Intravenous immunoglobulin in paediatric neurology: safety, adherence to guidelines, and long-term outcome

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***See Appendix for members of IVIG in Neurology Study Group.**

PUBLICATION DATA
Accepted for publication 9th April 2016.
Published online

ABBREVIATIONS

IVIG	Intravenous immunoglobulin
mRS	Modified Rankin Scale
NMDAR	*N*-methyl-D-aspartate receptor
PNS	Peripheral nervous system

AIM Intravenous immunoglobulin (IVIG) is an expensive therapy used in immunodeficiency and autoimmune disorders. Increasing demands and consequent shortages result in a need for usage to conform to guidelines.

METHOD We retrospectively evaluated IVIG use for neuroimmunological indications and adherence to existing guidelines in a major Australian paediatric hospital between 2000 and 2014.

RESULTS One-hundred and ninety-six children (96 male, 100 female; mean age at disease onset 6y 5mo [range 3mo–15y 10mo], mean age at first IVIG dose 7y 2mo [range 3mo–16y 5mo]) received IVIG for neuroimmunological indications during the study period (28.1% had Guillain–Barré syndrome), representing 15.5% of all hospital indications. In total, 1669 IVIG courses were administered (total 57 221g, median 78g/patient, range 12–5748g). The highest median numbers of courses were in chronic inflammatory demyelinating polyneuropathies, opsoclonus-myoclonus ataxia syndrome, suspected immune-mediated epilepsies, and Rasmussen's encephalitis. Adverse reactions occurred in 25.5% of patients, but these were mostly minor. Outcome at follow-up was best in anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, Guillain–Barré syndrome, and myasthenia gravis, and worst in Rasmussen's encephalitis and epilepsies. The total cost of IVIG was US$2 595 907 (median $3538/patient, range $544–260 766). Of patients receiving IVIG, 45.4% to 57.1% were given the therapy for 'weak' indications or indications 'not listed' in international guidelines. Some entities commonly treated with IVIG in current practice, such as anti-NMDAR encephalitis and transverse myelitis, are not listed in most guidelines.

INTERPRETATION Our study demonstrates that IVIG is generally well tolerated but expensive, and discloses discrepancies between guidelines and clinical practice in paediatric neurology, suggesting both the need for greater adherence to current recommendations, and for recommendations to be updated to accommodate emerging indications.

Intravenous immunoglobulin (IVIG) is a fractionated blood product made from pooled human plasma, that has been used in the treatment of immune deficiencies and autoimmune disorders for almost four decades.[1] Supplementation of the immune system with IVIG broadens the spectrum of a recipient's immune response and attenuates autoimmune reactivity,[1] although the precise mechanisms of anti-inflammatory and immunoregulatory action are not completely understood, and are thought to be diverse according to the underlying pathophysiology.[1–3]

The demand for IVIG has increased over the years, resulting in high cost to health providers and IVIG shortages.[2] Guidelines regulating IVIG use according to the evidence base have been created in different countries, to ensure its availability for patients who are most likely to benefit from the therapy.[4–9] However, recommendations vary across different guidelines. In Australia, the use of IVIG is regulated by the National Blood Authority of Australia Criteria. Based on the available evidence, these identify conditions for which the role of IVIG is 'established', 'emerging', 'supported in exceptional circumstances only', or 'not supported'.[9] The United Kingdom guidelines use a similar descriptive classification for the use of IVIG: 'highest priority', 'appropriate', 'limited/little/no evidence', 'not recommended'.[7] In other guidelines, such as those from North America and Europe, recommendations are based on levels of evidence categorized as 'A (established effective)', 'B (probably effective)', 'C (possible effective)', and 'U (inadequate data)'.[4,6,8]

To review the current clinical practice regarding the use of IVIG in paediatric neurology, we carried out a

retrospective study in a large paediatric neurology centre in Sydney, Australia, focusing on the clinical indications for IVIG administration, adherence to guidelines, cost, tolerability, and long-term outcome.

What this paper adds

- Intravenous immunoglobulin (IVIG) is an expensive but relatively well tolerated treatment commmonly used in paediatric neurology.
- Some indications for IVIG administration seem to respond poorly to treatment.
- Other conditions commonly treated with IVIG are not listed in most guidelines.
- Greater adherence to current recommendations is required, and recommendations need to be updated.

METHOD

Patient identification

The study was conducted at the Children's Hospital at Westmead, New South Wales, Australia, approved as service improvement (activity number: 4695). A list of all patients who received IVIG at the Children's Hospital at Westmead between January 2000 and June 2014 was provided by the hospital pharmacy and the blood bank (independent sources distributing all IVIG at the hospital). A total of 1264 children was treated with IVIG for any paediatric indication in the study period. To identify the patients who received IVIG for neurological indications only, the clinical files of the 1264 total patients were reviewed in the hospital informatic database (PowerChart; Cerner Corporation PTY Ltd., North Sydney, NSW, Australia). Seven patients were excluded because of insufficient clinical information, and 1038 because of IVIG administration for non-neurological indications (Fig. 1). Of the non-neurological indications, the most common were Kawasaki disease (312 of 1264, 24.7%) and acute lymphoblastic leukaemia (128 of 1264, 10.1%). A total of 219 children who received IVIG for neurological indications was identified (219 of 1264, 17.3%). Of these, 23 did not have a neuroimmunological disorder, and were excluded (Fig. 1). Therefore, 196 children received IVIG for neuroimmunological indications at the Children's Hospital at Westmead during the study period, and were included in our study (196 of 1264 of all patients, 15.5%).

Data collection

Data were collected via retrospective chart review of the hospital informatic database. The clinical diagnosis in the discharge letter was verified by correlating with the diagnostic investigations performed, and with the diagnosis at follow-up. The clinical indications for IVIG administration were grouped into central nervous system (CNS) and peripheral nervous system (PNS) indications (Fig. 1). The indications for which IVIG was dispensed were reviewed in light of the most recent available international guidelines on IVIG use.[4–7,9] Data collected on IVIG use included type, dose, number of courses, total quantity administered, and side effects. To calculate the cost of IVIG, we used the mean price of all IVIG products used at the Children's Hospital at Westmead as of July 2015 in Australian dollars (AUD), and then converted this to American dollars (USD) (currency conversion as of December 2015: 1 AUD=0.73 USD). Other immune therapies received besides IVIG were also recorded and categorized as first-line (corticosteroids, plasma exchange) and second-line (mycophenolate mofetil, cyclophosphamide, rituximab, azathioprine, methotrexate, and other).

With regard to the severity of disease, modified Rankin Scale (mRS) score[10] was assigned retrospectively by the main investigators (RCD, MN) based on the clinical data in the acute phase before receiving IVIG. Outcome was assessed retrospectively at the last follow-up available in the informatic database, and scored via mRS and via type of ongoing impairments (subdivided into: none, cognitive/learning, behavioural, motor, visual, epilepsy, and other). Scores of 0 to 2 were interpreted as a good outcome, as in previous studies.[11] For some patients, the available follow-up in the informatics database was ≤12 months from the first IVIG administration (and the patients were lost to follow-up). In these cases, we conducted telephone interviews to the patients (if current age ≥18y) or to their family (if current age <18y), to extend the length of follow-up (total 43 interviews). This was done after approval from the local ethics committee (LNR/15/SCHN/218) and after obtaining informed consent from the family. After extending follow-up, only 23 patients had follow-up ≤12 months (23 of 196, 11.7%).

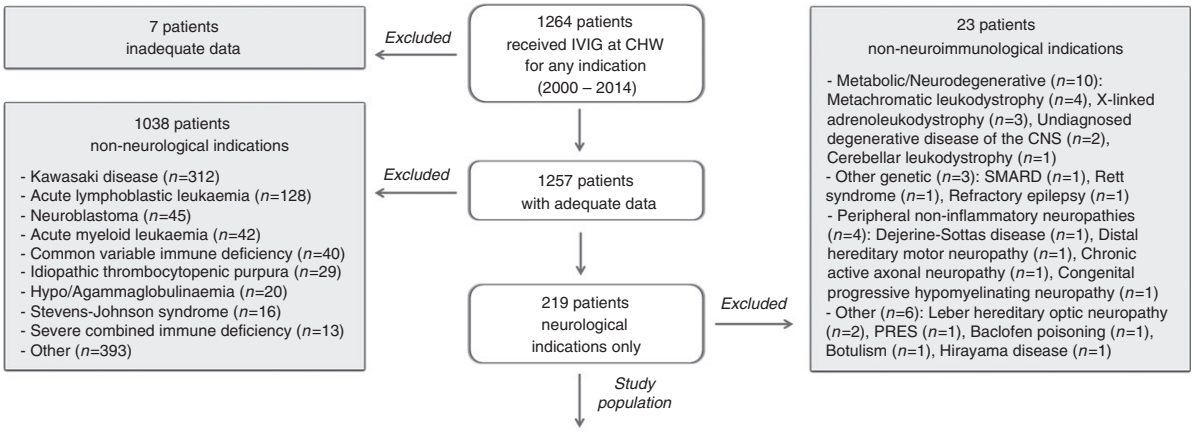
RESULTS

Demographics

There were similar distributions of male (96 of 196, 49%) and female (100 of 196, 51%) patients in our cohort. Mean age at disease onset was 6 years 5 months (median 5y 1mo, range 3mo–15y 10mo). Mean age at first IVIG dose was 7 years 2 months (median 6y 3mo, range 3mo–16y 5mo). An increasing number of patients was started on IVIG for neuroimmunological indications during the study period: 48 between 2000 and 2004, 57 between 2005 and 2009, and 91 between 2010 and 2014 (Fig. 2).

Clinical indications for IVIG administration

The clinical indications for IVIG administration in our cohort are detailed in Figure 1. Central neuroimmunological disorders (113 of 196, 57.7%) were slightly more common than peripheral neuroimmunological disorders (83/196, 42.3%). Over time, there was a relative rise in the proportion of patients who received IVIG for central, as opposed to peripheral, indications (Fig. 2). The most common central indications were encephalitis (47 of 196, 24%), followed by inflammatory demyelinating CNS disorders (29 of 196, 14.8%), and epilepsy (11 of 196, 5.6%). Among peripheral indications, the most common indications were demyelinating neuropathies (64 of 196, 32.6%), followed by disorders of the neuromuscular junction (12 of 196, 6.1%). The most common individual indication was Guillain–Barré syndrome (55 of 196, 28.1% of the whole cohort).



Indication categories	Indication groups: Specifications
CNS INDICATIONS (*n*=113, 57.7%)	
Encephalitis (n=47)[a]	Infectious and infection-associated encephalitis (*n*=11): Enterovirus (*n*=7), Mycoplasma (*n*=1), HSV (*n*=1), Acute necrotizing encephalopathy (*n*=1), Influenza (*n*=1) Anti-NMDAR encephalitis (*n*=8) Acute disseminated encephalomyelitis (*n*=7) Rasmussen's encephalitis (*n*=5) Other autoimmune or immune-mediated encephalitis (*n*=16): Basal ganglia (*n*=4), anti-VGKC (*n*=1), Suspected autoimmune encephalitis (*n*=11)
Inflammatory demyelinating CNS diseases (n=29)	Monophasic inflammatory demyelinating CNS diseases (*n*=22): Transverse myelitis (*n*=21), Optic neuritis (*n*=1) Relapsing inflammatory demyelinating CNS diseases (*n*=7): Multiple sclerosis (*n*=4), Neuromyelitis optica with anti-AQP4 or anti-MOG antibodies (*n*=3)[b]
Epilepsies (n=11)	Epilepsies (*n*=11): FIRES (*n*=3), Lennox-Gastaut (*n*=2), Landau-Kleffner (*n*=1), Other (*n*=5)
Autoimmune CNS syndromes (n=10)	Opsoclonus-myoclonus ataxia syndrome (*n*=9) ROHHAD syndrome (*n*=1)
Postinfectious movement disorders (n=6)	Sydenham chorea (*n*=4) Other (*n*=2): Acute cerebellar ataxia (*n*=1), Complex movement disorder (*n*=1)
Paediatric acute neuropsych. syndromes (n=3)	Paediatric acute neuropsych. syndromes (*n*=3): PANDAS/Tourette syndrome (*n*=2), PANS (*n*=1)
Genetic auto-inflammation (n=2)	Genetic auto-inflammation (*n*=2): Aicardi–Goutières syndrome (*n*=1), Suspected autoinflammatory neurodegenerative brain disorder (*n*=1)
CNS involvement in systemic inflammatory diseases (n=2)	Neuropsych. systemic lupus erythematosus (*n*=2)
Undiagnosed complex autoimmune disorders (n=3)[c]	Undiagnosed complex autoimmune disorders (*n*=3)
PNS INDICATIONS (*n*=83, 42.3%)	
Demyelinating neuropathies (n=64)	Acute demyelinating neuropathies (*n*=55): Guillain-Barré syndrome (*n*=55) Chronic demyelinating neuropathies (*n*=9): Chronic inflammatory demyelinating polyneuropathy (*n*=7), Mononeuritis (*n*=2)
Disorders of the neuromuscular junction (n=12)	Myasthenia gravis (*n*=12)
Inflammatory myopathies (n=7)	Inflammatory myopathies (*n*=7): Dermatomyositis (*n*=6), Orbital myositis (*n*=1)

Figure 1: Cohort selection. From the total 1264 children who received IVIG at the Childrens Hospital at Westmead between January 2000 and June 2014, only the 196 patients who received IVIG for neuroimmunological indications were included in our cohort (study population). The central nervous system (CNS) and peripheral nervous system (PNS) indications for IVIG administration in our cohort are shown. Of these, only the indication groups with at least five patients were used for the major analyses in the text and in Figure 3. [a]Classification of encephalitis adapted from Pillai et al.[37] [b]The diagnosis of neuromyelitis optica was made according to the revised Wingerchuk criteria,[38]and met also the latest criteria for neuromyelitisoptica spectrum disorder.[39] [c]Details on the patients in the group of undiagnosed complex autoimmune disorders are provided in the online supporting information. AQP4, aquaporin-4; CHW, the Childrens Hospital at Westmead, New South Wales, Australia; CNS, central nervous system; FIRES, febrile infection-related epilepsy syndrome; HSV, herpes simplex virus; IVIG, intravenous immunoglobulin; MOG, myelin oligodendrocyte glycoprotein; neuropsych, neuropsychiatric; NMDAR, *N*-methyl-D-aspartate receptor; PANDAS, paediatric autoimmune neuropsychiatric disorder associated with group A streptococci; PANS, paediatric acute-onset neuropsychiatric syndrome; PNS, peripheral nervous system; PRES, posterior reversible encephalopathy syndrome; ROHHAD, rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; SMARD, spinal muscular atrophy with respiratory distress; VGKC, voltage-gated potassium channel.

Severity of disease

In the patients with available information (190 of 196, 96.9%), the mean mRS before receiving IVIG was 3.7 (median 4, range 2–5). The mRS scores before IVIG initiation and on last follow-up according to category of clinical indication are shown in Figure 3. Of the patients in the cohort, 31.2% were admitted to the intensive care unit (60 of 192).

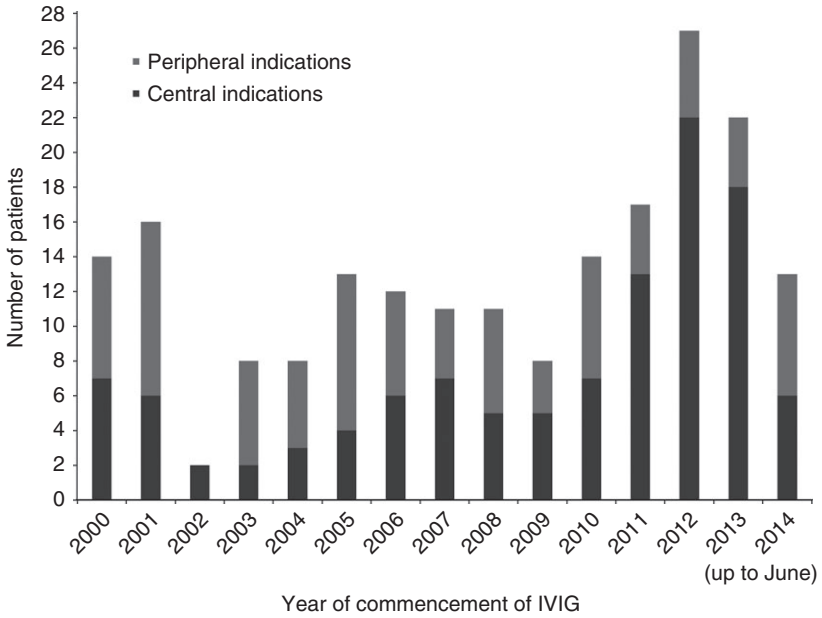


Figure 2: Number of patients started on intravenous immunoglobulin (IVIG), divided by year of IVIG initiation (year 2014 is up to June), and by central and peripheral indications. The number of children commenced on IVIG every year increased over the study period, mostly because of an increase of IVIG administration for central indications, while peripheral indications were relatively stable over time.

Other immune therapies

Data on other immune therapies are detailed in Table SI (online supporting information). The IVIG was the only immune therapy given in 25.5% of patients from the total cohort (50 of 196). The sole use of IVIG varied according to the clinical indication, and was highest in Guillain–Barré syndrome (41 of 55, 74.5%). Immune therapies other than IVIG were given in 74.5% of patients (146 of 196), most commonly corticosteroids (144 of 196, 73.5%; oral prednisone 121 of 196, 61.7%, and intravenous methylprednisolone 84 of 196, 42.8%). Plasma exchange was used in a limited number of cases (4 of 196, 2%). Second-line immune therapies were administered in 26.7% of patients (39 of 146), and included mycophenolate mofetil (16 of 146, 10.9%), rituximab (12 of 146, 8.2%), cyclophosphamide (7 of 146, 4.8%), azathioprine (7 of 146, 4.8%), and others (Table SI).

Immunoglobulin measurement before IVIG administration

Before commencement of IVIG treatment, IgG, IgA, and IgM were measured in 37.2% of patients (73 of 196), and some minor reductions in baseline immunoglobulin values were noted (IgG [2 of 73, 2.7%], IgA [2 of 73, 2.7%], and IgM [4 of 73, 5.5%]).

Number of courses and quantity of IVIG administered

A total of 1669 IVIG courses (mean 8.5 courses per patient, median 1, range 1–150) was administered in the 196 patients during the total cohort treatment time of 144.2 years (mean 1.7y, median 0.5, range 0.02–10.5) (with exclusion of the IVIG courses administered for Guillain–Barré syndrome: total 1603 IVIG courses, mean 11.4, median 2, range 1–150). The corresponding total quantity of IVIG was 57 221g in the whole cohort (mean 291.9g per patient, median 78, range 12–5748). Data on IVIG courses and quantity by clinical diagnosis are detailed in Table I and Figure S1 (online supporting information). In the indication groups with at least five patients, chronic demyelinating neuropathies were the indication with highest median number of IVIG courses per patient, followed by opsoclonus-myoclonus ataxia syndrome, epilepsies, and Rasmussen's encephalitis; the highest median quantity of IVIG per patient was administered in chronic demyelinating polyneuropathies, opsoclonus-myoclonus ataxia syndrome, myasthenia gravis, Rasmussen's encephalitis, epilepsies, and relapsing inflammatory demyelinating diseases (Table I).

Dose of IVIG and days of treatment

High dose IVIG (2g/kg given over 2–5d) was given for 408 courses in 177 patients, typically as the first course. In chronic therapy, lower doses were given per course: 1.2 to 1.8g/kg (116 courses in eight patients), 1g/kg (254 courses in 27 patients), and 0.2 to 0.8g/kg (891 courses in 25 patients).

Type of IVIG and cost

Intragam (CSL Pharma) accounted for over half of the total quantity of IVIG (32 100g/57 221g, 56.1%). Other types of IVIG used were Octagam (Octapharma) (11 610g/57 221g, 20.3%), Flebogamma (Grifols) (7587g/57 221g, 13.2%), Sandoglobulin (CSL Pharma) (5474g/57 221g, 9.6%),

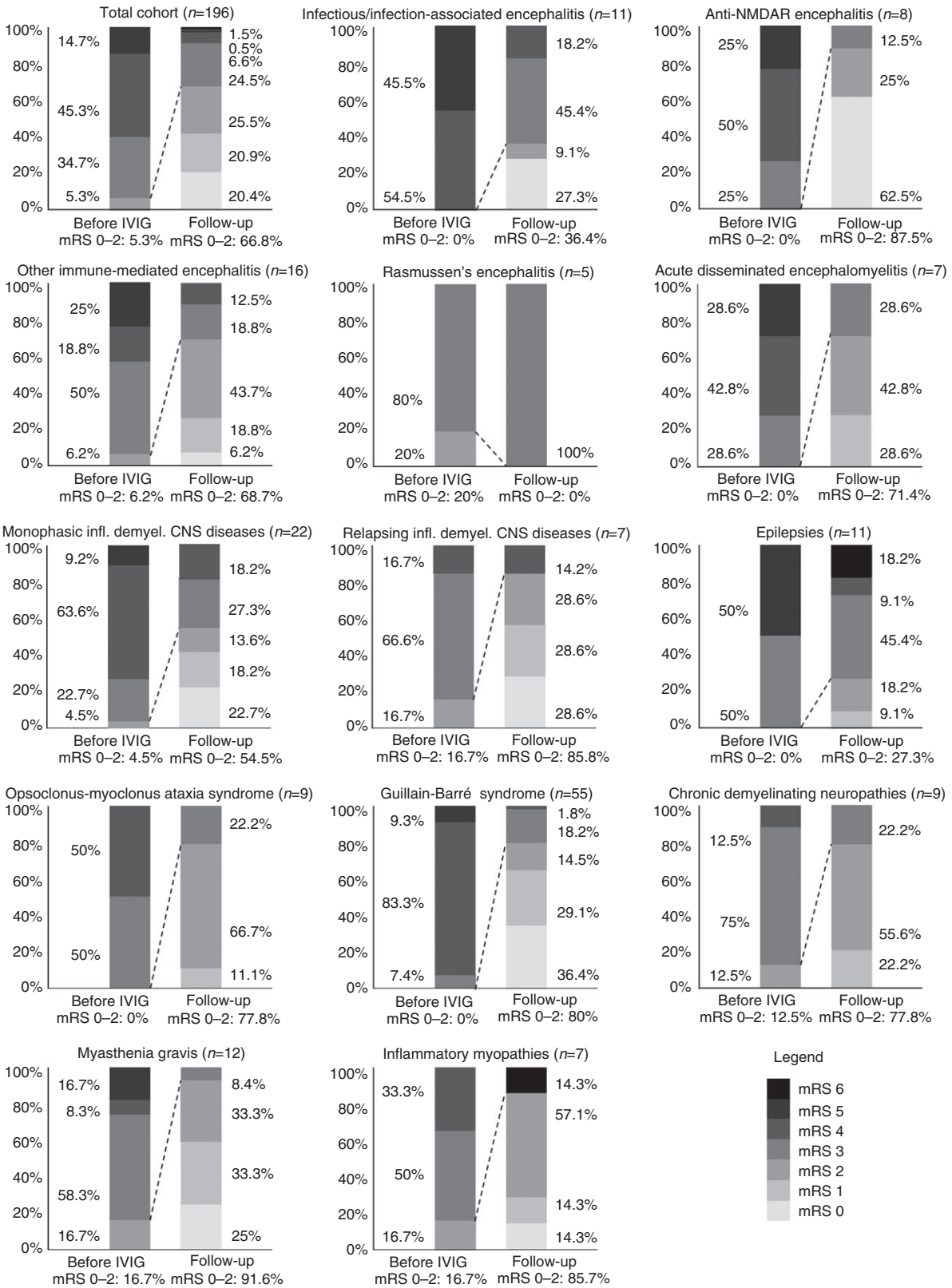


Figure 3: Modified Rankin Scale (mRS) in the acute phase of disease, before IVIG administration, in the total population and according to indication group (only the indications with at least five patients are represented, see Fig. 1). The change in mRS 0 to 2 is presented at IVIG administration, and at final follow-up. CNS, central nervous system; infl. demyel., inflammatory demyelinating; IVIG, intravenous immunoglobulin; neuropsych., neuropsychiatric; NMDAR, *N*-methyl-D-aspartate receptor; PNS, peripheral nervous system.

Table I: Number of IVIG courses and quantity of IVIG (g) administered by clinical indication

Indications for IVIG administration	Number of IVIG courses				Quantity of IVIG (g)				Cost per patient (USD)
	Total	Mean	Median	Range	Total	Mean	Median	Range	Mean (median)
CNS indications (*n*=113)									
Encephalitis (*n*=47)									
Infectious and infection-associated encephalitis (*n*=11)	14	1.3	1	1–3	530	48.2	24	12–246	2186 (1089)
Anti-NMDAR encephalitis (*n*=8)	51	6.4	3.5	1–23	1626.5	203.3	68	30–1020	9223 (3085)
Acute disseminated encephalomyelitis (*n*=7)	9	1.3	1	1–3	454	64.8	30	24–200	2940 (1361)
Rasmussen's encephalitis (*n*=5)	28	5.6	6	2–11	1147	229.4	220	54–420	10 407 (9981)
Other autoimmune or immune-mediated encephalitis (*n*=16)	111	6.9	1	1–56	3316	207.2	60	18–1661	9400 (2722)
Inflammatory demyelinating CNS diseases (*n*=29)									
Monophasic inflammatory demyelinating CNS diseases (*n*=22)	23	1	1	1–2	1367	62.1	36	12–275	2817 (1633)
Relapsing inflammatory demyelinating CNS diseases (*n*=7)	119	17	4	1–79	3022	431.7	180	90–1846	19 584 (8166)
Epilepsies (*n*=11)									
Epilepsies (*n*=11)	416	37.9	11	1–150	6748	613.4	180	48–2298	27 828 (8166)
Autoimmune CNS syndromes (*n*=10)									
Opsoclonus-myoclonus ataxia syndrome (*n*=9)	236	26.2	13	3–147	5237	581.9	260	60–2592	26 399 (11 795)
ROHHAD syndrome (*n*=1)	17	17	17	N/A	1200	1200	1200	N/A	54 440 (54 440)
Postinfectious movement disorders (*n*=6)									
Sydenham chorea (*n*=4)	8	2	1	1–5	482	120.5	90	40–262	5467 (4083)
Other (*n*=2)	4	2	2	1–3	129	64.5	64.5	24–105	2926 (2926)
Paediatric acute neuropsychiatric syndromes (*n*=3)									
Paediatric acute neuropsychiatric syndromes (*n*=3)	20	6.7	5	3–12	1917	639	321	150–1446	28 989 (14 562)
Genetic autoinflammation (*n*=2)									
Genetic autoinflammation (*n*=2)	8	4	4	3–5	260	130	130	60–200	5898 (5898)
CNS involvement in systemic inflammatory diseases (*n*=2)									
Neuropsych. systemic lupus erythematosus (*n*=2)	15	7.5	7.5	3–12	1707	853.5	853.5	267–1440	38 720 (38 720)
Undiagnosed complex autoimmune disorders (*n*=3)									
Undiagnosed complex autoimmune disorders (*n*=3)	21	7	10	1–10	2078	692.7	1010	48–1020	31 425 (45 820)
PNS indications (*n*=83)									
Demyelinating neuropathies (*n*=64)									
Acute demyelinating neuropathy (Guillain–Barré syndrome) (*n*=55)	66	1.2	1	1–4	4081.5	74.2	45	12–407	3366 (2041)
Chronic demyelinating neuropathies (*n*=9)	285	31.7	24	3–90	12504	1389.3	900	50–5748	63 028 (40 830)
Disorders of the neuromuscular junction (*n*=12)									
Myasthenia gravis (*n*=12)	100	8.3	2.5	1–29	4886	407.2	227.5	24–1299	18 473 (10 321)
Inflammatory myopathies (*n*=7)									
Inflammatory myopathies (*n*=7)	117	16.7	3	1–88	4529	647	141	75–3500	29 352 (6397)

CNS, central nervous system; IVIG, intravenous immunoglobulin; N/A, not applicable; NMDAR, *N*-methyl-D-aspartate receptor; PNS, peripheral nervous system; ROHHAD, rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; USD, US dollars.

Intraglobin F (Paviour Pharma) (325g/57 221g, 0.6%), and Kiovig (Baxter) (125g/57 221g, 0.2%). Based on a mean of the IVIG prices as at July 2015 in AUD (mean 620 AUD/10g=453.7 USD/10g), the total cost for IVIG in the whole cohort in the study period 2000 to 2014 was 2 595 907 USD (mean 13 244 USD per patient, median 3538, range 544–260 766). The IVIG cost per patient according to clinical indication group, reflecting the IVIG quantity administered per patient, is detailed in Table I. In the indication groups with at least five patients, the highest median costs per patient were in chronic demyelinating neuropathies, opsoclonus-myoclonus ataxia syndrome, myasthenia gravis, Rasmussen's encephalitis, epilepsies, and relapsing inflammatory demyelinating diseases. The lowest median costs per patient were in infectious and infection-associated encephalitis, acute disseminated encephalomyelitis, monophasic inflammatory demyelinating CNS diseases, Guillain–Barré syndrome, other autoimmune or immune-mediated encephalitis, and anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis.

IVIG tolerability

Adverse reactions or infusion reactions to IVIG of any severity were reported in 25.5% of the total cohort (50 of 196). Severe or medically significant (but not life-threatening) adverse events (grade 3), according to the National Institutes of Health Common Terminology Criteria for Adverse Events,[12] occurred in 2% of the total patients (4 of

196), whereas no life-threatening consequences (grade 4) or deaths related to adverse events (grade 5) occurred. Grade 3 adverse events included aseptic meningitis (defined as the presence of at least three of the following: fever, headache, altered mental status, stiff neck, photophobia) in 1.5% of cases (3 of 196), and by aseptic meningitis and hypotension requiring intervention in 0.5% of cases (1 of 196).

In the remaining 23.5% of patients (46 of 196), adverse events were mild or moderate (grade 1–2).[12] The most commonly reported adverse reactions were headache (12 of 196, 6.1%), vomiting, or nausea (11 of 196, 5.6%), local skin reactions or problems at the site of cannula insertion (9 of 196, 4.6%), fever (9 of 196, 4.6%), and hypotension not requiring intervention (3 of 196, 1.5%). Rarer adverse reactions were bradycardia (3 of 196, 1.5%), rash (3 of 196, 1.5%), hypertension, tachycardia, shortness of breath, flushing (each 2 of 196, 1%), pallor, abdominal pain, drowsiness, derangement of liver function tests, evidence of hepatitis B immunity (passive transfer of immunoglobulin, not infection), haemolytic reaction with fever and lethargy, increased respiratory rate, and intermittent apnoea, and sweatiness during infusion (each 1 of 196, 0.5%). Of the patients who received multiple IVIG courses, side effects most commonly occurred during the first course only (14 of 24, 58.3%).

Outcome

Data on outcome at last follow-up are detailed in Table II (and its extended legend provided in Appendix S1, online supplementary information), Table SII (online supplementary information), and Figure 3. The mean length of follow-up in the total cohort was 52 months (median 36, range 0.25–186). Of the patients, 173 of 196 (88.3%) had follow-up of more than 12 months. In the indication groups with at least five cases, patients with epilepsy and inflammatory myopathies had the longest follow-up periods, whereas patients with anti-NMDAR encephalitis and myasthenia gravis had the shortest follow-up (Table II). At last available follow-up, mean mRS in the total cohort was 1.8 (median 2, range 0–6). Of the patients, 20.4% (40 of 196) had mRS 0 (no symptoms at all), 20.9% (41 of 196) had mRS 1 (no significant disability despite symptoms), 25% (49 of 196) had mRS 2 (slight disability), 25% (49 of 196) had mRS 3 (moderate disability), 6.6% (13 of 196) had mRS 4 (moderately severe disability), 0.5% (1 of 196) had mRS 5 (severe disability), and 1.5% (3 of 196) of patients had died (mRS 6: one with febrile infection-related epilepsy syndrome, one with Lennox-Gastaut syndrome, one with dermatomyositis) (Table SII). At last follow-up, 20.4% (40 of 196) of patients reported ongoing cognitive or learning problems, 9.2% (18 of 196) behavioural problems, 46.9% (92 of 196) motor problems, 3.6% (7 of 196) visual impairment, 12.7% (25 of 196) epilepsy, and 37.2% (73 of 196) other problems.

In the indication groups with at least five cases, patients with anti-NMDAR encephalitis, Guillain–Barré syndrome, and myasthenia gravis had the lowest mean and median mRS at last follow-up, the highest proportion of good outcome (mRS 0–2), and the greatest change to mRS 0 to 2 from the acute phase to the last follow-up (see Fig. 3, Table II, and Appendix S1). By contrast, patients with Rasmussen's encephalitis and epilepsy had the highest mean and median mRS at follow-up, the lowest proportions of good outcome (mRS 0–2), and the smallest change to mRS 0 to 2 between the acute phase and the follow-up (Fig. 3).

Clinical indications for IVIG administration in our cohort: comparison with existing guidelines on the use of IVIG

Table III presents the role of IVIG according to different guidelines, in each of the clinical indications for which IVIG were administered in our cohort. With reference to the guidelines including both CNS and PNS indications,[4–7,9] the proportion of patients in our cohort who received IVIG for indications not strongly recommended or not listed in the guidelines ranged between 45.4% and 57.1%. Table SIII (online supporting information) gives details with regard to the Australian criteria for the clinical use of IVIG.[9]

DISCUSSION

To review the clinical practice regarding the use of IVIG in paediatric neurology, we carried out a retrospective study at the Children's Hospital at Westmead, Sydney, for the period 2000 to 2014. Kawasaki disease was the clinical indication for which IVIG was most commonly administered, outnumbering all neurological indications, which represented about one-sixth of all patients given IVIG in our institution.

Neurological indications for IVIG treatment were similarly distributed between CNS and PNS indications in our cohort, but the increase in use of IVIG for neurological disorders over the study period is mostly a result of the rise in CNS indications. This is at least partly because the description of some of these disorders, including anti-NMDAR encephalitis, is relatively recent. The understanding of the immunological basis for anti-NMDAR encephalitis and other cell surface autoimmune encephalitis has likely resulted in an increased willingness to use immune therapy in patients with encephalitis.

These observations may also partly explain why about half of the patients in our cohort (45.4–57.1%) received IVIG for indications not strongly recommended or not listed in the most recent available international guidelines for the use of IVIG. Besides, some of these disorders are very rare, such as rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation syndrome, and the evidence on the efficacy of immune therapy is limited. Others, such as transverse myelitis, are more common, but quality evidence on the efficacy of IVIG is lacking; a randomized controlled trial is currently under way.[13] Given that transverse myelitis can have a poor prognosis, with less than 50% making a full recovery,[14] it is understandable that clinicians are more likely to

Table II: Length of follow-up and neurological outcome by clinical indication

Indications for IVIG administration	Mean length of follow-up in months (median, range)	Mean mRS at follow-up (median, range)	Proportion of patients with complete recovery and good outcome	
			mRS 0, complete recovery (%)	mRS 0–2, good outcome (%)
CNS indications (*n*=113)				
Encephalitis (*n*=47)				
Infectious and infection-associated encephalitis (*n*=11)	48.3 (32, 13–160)	2.3 (3, 0–4)	3/11 (27.3)	4/11 (36.4)
Anti-NMDAR encephalitis (*n*=8)	36 (23.5, 10–98)	0.9 (0, 0–3)	5/8 (62.5)	7/8 (87.5)
Acute disseminated encephalomyelitis (*n*=7)	54 (51, 27–99)	2 (2, 1–3)	0/7 (0)	5/7 (71.4)
Rasmussen's encephalitis (*n*=5)	80.4 (83, 8–164)	3 (3, 3)	0/5 (0)	0/5 (0)
Other autoimmune or immune-mediated encephalitis (*n*=16)	39.1 (33, 14–117)	2.1 (2, 0–4)	1/16 (6.2)	11/16 (68.7)
Inflammatory demyelinating CNS diseases (*n*=29)				
Monophasic inflammatory demyelinating CNS diseases (*n*=22)	45.9 (30.5, 0.5–169)	2 (2, 0–4)	5/22 (22.7)	12/22 (54.5)
Relapsing inflammatory demyelinating CNS diseases (*n*=7)	59.4 (36, 7–139)	1.4 (1, 0–4)	2/7 (28.6)	6/7 (85.7)
Epilepsies (*n*=11)				
Epilepsies (*n*=11)	89.4 (94, 25–151)	3.3 (3, 1–6)	0/11 (0)	3/11 (27.3)
Autoimmune CNS syndromes (*n*=10)				
Opsoclonus-myoclonus ataxia syndrome (*n*=9)	64.9 (40, 10–181)	2.1 (2, 1–3)	0/9 (0)	7/9 (77.8)
ROHHAD syndrome (*n*=1)	18	4	0/1 (0)	0/1 (0)
Postinfectious movement disorders (*n*=6)				
Sydenham chorea (*n*=4)	10.1 (11.5, 0.25–17)	1.5 (1.5, 1–2)	0/4 (0)	4/4 (100)
Other (*n*=2)	43 (43, 38–48)	2 (2, 1–3)	0/2 (0)	1/2 (50)
Paediatric acute neuropsychiatric syndromes (*n*=3)				
Paediatric acute neuropsychiatric syndromes (*n*=3)	33.7 (29, 13–59)	2.3 (3, 1–3)	0/3 (0)	1/3 (33.3)
Genetic autoinflammation (*n*=2)				
Genetic autoinflammation (*n*=2)	12.5 (12.5, 6–19)	4.5 (4.5 (4–5)	0/2 (0)	0/2 (0)
CNS involvement in systemic inflammatory diseases (*n*=2)				
Neuropsych. systemic lupus erythematosus (*n*=2)	44.5 (44.5, 29–60)	2.5 (2.5 (2–3)	0/2 (0)	1/2 (50)
Undiagnosed complex autoimmune disorders (*n*=3)				
Undiagnosed complex autoimmune disorders (*n*=3)	20 (18, 17–25)	2.3 (3, 1–3)	0/3 (0)	1/3 (33.3)
PNS indications (*n*=83)				
Demyelinating neuropathies (*n*=64)				
Acute demyelinating neuropathy (Guillain–Barré syndrome) (*n*=55)	55.7 (44, 0.25–186)	1.2 (1, 0–4)	20/55 (36.4)	44/55 (80)
Chronic demyelinating neuropathies (*n*=9)	49 (32, 15–110)	2 (2, 1–3)	0/9 (0)	7/9 (77.8)
Disorders of the neuromuscular junction (*n*=12)				
Myasthenia gravis (*n*=12)	37.7 (30, 4.5–123)	1.25 (1, 0–3)	3/12 (25)	11/12 (91.7)
Inflammatory myopathies (*n*=7)				
Inflammatory myopathies (*n*=7)	84.3 (85, 1.5–175)	2.1 (2, 0–6)	1/7 (14.3)	6/7 (85.7)

In the indication groups with at least five cases, the greatest change to mRS 0–2 from the acute phase to the last follow-up occurred in patients with anti-NMDAR encephalitis, Guillain–Barré syndrome, and myasthenia gravis (see also Fig. 3). By contrast, Rasmussen's encephalitis and epilepsy had the lowest proportions of patients with good outcome (mRS 0–2) and the smallest change to mRS 0–2 between the acute phase and the follow-up. See Appendix S1 for an extended version of Table II legend. CNS, central nervous system; IVIG, intravenous immunoglobulin; mRS, modified Rankin Scale; NMDAR, *N*-methyl-D-aspartate receptor; PNS, peripheral nervous system; ROHHAD, rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation.

treat these patients more aggressively with multiple immune therapies including IVIG. Furthermore, some of the indication categories in our cohort are poorly defined entities (such as 'suspected autoimmune encephalitis' and 'undiagnosed complex autoimmune disorders'), and these are therefore not dealt with in the available guidelines, as expected. It is likely that future revisions of the existing recommendations will include some of these currently unlisted diagnostic entities, or accommodate for the uncertainty in some of the disorders in which an autoimmune mechanism is suspected but unproven.

In general, the available evidence for the benefit of IVIG in neurological conditions is limited, and Cochrane reviews are available only for Guillain–Barré syndrome,[15] chronic inflammatory demyelinating polyneuropathy,[16] myasthenia gravis,[17] dermatomyositis,[18] and multiple sclerosis.[19] A Cochrane review on the use of IVIG in childhood encephalitis, the second most common indication category for IVIG administration in our cohort, is under way.[20] Given the increasing description of autoantibody-associated encephalitis syndromes and the emerging evidence of improved outcomes with early immune therapy, it seems fair to consider IVIG treatment for these.[21]

In our cohort, the proportion of patients who received IVIG for indications not strongly recommended or not listed in the current available guidelines was higher than in previous studies.[22–24] In an audit on the use of IVIG in clinical practice in adults, conducted in Sydney about 12 years ago,[23] 25.5% of patients received IVIG for indications not strongly recommended in the existing criteria at the time.[25] Similarly, 30% of patients in a more recent French study in adults also received IVIG 'off-label'.[24,26]

Table III: Indications for IVIG administration in our cohort: role for IVIG according to different guidelines

Role for IVIG in different guidelines including CNS and PNS indications	2012, NBA	2011, Wimperis	2008, Elovaara[a]	2007, Feasby[b]	2006, Orange[c]
Committee issuing the guidelines (Country) (see legend for details on the recommendations in each guideline)	National Blood Authority Australia (NBA) (Australia)	Department of Health (UK)	EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases (Europe)	IVIG Hematology and Neurology Expert Panels (Canada)	Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma And Immunology (USA)
Recommendations for the use of IVIG (subdivided into stronger and weaker by the authors)					
Stronger recommendation categories	Established Emerging	Highest priority Appropriate	Established effective (LoE A) Probably effective (LoE B)	Recommended (based on LoE 1a to 6)	Definitely beneficial Probably beneficial Might provide benefit (A, B)
Weaker recommendation categories/Not recommended	Exceptional circumstances only Not supported	Limited/little/no evidence Not recommended	Possibly effective (LoE C) Good practice point (class IV evidence)	Not recommended (based on LoE 1a to 6)	Might provide benefit (C, D)
Indications for IVIG administration in our cohort: role for IVIG according to different guidelines					
Central indications (*n*=113)					
Encephalitis (*n*=47)					
Infectious/infection-associated encephalitis (*n*=11): Enterovirus (*n*=7), Mycoplasma (*n*=1), HSV (*n*=1), Influenza (*n*=1), Acute necrotizing encephalopathy (*n*=1)	–	–	–	–	–
Anti-NMDAR encephalitis (*n*=8)	–	Limited evidence	–	–	–
Acute disseminated encephalomyelitis (*n*=7)	Emerging	Limited evidence	Good practice point (class IV)	Recommended (LoE 4)	Might provide benefit (III C)
Rasmussen's encephalitis (*n*=5)	Exceptional	Appropriate	Good practice point (class IV)	Recommended	Might provide benefit (IIb B)
Basal ganglia (*n*=4)	–	–	–	–	–
Anti-VGKC encephalitis (*n*=1)	Exceptional	Limited evidence	–	–	–
Other suspected autoimmune encephalitis (*n*=11)	–	Limited evidence	–	–	–
Inflammatory demyelinating diseases (*n*=29)					
Transverse myelitis (*n*=21)	–	–	–	–	–
Optic neuritis (*n*=1)	Not supported	–	–	–	–
Multiple sclerosis (*n*=4)	Emerging	Not recommended	Probably effective (LoE B)	Recommended (LoE 1a)	–
Neuromyelitis optica (*n*=3)	Exceptional	–	Good practice point (class IV)	–	–
Epilepsies (*n*=11)					
FIRES (*n*=3), Lennox-Gastaut (*n*=2), Landau-Kleffner (*n*=1), Other (*n*=5)	Exceptional	Limited evidence	Good practice point (class IV)	Not recommended (LoE 1b)	Might provide benefit (Ia A)
Autoimmune CNS syndromes (*n*=10)					
Opsoclonus-myoclonus ataxia syndrome (*n*=9)	Emerging	Limited evidence	–	Recommended (LoE 4)	Might provide benefit (III C)
ROHHAD syndrome (*n*=1)	–	–	–	–	–
Postinfectious movement disorders (*n*=6)					
Sydenham chorea (*n*=4)	–	–	–	–	–
Other (*n*=2)	–	–	–	–	–
Paediatric acute neuropsychiatric syndromes (*n*=3)					
PANDAS/Tourette syndrome (*n*=2)	Exceptional	Little/No evidence	–	Recommended (LoE 1b)	Might provide benefit (IIb B)

Table III: Continued

Role for IVIG in different guidelines including CNS and PNS indications	2012, NBA	2011, Wimperis	2008, Elovaara[a]	2007, Feasby[b]	2006, Orange[c]
PANS (*n*=1)	Not supported	–	–	–	–
Genetic autoinflammation (*n*=2)					
Aicardi–Goutiéres syndrome (*n*=1), Suspected autoinflammatory neurodegen. brain disorder (*n*=1)	–	–	–	–	–
CNS involvement in systemic inflammatory diseases (*n*=2)					
Neuropsychiatric systemic lupus erythematosus (*n*=2)	Not supported	Little/no evidence	–	–	Might provide benefit (III D)
Undiagnosed complex autoimmune disorders (*n*=3)					
Undiagnosed complex autoimmune disorders (*n*=3)	–	–	–	–	–
Peripheral indications (*n*=83)					
Demyelyinating neuropathies (*n*=64)					
Acute demyelinating neuropathy (Guillain–Barré syndrome) (*n*=55)	Established	Highest priority	Established effective (LoE A)	Recommended (LoE 1a)	Definitely beneficial (Ia A)
Chronic inflammatory demyelinating polyneuropathy (*n*=7)	Established	Highest priority	Established effective (LoE A)	Recommended (LoE 1a)	Definitely beneficial (Ia A)
Mononeuritis (*n*=2)	–	–	–	–	–
Disorders of the neuromuscular junction (*n*=12)					
Myasthenia gravis (*n*=12)	Established	Appropriate	Established effective (LoE A)	Recommended (LoE 1b)	Probably beneficial (Ib-IIa B)
Inflammatory myopathies (*n*=7)					
Dermatomyositis (*n*=6)	Established	Appropriate	Probably effective (LoE B)	Recommended (LoE 1b)	Probably beneficial (IIa B)
Orbital myositis (*n*=1)	–	–	–	–	–
Total quantity of IVIG (g) given for weaker indications, or not recommended/not listed	41.4% (23 682.5g/ 57 221g)	53% (30 349g/ 57 221g)	48.8% (27 928.5g/57 221g)	36.4% (20 858.5g/57 221g)	38.4% (22 004.5g/57 221g)
Total patients who received IVIG for weaker indications, or not recommended/not listed	49% (96/196)	56.6% (111/196)	57.1% (112/196)	45.4% (89/196)	50% (98/196)

See Appendix S1 for an extended version of Table III legend. [a–c] EFNS, European Federation of Neurological Societies; FIRES, febrile infection-related epilepsy syndrome; HSV, herpes simplex virus; IVIG, intravenous immunoglobulin; LoE, level of evidence; NMDAR, *N*-methyl-D-aspartate receptor; PANDAS, paediatric autoimmune neuropsychiatric disorder associated with group A streptococci; PANS, paediatric acute-onset neuropsychiatric syndrome; PNS, peripheral nervous system; ROHHAD, rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; VGKC, voltage-gated potassium channel.

In these studies,[23,24] the most common neurological indications for IVIG included chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, multifocal motor neuropathy, and dermatomyositis, reflecting the different age in the study population (adult only) compared with ours.

The dose of IVIG used in our cohort was variable, but generally 2g/kg was used in acute diseases that required only one course (i.e. Guillain–Barré syndrome), whereas smaller doses and a high number of courses were used in chronic diseases, such as chronic inflammatory demyelinating polyneuropathy. Adverse reactions to IVIG occurred in 25.5% of patients in our cohort, but serious events were rare. It is possible that the actual rate of non-serious adverse reactions is higher because of under-reporting given the retrospective design of this study, especially in the case of patients who were discharged soon after receiving IVIG. Most of the patients were very impaired before receiving IVIG (mRS 3–5 in 94.7%), and most were given other immune therapies, with the exception of patients with Guillain–Barré syndrome in whom most received IVIG monotherapy. The length of follow-up was relatively long in our population, and generally there was a good recovery, with mRS 0 to 2 in 66.8% of cases, although three patients did die. The improvement at last follow-up was most marked in the patients with anti-NMDAR encephalitis, Guillain–Barré syndrome, and myasthenia gravis. It is significant that some of these entities, such as anti-NMDAR encephalitis, are not specifically mentioned in most of the existing guidelines for the use of IVIG, even though their description predates the publication date of the guideline.

The least marked improvement at follow-up was observed in patients with Rasmussen's encephalitis and epilepsy (Fig. 3), questioning the role of IVIG in these conditions. It is the personal experience of the authors that some patients with Rasmussen's encephalitis and epilepsy do benefit from IVIG and other immune therapies, whereas other patients get no apparent benefit. Even though some evidence for a role of IVIG in epilepsy is available,[27] according to two Cochrane reviews no reliable conclusions can be drawn regarding the efficacy of IVIG in epilepsy.[28,29] Recently, the efficacy of immune therapy over antiepileptic drugs has been reported in specific types of seizures with autoimmune aetiology, such as faciobrachial dystonic seizures,[30] and in patients with positive neuronal surface antibodies with exclusive or prevalent seizure presentations.[31] Therefore, IVIG likely does have a role in some types of immune-mediated epilepsy, although our data suggest the benefits are equivocal outside of proven autoimmune encephalitis with seizures. Even though IVIG does seem to have a role in adult-onset Rasmussen's encephalitis,[32,33] the results of our study support other data in the literature suggesting limited efficacy of IVIG in paediatric Rasmussen's encephalitis.[34,35] It is noteworthy that the subgroups receiving less benefit (Rasmussen's encephalitis, epilepsies) received a large amount of IVIG at a high financial cost. Therefore when using IVIG for less accepted indications, clinicians should try to define clear outcome targets, and be willing to stop IVIG if those targets are not met; this is not easy to achieve in patients with refractory syndromes when families describe modest benefits.

A very limited number of patients in our cohort were treated with plasma exchange. The use of plasma exchange in children may present unique challenges and higher complication rates compared with adults, especially in patients who are poorly cooperative or have autonomic instability.[36] In addition, the use of plasma exchange is at least partly subject to the experience and expertise of individual centres, and our centre has generally used IVIG rather than plasma exchange. We have only recently started using plasma exchange in neurological patients.

The long study period, large cohort, long follow-up, and comparison with different guidelines are among the strengths of this study. Its limitations are primarily a result of its retrospective nature, including the retrospective assignment of mRS disability score and the detection of side effects to IVIG. In addition, the natural history of different clinical conditions and the use of other immune therapies as well as IVIG will have influenced the clinical outcomes at last follow-up, and make the efficacy of IVIG difficult to define with confidence in our study. We decided to exclude the 23 patients initially treated with IVIG for suspected neuroimmunological conditions who were subsequently found to have other disease mechanisms (Fig. 1), because the natural disease history in these patients may be different.

In summary, IVIG represents an expensive resource, and demand has increased worldwide in recent years. Updated guidelines for the clinical use of IVIG are essential to rationalize the use of IVIG in an evidence-based fashion, ensuring availability for the conditions for which IVIG use is clearly beneficial, and limiting unnecessary expenses. Our study captures the recent clinical practice as regards the use of IVIG in a large paediatric neurology centre, further highlighting an imbalance between generally accepted clinical practice (e.g. use of IVIG for transverse myelitis and anti-NMDAR encephalitis), and clinical guidelines that are usually generated based on randomized controlled trial evidence. Furthermore, future studies to prove efficacy of IVIG, such as IVIG versus placebo, are likely to be considered unethical for most of these conditions, whereas 'head-to-head' studies comparing IVIG with other first-line agents may require large numbers to generate statistical significance.

APPENDIX: MEMBERS OF THE IVIG IN NEUROLOGY STUDY GROUP

In addition to the authors listed at the top of this article, the IVIG in Neurology Study Group consists of:

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ACKNOWLEDGEMENTS

The authors thank Prof Peter Procopis, Dr Deepak Gill, Dr Jayne Antony, Dr Christopher Troedson, Dr Manoj Menezes, Dr Sachin Gupta, Prof Robert Ouvrier, and Dr Simone Ardern-Holmes for the care offered to the patients included in the study, and for giving their consent to contact the patients. Dr Shekeeb S. Mohammad has received a postgraduate scholarship from the National Health and Medical Research Council (Australia). Dr Sudarshini Ramanathan has received a postgraduate scholarship from the National Health and Medical Research Council (Australia) and the Petre Foundation (Australia). Dr Russell C. Dale has received research funding from the National Health and Medical Research Council, MS Research Australia, Star Scientific Foundation, Pfizer Neuroscience, Tourette Syndrome Association, University of Sydney, and the Petre Foundation. Russell Dale has received honoraria from Biogen-Idec and Bristol-Myers Squibb as an invited speaker. The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Number of IVIG courses per patient (mean, median range) by clinical indication group (only the indications with at least five patients are represented, see Fig. 1).

Table SI: First-line and second-line immune therapies administered beside IVIG according to indication group.

Table SII: Detailed data on outcome at last follow-up by clinical indications.

Table SIII: Role for IVIG in the clinical indications of our cohort according to the National Blood Authority Australia, Criteria for the clinical use of intravenous immunoglobulin in Australia, 2nd edition, July 2012.

Appendix S1: Patients with undiagnosed complex autoimmune disorders; extended legends to Tables II and III.

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