers in the USA, Canada, Europe, Japan, and Australia to gain insights into the current and future demand for IG with the objectives of evaluating IG usage patterns from 2017 to 2020 and understanding shortage mitigation strategies used.

## 2 | METHODS

Study data were collected and managed using REDCap electronic data capture tools hosted by the BEST Collaborative. The survey was directed to hospital pharmacists and blood bank transfusion professionals, who were identified as the IG providers within their hospital (Appendix: survey questions). The respondents were asked for their willingness to participate via email and were subsequently sent an individual survey link. Reminder emails were sent after 3 and 6 weeks. Data were collected from March to August 2022. To analyze the responses, the mean and SD

were reported for continuous variables, unless data were skewed when medians and interquartile range (IQR) were reported. Ethical committees from two different countries (the United Kingdom and the Netherlands) were consulted and ethical approval was found to be unnecessary, as the survey did not collect individual patient data.

## 3 | RESULTS

From 21 invitations sent, 14 institutions agreed to participate and 13 (62%) completed the survey. Responses were received from institutions from eight countries: Canada, the United States of America, Japan, Australia, the United Kingdom, France, Spain, and the Netherlands (Figure 1). All respondents reported on local hospital usage, apart from Wales that reported on nationwide usage. All but one institution were university/academic hospitals; one was a blood service that reported on IG use in Wales. Nine institutions reported on both inpatient and outpatient practices, while four focused solely on inpatient care. Four institutions included both adult and pediatric patients, and one was a pediatric university hospital and included only pediatric patients. The median total IG dose per institution for all diagnoses in 2019 and 2020 was 70–73 kg (IQR 21–43 to 94–137) and 62–74 kg (IQR 24–40 to 112–123), respectively (Table 1). The highest usage of IG was in adult patients with neurological, immunological, and hematological diagnoses. In 2020, 91% (IQR 77%–99%) of IG was prescribed as intravenous IG (IVIg) and 9% as subcutaneous Ig (SCIg) (IQR 4%–28%). Of note, one institution in Spain also reported usage of facilitated SCIg.

From January 2017 to December 2020, five (38%) institutions showed no change in usage, while other centers reported variable increases and decreases in the use of IG across hematology, neurology, immunology,



FIGURE 1 Global distribution of responses. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/traf.17801)]

rheumatology, and pediatric patients. During this period, one institution noted a reduced utilization of general medicine, while another reported a decrease in solid organ transplant patients. The reasons for change in usage are outlined in Table 1.

Individual patient IG orders were reviewed at 12 (92%) institutions; most before the prescription was approved (62%;  $n = 8$ ). All institutions adhered to approved guidelines, with additional reasons outlined in Table 1A. Approval for standard (on-label) indications for IG was predominantly carried out by the IG provider (46%), closely followed by a dual decision involving both the clinician and IG provider (15%). One institution utilized a national centralized approval system. For off-label use approval, 38% of centers used an approval process with dual decision-makers, both the clinician and IG provider, and 15% of centers employed approval by the IG provider only. Monitoring of overall IG usage was performed in 9 of 13 (69%) institutions (Table 1).

Shortages of IG were observed in 9 of 13 (69%) institutions in 2019 and 8 of 13 (62%) institutions in 2020 (Table 1). One institution experienced a 20% decrease in IG supply from March 2020 onward imposed by the Ministry of Health as a direct consequence of the COVID-19 pandemic.

Institutions were mainly notified regarding shortages by the manufacturers and regional hospital networks and used various strategies in these circumstances (Table 2). Local mitigation strategies mainly included substitution with other products (other IG brands or non-IG products,  $n = 8$ ),

switching to a lower dose of IG ( $n = 5$ ) or delaying treatment ( $n = 4$ ). Protocols to triage IG use based on prioritization were available in seven institutions (54%), while other institutions had other methods to prioritize (decisions based on an individual, department, or committee). Eight institutions (62%) expect future shortages in IG.

## 4 | DISCUSSION

This survey provides an overview of IG usage from 2017 to 2020 of 13 institutions in eight countries. Although it was difficult to identify participants who had the required knowledge of IG use to respond, the confirmed response rate was relatively high (62%) with a wide geographical spread from four continents (North America, Europe, Asia, and Australia). Adult neurology, immunology, and hematology patients were the patient groups having the highest usage of IG by the participants, which is in line with other recent studies.<sup>2-4</sup> There were no obvious changes found in total IG usage (kg) from 2017 to 2020 with varied responses on the direction of change (increase or decrease in IG usage).

Although data were limited, the period of the COVID-19 pandemic did not impact IG supply leading to shortages, except for one institution in Canada. In both 2019 and 2020, shortages were reported by the majority of respondents, of whom seven had priority protocols in place to mitigate the problems in IG supply. Previous studies have indicated an expected yearly increase in the IG

TABLE 1 IG usage, experienced shortages, changes in usage, and approval-and-monitoring strategies.

Institutions (n = 13)	2019 inpatients	2019 Outpatients	2020 Inpatients	2020 Outpatients
Median total IG usage (kg) Interquartile range (IQR)	70.0 (43.0–137.1)	73.1 (21.2–93.9)	61.5 (39.5–112.1)	74.3 (24.0–123.0)
Experienced shortages in 2019 and 2020: number of institutions (%)				
Yes/no	2019 Yes: n = 9 (69) No: n = 4 (31)		2020 Yes: n = 8 (62) No: n = 5 (38)	
If yes, frequency				
Monthly	3/9 (33)		2/8 (25)	
Quarterly	2/9 (22)		3/8 (37.5)	
Weekly	1/9 (11)		0	
Once or twice per year	1/9 (11)		0	
Comments from respondents	2 (22) -“Using our guidelines/criteria allowed us to weekly track the shortage, but maintain adequate supply despite ongoing shortages/allocations”. -Brand vial shortages in Aug 2019.		3 (37.5) -“Using our guidelines/criteria allowed us to weekly track the shortage, but maintain adequate supply despite ongoing shortages/allocations” -Change in formulations to utilize brand in May 2020 to help transition national Ig brand shares -Occurred in March 2020 and the Ministry of Health imposed a 20% decrease that is still ongoing.	
Change in usage from 2017 to 2020: number of institutions (%)				
Yes/no	For outpatients:		For inpatients:	
If yes, reasons for change	Yes: n = 8 (62) No: n = 5 (38)		Yes: n = 8 (62) No: n = 5 (38)	
Change in route of administration	4/8 (50)		1/8 (12.5)	
Changes in indications	3/8 (37.5)		2/8 (25)	
Change in costs	2/8 (25)		0	
Change in hospital/regional/international policies	2/8 (25)		2/8 (25)	
Comments from respondents	“Use of monoclonal antibodies (mAB) resulted in IG increase in secondary immune deficiencies (SID)”		“Natural growth due to increase in number of patients” -“More scrutiny of requests due to fluctuation of IG supply” “Increased volume of patients served”	
Basis for IG approval: number of institutions (%) <sup>a</sup>				
Guidelines	13 (100)			
Clinician input	10 (77)			
On-/off-label use	10 (77)			
Supply sufficiency	7 (54)			
Costs/reimbursement	2 (15)			
Monitoring of IG demand: number of institutions (%)				
Yes/no	Yes: n = 9 (69)			
If yes, by whom?	No: n = 4 (31)			
By a committee	5/9 (56)			
Individually	2/9 (22)			
By the IG provider	1/9 (11)			
National system managed by National Blood Authority (government agency). Product only dispensed after central approval.	1/9 (11)			

<sup>a</sup>More than one answer possible.

**TABLE 2** Routes of communication in case of shortages, mitigation, and priority strategies.

In case of shortages			
External notifications <sup>a</sup>		Internal communication <sup>a</sup>	
-From manufacturers	6	-By a committee	5
-From hospital region	3	-To physicians	6
-No	1	-Combat strategy	7
-Not reported	5	-BTC and inform main users	1
Mitigation strategies <sup>a</sup>		Priority strategies	
-Substitution with other therapies: e.g., brand change	8 3	-Priority protocol (local)	4
-Lower dose	5	-Priority protocol (national)	3
-Delay treatment	4	-Transfusion medicine department decision	1
-Import from abroad	2	-Clinicians decision	1
-Referral to another hospital	0	-Pharmacy committee decision	1
		-Not reported	3

Abbreviations: BTC; blood transfusion committee; Combat strategy, Making a strategy to combat shortage.

<sup>a</sup>More than one answer possible.

usage of around 6%<sup>2,5</sup> and highlighted consequent insufficiency in the plasma supply, especially when collected from non-remunerated donors. Currently, the European Blood Association (EBA) together with the European Hematology Association (EHA) and the International Plasma and Fractionation Association (IPFA) aim to increase and strengthen the resilience of plasma collection in the EU to enable a stable and adequate plasma supply. It plans to monitor IG demand in the strengthening voluntary non-remunerated plasma collection capacity in Europe (SUPPLY) project, an EU4Health granted program (6). That project also intended to develop recommendations and guidance for the development of common EU policies and legal frameworks on the provision and usage of IG and was recently finalized.

The strengths of this study were a global representation of IG usage, collection of data on adult and pediatric patients with a focus on shortages, and subsequent mitigation and prioritizing strategies. The limitations of the study include a low total number of participating institutions. Furthermore, data were only collected from university hospitals and one national blood service. Therefore, the results should be interpreted with caution and should not be extrapolated to or will not be representative of all institutions and countries. Finally, we did not address albumin shortages but only focused on IG.

In conclusion, this global survey confirmed that the main medical IG using specialties are neurology, hematology, and immunology in a number of countries. More than 60% of respondents reported shortages in IG supply, but mitigation strategies were not always well developed. As IG is the leading driver in plasma demand, more studies are needed to understand current and future demand for IG from the clinical perspective and to collect more

evidence for guideline development. These studies could include prospective clinical intervention studies comparing IG versus alternatives such as antibiotics in hematology patients with secondary immune deficiencies following CAR-T cell therapies. In case of rare diseases (e.g., in neurology or dermatology), registries with IG data on usage at a granular patient level could be helpful to understand current demand and to investigate clinical outcome in (case-controlled) observational studies. More consideration and guidance are required on how to address shortages.

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## BIG study group members (in addition to the authors)

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All authors were involved in the study design, CS-O analyzed the data and drafted the paper, and all authors revised it critically and approved the final version.

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## CONFLICT OF INTEREST STATEMENT

All authors have no conflicts of interest to declare.

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## APPENDIX A: (survey)

Dear hospital pharmacist,

We would like to gain your insights into the situation of immunoglobulin (Ig) shortages and the decision-making process regarding it within your hospital.

We have created a short survey that will take approximately 20 min to complete. This was originally meant to measure Ig usage until 2019 but due to the COVID-19 pandemic, we would like to know whether the pandemic has affected Ig usage as well. Therefore, 2020 will also be included in this survey.

Your participation is completely voluntarily, and your responses will be kept confidential and anonymous. If you agree, please click ‘yes’ below. Thank you in advance.

Yes/No (if no, skip to the thank you screen at the end of the survey).

- Could you identify your area(s) of responsibility as a pharmacist?
  - Inpatient only
  - Inpatient and outpatient** (only if they choose ‘b’ will the rest of the survey follow)
  - Outpatient only

### Immunoglobulin use

- Approximately how much immunoglobulins did your hospital use in 2019? (Total amount in kilograms)
- Approximately how much immunoglobulins did your hospital use in 2020? (Total amount in kilograms)
- Was there a difference in immunoglobulin usage between 2019 and 2020 due to COVID-19? (If no, the rest of the survey will be populated with the year 2020. If yes, separate questions will be asked per calendar year.)
  - No
  - Yes

(If no, the rest of the survey will only have the 2020 questions from #6 onwards. If yes, include both 2019 and 2020 questions from #5 onwards)

- Did COVID-19 impact usage in any of these specialties in 2020 and how? (Please indicate all relevant specialties below and type how it was affected, i.e., increased or decreased)
  - Adult neurology (with free text)
  - Adult immunology (with free text)
  - Adult hematology (with free text)
  - Adult infectious diseases (with free text)

- e. Adult rheumatology (with free text)
  - f. Adult dermatology (with free text)
  - g. Adult nephrology (including kidney transplant surgery) (with free text)
  - h. Adult general medicine (with free text)
  - i. Pediatrics (includes all sub-specialties related to pediatrics) (with free text)
  - j. Other (with free text)
  - k. None of these specialties were affected
5. Which specialties (as defined by the specialty of the ordering physician) used the most Ig (in terms of volume) in your hospital setting **in 2019**? (Please indicate all relevant specialties below)
    - a. Adult neurology
    - b. Adult immunology
    - c. Adult hematology
    - d. Adult infectious diseases
    - e. Adult rheumatology
    - f. Adult dermatology
    - g. Adult nephrology (including kidney transplant surgery)
    - h. Adult general medicine
    - i. Pediatrics (includes all sub-specialties related to pediatrics)
    - j. Other
  6. Which specialties (as defined by the specialty of the ordering physician) used the most Ig (in terms of volume) in your hospital setting **in 2020**? (Please indicate all relevant specialties below)
    - a. Adult neurology
    - b. Adult immunology
    - c. Adult hematology
    - d. Adult infectious diseases
    - e. Adult rheumatology
    - f. Adult dermatology
    - g. Adult nephrology (including kidney transplant surgery)
    - h. Adult general medicine
    - i. Pediatrics (includes all sub-specialties related to pediatrics)
    - j. Other
  7. What percentage of each application route for Ig used **in 2019** (It should total 100%)
    - a. Intravenous immunoglobulins (IVIg) \_\_\_\_
    - b. Subcutaneous immunoglobulins (SCIg) \_\_\_\_
    - c. Facilitated/Self-administered hyaluronidase facilitated subcutaneous Ig(fSCIg) \_\_\_\_
  8. What percentage of each application route for Ig used **in 2020** (It should total 100%)
    - a. Intravenous immunoglobulins (IVIg) \_\_\_\_
    - b. Subcutaneous immunoglobulins (SCIg) \_\_\_\_
  - c. Facilitated/Self-administered hyaluronidase facilitated subcutaneous Ig(fSCIg) \_\_\_\_
  9. Approximately how much immunoglobulins were prescribed through an outpatient pharmacy or home care **in 2019**? (Total amount in kilograms)
  10. Approximately how much immunoglobulins were prescribed through an outpatient pharmacy or home care **in 2020**? (Total amount in kilograms)
  11. From January 2017–December 2020 (4 calendar years), did you notice a change in Ig usage in your hospital?
    - a. Yes
    - b. No
    - c. I don't know

(If 'yes' go to #11. If 'no' or 'I don't know,' go to #14)
  12. Do you know why a change in usage occurred? (Please indicate all that apply)
    - a. Due to a change in cost or reimbursement
    - b. Due to a change in indications/posology
    - c. Due to a change in hospital/regional/national policies
    - d. Due to a change in application route to subcutaneous (SC) instead of IV route
    - e. Due to a change in dosage
    - f. Due to the COVID-19 pandemic
    - g. Other (briefly describe)
  13. Which specialties (as defined as the specialty of the ordering physician) did you notice **increased** usage between 2016–2020? (Please indicate all specialties below)
    - a. Neurology
    - b. Immunology
    - c. Hematology
    - d. Infectious diseases
    - e. Rheumatology
    - f. Dermatology
    - g. Nephrology
    - h. General medicine
    - i. Pediatrics
    - j. Other
    - k. I did not notice any increase
  14. Which specialties (as defined by the ordering physician) did you notice **decreased** usage between 2016–2020? (Please indicate all specialties below)
    - a. Neurology
    - b. Immunology
    - c. Hematology
    - d. Infectious diseases
    - e. Rheumatology
    - f. Dermatology
    - g. Nephrology

- h. General medicine  
 i. Pediatrics  
 j. Other  
 k. I did not notice any decrease
15. Who monitors overall Ig usage in your hospital?  
 a. Through a committee  
 b. Primarily through an individual  
 c. Usage is not monitored  
 d. Other (free text)
16. Are all individual Ig orders reviewed?  
 a. Yes, prior to approval  
 b. Yes, after approval  
 c. No  
 d. Other (free text)
17. Who are the key individuals who approve Ig orders for **standard** indications? (Please indicate all who apply)  
 a. Pharmacists alone  
 b. Dual clinician-pharmacist  
 c. The requesting department  
 d. The blood bank./transfusion medicine dept  
 e. Other (free text)
18. Who are the key individuals who approve Ig orders for **non-standard** indications? (Please indicate all who apply)  
 a. Pharmacists alone  
 b. Dual clinician-pharmacist  
 c. The requesting department  
 d. The blood bank/transfusion medicine dept  
 e. Other (free text)
19. In general, what are factors taken into consideration when approving Ig use in your hospital? (Please indicate all that apply)  
 a. Guidelines (international, national, local)  
 b. Clinician input  
 c. Statistics  
 d. Off-label usage (indications not listed in SmPC - summary of product characteristics/product insert)  
 e. Cost/reimbursement to hospital for use  
 f. Contextual circumstances (i.e., whether there is sufficient supply or not)  
 g. Other (free text)
20. **In 2019**, did your hospital experienced Ig shortages? (By 'shortages,' we mean insufficient supply/stock overall, from brand and/or administration route shortages, in which the need to potentially decline or deny Ig requests as orders are reviewed more than usual)  
 a. Yes  
 b. No
21. **In 2020**, did your hospital experienced Ig shortages? (By 'shortages,' we mean insufficient supply/stock overall, from brand and/or administration route shortages, in which the need to potentially decline or deny Ig requests as orders are reviewed more than usual)  
 a. Yes  
 b. No
22. How frequently did these shortages occurred on average in 2019?  
 a. On a weekly basis  
 b. On a monthly basis  
 c. On a quarterly basis  
 d. Once or twice a year  
 e. Other (free text)
23. How frequently did these shortages occurred on average in 2020?  
 a. On a weekly basis  
 b. On a monthly basis  
 c. On a quarterly basis  
 d. Once or twice a year  
 e. Other (free text)
24. Is there an **external** notification process regarding Ig shortages? (Indicate all that apply)  
 a. Yes, the manufacturers/distributors notify me and/or other relevant hospital personnel  
 b. Yes, there is a notification process within our hospital region  
 c. No, there is no notification process
25. In case of an Ig shortage, what **internal** communication measurements are taken within your hospital? (Indicate all that apply)  
 a. Meetings with the committee in charge of Ig monitoring  
 b. Regular communication with physicians on supply shortage and provide resources on usage  
 c. Making a strategy to combat shortage  
 d. Other (free text)
26. In case of an Ig shortage, what are your mitigating measures? (multiple options possible)  
 a. Referral to another hospital  
 b. Switching to a lower dose  
 c. Substitution with other drugs/products/treatments  
 d. Delay of Ig treatment  
 e. Importing products from another country  
 f. Other (free text)
27. How do you prioritize which patients receive Ig?  
 a. Use of priority protocols  
 b. Clinician input  
 c. Other (free text)
28. Do you expect future shortages?  
 a. Yes  
 b. No  
 c. I don't know
- (If 'yes,' then go to #21, if 'no' go to #23)



### Descriptives

29. Where is your hospital located? → filter by country and state/province/city
30. What type of hospital do you work in? (e.g. urban, rural, community, critical access, NL: general, teaching, university, specialty)
31. How is Ig paid for in your hospital? (Multiple options possible; perhaps use %s)
  - a. Health insurance
  - b. Government
  - c. Hospital budget, not reimbursed
  - d. Other (free text)

### Future involvement

32. Would you be willing to complete another survey or participate in interviews or focus groups? If yes, please leave your name and email address where we can contact you. This will NOT be linked with your answers.
  - a. Yes \_\_\_\_\_
  - b. No

### Thank you message (shown at the end of the survey or when respondent does not consent)

Thank you for your participation.

If you have questions or comments, please contact \_\_\_\_\_.