Multispecialty Rating of Evidence-Based Conditions for Intravenous Immunoglobulin Therapy Using a 3-Axis Prioritization Algorithm

Jordan S. Orange, MD, PhD; Matt Johnson, BA; Barb Lennert, RN, BSN, MAOM; Katarzyna Shields, PharmD, MBA, BCOP, BCPS; Michael Eaddy, PharmD, PhD

BACKGROUND: A 3-axis prioritization algorithm was proposed and was evaluated in a US multispecialist pilot study to obtain uniform consensus regarding effective practices for the use of intravenous immunoglobulin (IVIG) therapy.

OBJECTIVE: The primary objective was to use consensus-building methodologies to rate disease states for IVIG utilization while considering disease severity and the efficacy of alternative therapeutic options to IVIG from the perspective of US multispecialists.

METHODS: A 7-member multispecialty physician expert panel was surveyed to rate 50 disease states and to determine their level of agreement with the American Academy of Allergy, Asthma & Immunology (AAAAI) evidence-based medicine (EBM) ratings. The disease states were then rated across the 2 domains of disease severity and the perceived efficacy of therapeutic alternatives. An interquartile deviation (IQD) of ≤0.5 was used to determine consensus for disease states within each domain. Disease states reaching consensus across both domains were ranked according to a 2 × 4 algorithmic scale to establish priority for IVIG utilization.

RESULTS: Overall, a high level of agreement was found with the AAAAI ratings for EBM. Based on an IQD of ≤0.5, the panel reached consensus on the severity of all 50 disease states. Of the 50 disease states, consensus was reached on the efficacy of therapeutic alternatives for 39 disease states. Using the same panel of experts, the 11 disease states without consensus in the first survey were resurveyed, and consensus was subsequently reached on 4 of them. Discussion among the experts, and the resurvey, resulted in expert consensus increasing from 78% to 86% postdiscussion and a change in the overall rating of IVIG on 4 conditions.

CONCLUSIONS: Multispecialty input of 7 experts on evidence-based IVIG use, augmented with disease severity and efficacy of therapeutic alternatives, enables a balanced perspective on IVIG therapy prioritization. Moreover, multispecialty dialogue improved consensus building among panel members on the effective use of IVIG therapy in several clinical conditions.

KEY WORDS: AAAAI, consensus building, disease severity, disease state, efficacy, evidence-based medicine, intravenous immunoglobulin, prioritization algorithm

Immunoglobulins are proteins produced by B-cells that are used by the immune system to identify and act on foreign objects, such as bacteria and viruses. Therapeutic preparations of human immunoglobulin have provided substantive opportunity for their application in a wide variety of clinical contexts. Although the mechanism of action of intravenous immunoglobulin (IVIG) is complex, it is known that in addition to its anti-infective activity, IVIG exhibits immunoregulatory
Multi-specialty Rating of Evidence-Based Conditions for IVIG

Intravenous immunoglobulin (IVIG) is a fundamental replacement therapy for many debilitating and/or life-threatening immunodeficiency disorders for patients who have decreased or abolished antibody production capabilities and is a critical immune-modulating agent in an array of immune dysregulatory disorders.

In the United States, currently 8 uses have been approved by the US Food and Drug Administration (FDA) for IVIG, including primary immunodeficiency disease or primary antibody immunodeficiency, idiopathic thrombocytopenic purpura, Kawasaki disease, B-cell chronic lymphocytic leukemia, bone marrow transplantation, pediatric HIV-1 infection, multifocal motor neuropathy, and chronic inflammatory demyelinating polyneuropathy.

However, in clinical practice, IVIG therapy is frequently used for other conditions, without FDA approval, when clinicians perceive a clinical benefit for its use. Common off-label uses include several neurologic conditions, such as relapsing-remitting multiple sclerosis (RRMS), Guillain-Barré syndrome, and Lennox-Gastaut syndrome; infection prophylaxis in patients undergoing transplant, such as cytomegalovirus prevention in lung and bone marrow transplantation; for the treatment of rheumatoid arthritis in certain subgroups; and for the prevention of miscarriage in individuals with antiphospholipid syndrome, among many others.

An exhaustive list of off-label uses is beyond the scope of this overview, but many payers (Medicare or commercial insurers) have approved reimbursement (in some cases provisionally) for various off-label uses of IVIG, by establishing criteria such as a lack of response to conventional therapies or evidence of contraindications. Furthermore, although various levels of clinical evidence are available to support the use of IVIG therapy in these and other conditions, a comprehensive review is not part of this analysis. Rather, the reader may refer to published case reports, review articles, US-specific and international guidelines, and various compendia (eg, DRUGDEX Drug Evaluations) for information about a specific unlabeled use.

For example, the American Academy of Neurology rated evidence for the use of IVIG therapy in adults with Guillain-Barré syndrome as level A, whereas the evidence is insufficient to support or refute its use in children with Guillain-Barré syndrome (Level U). However, a previous Cochrane systematic review of immunotherapy for recurrent miscarriage showed that IVIG did not improve the live birth rate in unexplained recurrent miscarriage and, thus, concluded that IVIG should not be offered for this use.

Although the administration of IVIG therapy can be life-saving, including some of its off-label uses, it can also be associated with many adverse effects, reimbursement challenges, and even limited availability (because its production is dependent on the supply of qualified human plasma). As a result, several national and international treatment guidelines have been developed to direct treatment for conditions requiring IVIG therapy.

An ongoing evaluation of IVIG uses is crucial because of the limited donor pool, complex production and distribution process, the high cost of therapy, and the increasing number of clinical conditions supported by at least some experimental evidence. In 2006, expert immunologists from the American Academy of Allergy, Asthma & Immunology (AAAAI) reviewed the use of IVIG therapy from an American perspective and published recommendations based on the degree of available clinical evidence for FDA-approved and unapproved conditions. There was limited emphasis placed on different off-label uses.
The current study was undertaken to address these limitations and promote cross-specialty dialogue about EBM for a wide range of FDA-approved and off-label uses of IVIG therapy, based on a previously proposed IVIG therapy prioritization algorithm across approved and off-label conditions by a multispecialty/disciplinary medical panel consisting of experts in IVIG therapy in each respective field. The engagement’s primary objective in this study was to use consensus-building methodologies to rate the disease states for IVIG utilization while considering disease severity (Axis 2) and the efficacy of alternative therapeutic options (Axis 3) from the perspective of US multispecialists to strengthen the best practices for the use of IVIG therapy.

### Methods

This study evaluated the previously proposed addition of 2 axes—disease severity and the efficacy of therapeutic alternatives—in addition to the AAAAI’s EBM ratings for the consideration of IVIG therapy prioritization for clinical conditions. To strengthen the application of AAAAI’s ratings, we used a 3-axis IVIG prioritization algorithm for strong evidence-based indications previously considered by a panel of expert immunologists. Because the quality of evidence alone does not convey the full range of therapeutic utility of IVIG across all clinical conditions, we considered the hypothesis that the application of the algorithm’s second and third axes can offer enhanced perspective that could prove advantageous in meeting the increased demand for a limited supply of IVIG.

The 3-axis IVIG prioritization algorithm, incorporating 16 ratings and a linear scale, is shown in Figure 1. For example, the highest-priority condition (A1) according to this 3-axis algorithm was classified as an immediately life-threatening disease with no reasonable alternative therapies to IVIG utilization. More recently, the question arose whether using a single axis in the AAAAI’s algorithm was consistent with the full spirit of EBM for a limited resource such as IVIG, considering the definition of EBM advocating for “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.” Furthermore, for patients awaiting treatment with IVIG, decisions made by Pharmacy & Therapeutics (P&T) committees that are typically composed of knowledgeable multispecialty healthcare providers (eg, practicing physicians, pharmacists, nurses, administrators, quality improvement managers) involved in the medication-use process are critical when the availability of IVIG is limited. However, relatively few (37%) hospitals have a P&T committee that is specifically tasked with determining which patients are to be treated under established priority protocols, and even fewer (27%) have priority protocols specifying which patients are to be treated first. This is surprising, given the relatively little guidance provided in the peer-reviewed medical literature.

The current study was undertaken to address these limitations and promote cross-specialty dialogue about EBM for a wide range of FDA-approved and off-label uses of IVIG therapy, based on a previously proposed IVIG therapy prioritization algorithm across approved and off-label conditions by a multispecialty/disciplinary medical panel consisting of experts in IVIG therapy in each respective field. The engagement’s primary objective in this study was to use consensus-building methodologies to rate the disease states for IVIG utilization while considering disease severity (Axis 2) and the efficacy of alternative therapeutic options (Axis 3) from the perspective of US multispecialists to strengthen the best practices for the use of IVIG therapy.

### Methods

This study evaluated the previously proposed addition of 2 axes—disease severity and the efficacy of therapeutic alternatives—in addition to the AAAAI’s EBM ratings for the consideration of IVIG therapy prioritization for clinical conditions. To strengthen the application of AAAAI’s ratings, we used a 3-axis IVIG prioritization algorithm for strong evidence-based indications previously considered by a panel of expert immunologists. Because the quality of evidence alone does not convey the full range of therapeutic utility of IVIG across all clinical conditions, we considered the hypothesis that the application of the algorithm’s second and third axes can offer enhanced perspective that could prove advantageous in meeting the increased demand for a limited supply of IVIG.

The 3-axis IVIG prioritization algorithm, incorporating 16 ratings and a linear scale, is shown in Figure 1. For example, the highest-priority condition (A1) according to this 3-axis algorithm was classified as an immediately life-threatening disease with no reasonable alternative therapies to IVIG utilization.
Multispecialty Rating of Evidence-Based Conditions for IVIG

(Figure 2). All panelists were compensated for the actual time they spent participating in the study, at fair market value rates by ASD Healthcare.

The consensus process encompassed a 3-step modified Delphi method. This method is advocated for use in healthcare as a dependable tool for establishing consensus for a stated clinical dilemma. The modified Delphi method uses an iterative systematic progression of repetitive rounds of voting and has been shown to be an effective process for establishing expert group consensus where there is inadequate or absent definitive evidence and where opinion is imperative.

Specific to the 3 steps of the modified Delphi method, the panel initially convened in a virtual meeting to review the prioritization algorithm and then independently completed an online prioritization survey, with a second virtual consensus meeting to review the results. Subsequently, a follow-up online rating survey was independently completed to achieve consensus on nonconsensus-forming items. The full process is illustrated in Figure 2 and is described in more detail below.

First virtual multispecialty expert meeting. The 3-axis algorithm for IVIG therapy prioritization was introduced during the first virtual meeting, which was a web conference with audio and visual capabilities. During this engagement, the 3-axis IVIG prioritization model was introduced. The survey methodology and approach to follow-up meetings was also explained to the participating experts.

Initial online survey. After the first virtual consensus meeting, the experts were asked to assess their level of agreement with the AAAAI’s categorization of evidence rating (Axis 1), the strength of the recommendation, and the interpretation of perceived benefit of IVIG therapy for each condition as published, in an online survey that lasted approximately 75 minutes.

These questions were based on a scale from 1 to 7, where 1 meant strongly disagree and 7 meant strongly agree. When no AAAAI rating was available, the experts were asked to provide their own assessment of treatment benefit based only on the existing data (ie, not relative to anything else) using the defined descriptors of perceived benefit (ie, definitely beneficial, probably beneficial, may provide benefit, or unlikely to be beneficial).

Next, the experts were asked to independently rate 50 disease states across 2 domains (axes) on a 4-point Likert scale that included disease severity (Axis 2) immediately life-threatening; [2] life-threatening; [3] life-modifying; [4] other), and perceived efficacy of therapeutic alternatives to IVIG (Axis 3 [1] none; [2] low; [3] medium; and [4] high). The most frequently used therapeutic alternatives across these 50 disease states are corticosteroids; various immunosuppressive therapies, including cytotoxic agents; and plasma exchange. It was up to each panel member to decide what was a viable therapeutic alternative to IVIG in each case, as well as the perception of the treatment efficacy.

Second virtual consensus meeting. The findings from the online survey were presented during the second meeting, and 8 conditions with either low consensus or those representing IVIG utilization in highly variable conditions were identified for further discussion. Consistent with the Delphi method, a group discussion followed, during which panelists with specific expertise

AAAI indicates American Academy of Allergy, Asthma & Immunology; IVIG, intravenous immunoglobulin.
presented their views on the selected disease states and IVIG use in the treatment of these conditions.

The discussion allowed the experts to present and rationalize their opinions and facilitated the opportunity to consider the opinions of others, reconsider their own opinions, and assess the relative importance of each opinion presented.

**Follow-up online survey.** After the group discussion, a second online survey, lasting approximately 30 minutes, was administered. The experts were asked to rater nonconsensus-forming items on Axis 2 (disease severity) and Axis 3 (efficacy of alternative therapies) as a result of the group discussion. To ensure the soundness of the data, close attention was given to upfront expert selection and motivation, survey construction, and process management. The experts were also instructed to provide any outstanding comments on the IVIG rating for disease states where there was relatively good consensus in the first survey.

**Analyses**

Interquartile deviation (IQD), a measure of data dispersion, was used to measure the degree of consensus. IQD is based on the lower quartile Q1 (25th percentile) and the

### Table 1 Axes 2 and 3 Consensus Levels for 50 Conditions Surveyed

<table>
<thead>
<tr>
<th>Condition</th>
<th>Perceived severity</th>
<th>Efficacy of therapeutic alternatives</th>
<th>Condition</th>
<th>Perceived severity</th>
<th>Efficacy of therapeutic alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO-incompatible kidney transplant</td>
<td>✓</td>
<td>✓</td>
<td>Neonatal sepsis (treatment of)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>✓</td>
<td>✓</td>
<td>Opsoclonus myoclonus syndrome</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>✓</td>
<td>✓</td>
<td>Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Autism</td>
<td>✓</td>
<td></td>
<td>Pemphigus vulgaris</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>✓</td>
<td></td>
<td>Polyaartitis nodosa</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Autoimmune neutropenia</td>
<td>✓</td>
<td></td>
<td>Posthematopoietic stem-cell transplantation</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Autoimmune enteritis</td>
<td>✓</td>
<td></td>
<td>Prevention of infection in pediatric AIDS</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>✓</td>
<td></td>
<td>Prevention of sepsis in neonatal intensive care unit</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>✓</td>
<td></td>
<td>Primary hypogammaglobulinemia</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Chronic immune demyelinating polyneuropathy</td>
<td>✓</td>
<td></td>
<td>Primary immunodeficiency diseases with absent B-cells</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Chronic urticaria</td>
<td>✓</td>
<td></td>
<td>Primary immunodeficiency diseases with hypogammaglobulinemia and impaired specific antibody function</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Clostridium difficile colitis</td>
<td>✓</td>
<td></td>
<td>Primary immunodeficiency diseases with normogammaglobulinemia and impaired specific antibody function</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Common variable immunodeficiency</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus pneumonitis in solid organ transplantation</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felomaternal alloimmune thrombocytopenia</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves ophthalmopathy</td>
<td>✓</td>
<td></td>
<td>Recurrent spontaneous abortion (to promote successful pregnancy)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>✓</td>
<td></td>
<td>Relapsing-remitting multiple sclerosis</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Idiopathic thrombocytopenic purpura</td>
<td>✓</td>
<td></td>
<td>Secondary hypogammaglobulinemia</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulin A deficiency (selective)</td>
<td>✓</td>
<td></td>
<td>Severe combined immunodeficiency</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulin G subclass deficiency</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion body myositis</td>
<td>✓</td>
<td></td>
<td>Severe eczema</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td>✓</td>
<td></td>
<td>Specific antibody deficiency</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney transplantation for highly human leukocyte antigen–sensitized recipients</td>
<td>✓</td>
<td></td>
<td>Stiff person syndrome</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Multifocal motor neuropathy</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>✓</td>
<td></td>
<td>Toxic epidermal necrolysis</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>X-linked agammaglobulinemia</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

✓ Indicates reached consensus (ie, an interquartile deviation of \(\leq 0.5\)).

✓ Reached consensus with an interquartile deviation of 0.
upper quartile Q3 (75th percentile) of responses. The difference of Q3−Q1 divided by 2 is the semi-interquartile range or the quartile deviation. Raskin identified an IQD of 1.00 or less as an indicator of consensus. This study used an IQD of ≤0.5 as an indication of consensus. Disease states reaching consensus across both domains were plotted on a 2 × 4 algorithmic matrix (ie, the consensus rating of Axis 2 on its 4-point Likert scale was plotted against the Axis 3 rating) to establish priority recommendations.

Results

In distinction from the design of many consensus projects, 7 experts, including 2 physicians with 2 or more specialties, were assembled from across 8 clinical disciplines (not mutually exclusive). The first meeting was held as a virtual consensus meeting paired with the initial online survey. No results were presented at this first virtual consensus meeting, because it was a didactic event to provide the experts with the background information necessary regarding the 3-axis IVIG prioritization methodology being used in this study and the completion of the IVIG surveys. The results of the online survey that the experts completed after this meeting showed several points.

Axis 1. Overall, with the exception of 4 conditions (ie, Alzheimer’s disease, fetomaternal alloimmune thrombocytopenia, neonatal sepsis, and pemphigus vulgaris), the results of the online survey demonstrated high agreement among the respondents and the AAAAI’s IVIG ratings. For each disease state, the mean score for Axis 2 was plotted against the mean score for Axis 3 to get an overall rating ranging from A1 to D4 (Figure 1).

Axis 2. Based on an IQD of ≤0.5, the panel reached consensus on the severity (Axis 2) of all 50 disease states; 12 of those showed a tight grouping of scores, with an IQD of 0 (Table 1).

Axis 3. Of the 50 disease states, 39 reached consensus on the efficacy of therapeutic alternatives (Table 1). Four conditions (ie, autoimmune uveitis, posthematopoietic stem-cell transplantation, severe eczema, and specific antibody deficiency) had an IQD of 0 on perceived efficacy of therapeutic alternatives (Axis 3). These 4 disease states, except for specific antibody deficiency, also had an IQD of 0 in the assessment of severity (Axis 2).

The panel was reconvened for a second virtual consensus meeting to discuss the findings from the first survey and to have a more in-depth discussion on selected disease states. Here, the axis-specific concerns were raised, and conditions were selected for consideration.

Axis 2. After evaluating the degree of consensus on the severity rating of all 50 disease states, 4 (ie, myasthenia gravis, toxic epidermal necrolysis, Kawasaki disease, and Guillain-Barré syndrome) with IVIG utilization in highly variable conditions (ie, highly variable in presentation and/or progression) were selected for additional discussion.

Axis 3. The 11 disease states where consensus was not reached on perceived efficacy of therapeutic alternatives (Tables 2 and 3)—none of which were deemed immediately life-threatening on Axis 2—were severe combined immunodeficiency, fetomaternal alloimmune thrombocytopenia, adrenoleukodystrophy, prevention of infection in pediatric AIDS, autoimmune hemolytic anemia, cytomegalovirus pneumonia in solid organ transplant, autism, idiopathic thrombocytopenic purpura, RMS, chronic fatigue syndrome, and recurrent spontaneous abortion (to promote successful pregnancy).

Of these, the 4 conditions (ie, severe combined immunodeficiency, autoimmune hemolytic anemia, RMS, and cytomegalovirus) closest to consensus on the initial survey, and therefore the most likely to reach consensus within the study time frame, were chosen for additional discussion at the second virtual consensus meeting.

Of the 39 conditions reaching consensus, only 2 were rated as immediately life-threatening (ie, prevention of sepsis in neonatal intensive care unit and neonatal sepsis [treatment]) and were perceived to have medium and high efficacy as therapeutic alternatives, respectively.

After the discussion at the second virtual consensus meeting, the experts completed a follow-up online survey, thus allowing for the evaluation of any alteration in

---

**Table 2**

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Efficacy of therapeutic alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Immediately life-threatening</td>
<td>–</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>2</td>
</tr>
<tr>
<td>Life-modifying</td>
<td>–</td>
</tr>
<tr>
<td>Other</td>
<td>–</td>
</tr>
</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Efficacy of therapeutic alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Immediately life-threatening</td>
<td>–</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>–</td>
</tr>
<tr>
<td>Life-modifying</td>
<td>–</td>
</tr>
<tr>
<td>Other</td>
<td>–</td>
</tr>
</tbody>
</table>

*Common variable immunodeficiency, primary immunodeficiencies with absent B-cells.*
consensus (or lack thereof) for the discussed indications. The follow-up survey demonstrated 2 key points.

**Axis 2.** Myasthenia gravis, Kawasaki disease, toxic epidermal necrolysis, and Guillain-Barré syndrome were subsequently resurveyed, with only myasthenia gravis showing movement in IQD, moving from an IQD of 0.5 to an IQD of 0 (ie, a higher degree of consensus).

**Axis 3.** The 11 disease states without consensus in the first survey were resurveyed, with 4 of them (ie, autoimmune hemolytic anemia, severe combined immunodeficiency, RRMS, and cytomegalovirus pneumonitis in solid organ transplantation) subsequently reaching consensus; severe combined immunodeficiency and RRMS also showed consolidations on severity, moving from an IQD of 0.5 to an IQD of 0.

Overall, the discussion among the clinical experts and the resurvey resulted in an increasing consensus from 78% to 86% (ie, an IQD ≥0.5 on Axes 2 and 3), with 3 disease states reaching an IQD of 0 on Axes 2 and 3, and a change in the overall IVIG rating of 3 conditions.

### Discussion

The number of disease states for which some level of clinical evidence regarding the use of IVIG therapy exists is increasing. However, because IVIG therapy is a finite resource with high costs, the rating of its use is critical. As previously proposed by Orange and colleagues, our study investigated the use of a more refined algorithm for IVIG therapy prioritization, incorporating 3 axes to account for strength of clinical evidence, disease severity, and efficacy of therapeutic alternatives. Through a multistep process, a 7-member multispecialty expert panel established consensus in 86% of the disease states evaluated for which IVIG therapy could be considered. The findings were consistent with the previously published guideline recommendations; however, because of the opinion-based nature of this pilot study, a definitive stratification of IVIG off-label uses was not feasible.

Specific to the degree of consensus, a total of 15 disease states reached an IQD of 0, indicating a high degree of consensus on disease severity, and 4 disease states reached this level of consensus on the efficacy of therapeutic alternatives. Three disease states (ie, autoimmune uveitis, posthematopoietic stem-cell transplantation, and severe eczema) reached an IQD of 0 on Axes 2 and 3.

There was also a change after step 3 (ie, the follow-up online survey) in the overall IVIG therapy rating of 3 conditions, with changes on resurvey in the mean disease severity rating of 2 conditions and the mean efficacy of therapeutic alternatives rating of 2 conditions. Severe combined immunodeficiency increased in severity rating from life-threatening to immediately life-threatening, and autoimmune hemolytic anemia decreased in severity rating from life-threatening to life-modifying. The mean score for the efficacy of therapeutic alternatives changed from medium to high efficacy for autoimmune hemolytic anemia and for myasthenia gravis. The follow-up discussion and resurvey emphasized the need for case-by-case discussion of the more variable and complex autoimmune diseases to determine IVIG therapy priority.

Although transcripts of the discussions were not collected, an important topic for future research would encompass the consensus-building dialogues and the key subjective drivers of outcomes toward consensus in specific applications. This could potentially identify key decision points to arm and inform local groups, such as multidisciplinary institutional P&T committees, in making decisions regarding IVIG-related formularies.

Overall, our evaluation of consensus might have been potentially further improved by supplementing it with additional axes, having a higher number of meetings, subdividing the disease categories in the AAAAI list, and hosting 1 or 2 virtual consensus meetings as live events. As noted, the analysis of transcripts and subjective research techniques may also be of value in informing future directions.

In this study, conditions with less variability in disease severity and course demonstrated higher consensus and, as a result, may be more amenable to standard policy regarding the priority of the need for IVIG therapy. For highly variable conditions, discussion by a multispecialist panel improved the consensus on the IVIG therapy rating. The experts were likely to reach agreement for the use of IVIG therapy based on dialogue with peers and clinical experts. The follow-up discussion and survey emphasized the need for a case-by-case discussion of the more variable or complex autoimmune diseases to determine the priority of IVIG therapy. Furthermore, the panel concluded that evidence-based evaluation should start with Axis 1 (ie, evidence-supported conditions), and once this threshold is met, then Axis 2 (disease severity) and Axis 3 (efficacy of therapeutic alternatives) should be used for rating.

The complicated nature of many rare diseases, and their high variability, underscores the need for institutions to have a P&T committee or similar decision-making body that includes expert clinicians and decision makers from multiple disciplines for discussions of IVIG therapy application and rating utilizing expert perspective and data from the peer-reviewed medical literature.

### Conclusions

An IVIG therapy prioritization algorithm, augmented with disease severity and the efficacy of therapeutic alternatives, is a valuable clinical decision-making tool. A multidisciplinary panel improved consensus building
among the 7 panel members on the effective use of IVIG therapy in several clinical conditions. Applying this 3-axis consensus-building approach, an expert multidisciplinary panel reached consensus on almost 90% of disease states considered in this study in which IVIG therapy may be used.

Although there was generally high agreement with the AAAAI evidence ratings for the use of IVIG therapy for the surveyed conditions, dialogue among multispecialty panel members addressed the need for the case-by-case discussion of patients with the most variable and complex diseases and improved consensus for the use of IVIG therapy in these conditions. The use of expert multispecialty dialogue is valuable and something that may be considered on a larger scale for coverage decisions by formulary decision makers, potentially even within the FDA or among specialty medical societies. Nevertheless, it is unlikely that there will be a replacement for considering rare cases on an individual basis regarding their suitability for IVIG treatment.

Source of Funding

This study was funded by ASD Healthcare.

Author Disclosure Statement

Dr Orange is a consultant to ASD Healthcare, Baxtera, CSL Behring, Griffols, and Walgreens and is on the scientific advisory board for ADMA Biologics. Mr Johnson, Ms Lennert, Dr Shields, and Dr Eaddy are employees of Xenda, which was paid by ASD Healthcare to complete this study.

References


Stakeholder Perspective next page
A Useful Tool for Evaluating Disease Severity and Alternative Treatments Efficacy

By Gary Branning, MBA
Associate Professor, Rutgers Graduate School of Business; President, Managed Market Resources, Mt Olive, NJ

PAYERS/PATIENTS: Traditionally, payers have not managed aggressively treatments for rare and life-threatening diseases, such as intravenous immunoglobulin (IVIG). US Food and Drug Administration approvals of specialty pharmaceuticals continue to outpace those of traditional drugs; however, payers are exploring additional approaches, such as instituting greater restrictions and using specialty pharmacy providers to control drug costs and utilization. For example, the percentage of commercial plans requiring prior authorization (PA) for 6 categories of provider-administered therapies increased considerably between 2007 and 2014 (eg, from 61% to 89% for rheumatoid arthritis, psoriasis, and Crohn’s disease, and from 54% to 87% for IVIG, respectively).2

At times, payers refer to such strategies as “death by a thousand cuts.” Payers believe that any drug that is a life-saving or a new treatment option for their members with undertreated or untreated diseases should be available to patients, but they are beginning to look for ways to control overall pharmacy spending across all specialty drugs.

With increasing attention paid to the appropriate management of specialty medications, the algorithm introduced in the article by Orange and colleagues to evaluate disease severity and the efficacy of therapeutic alternatives may be a useful decision-making tool.3 And because many specialty drugs have multiple indications, payers and drug manufacturers have begun to consider contracting options whereby a drug’s price can better reflect its varying benefit by indication; therefore, the algorithm may have broader application beyond IVIG.

Express Scripts catalyzed interest in indication-specific pricing with the launch of its indication-specific pricing initiative for certain cancer drugs in 2016.4 According to a recent IMS report, the number of multi-indication oncology medications is rising, accounting for approximately 50% of major cancer drugs marketed in 2014 and estimated to increase to approximately 75% by 2020.5

The current US pricing and reimbursement methodologies assign a single price to each drug, regardless of how it is used. As a result, price and clinical value do not necessarily align across all indications. Because relative clinical benefits vary widely across these multiple indications, a process such as the algorithm outlined by Orange and colleagues3 may be needed to evaluate the relative value of a drug by indication, depending on the distinct patient population treated.

Payers will appreciate an algorithm that can help to define their utilization management techniques to ensure that the appropriate patients, who are often in underserved populations, can obtain these medications.

PAYERS/PROVIDERS: Payers and providers have traditionally had a slightly adversarial relationship; despite a shared commitment to patients’ best interests, their approach to achieving high-quality care differs. Although providers typically focus on the needs and wants of an individual patient, payers take responsibility for managing the health of an entire population of patients. This discrepancy often creates a conflict of interest between the 2 stakeholders. The algorithm presented in the present article3 establishes a foundation for case-by-case discussions of patients with rare or complex conditions, which may help to align the interests of payers and providers in support of individual patients.

A payer-designed PA and a physician-designed protocol that are aligned with these specific patients’ needs could provide a solution for these important patients. There can be considerable variability in PA requirements, which can frustrate providers, who need to approach a PA differently for every patient.