# ACTA NEUROLÓGICA COLOMBIANA

**Vol 23 No. 1 • SUPLEMENTO (1:1) • 2007 ISSN 0120-8748**

PUBLICACIÓN OFICIAL DE LA ASOCIACIÓN COLOMBIANA DE NEUROLOGÍA

Permiso Tarifa Postal Reducida Nº 738 de Adpostal





**PORTADA: JAVIER ARANGUREN MORENO,** MAESTRO EN ARTES PLÁSTICAS, UNIVERSIDAD NACIONAL DE COLOMBIA.
**TÍTULO:** VERGEL ESMERALDA **TÉCNICA:** ACUARELA
**DISEÑO Y DIAGRAMACIÓN:** JANETH ALBARRACÍN G.
**COORDINACIÓN COMERCIAL:** SANDRA LILIANA CORREA
**IMPRESIÓN:** GRAFICOOP


## CONTENIDO

# ACTA NEUROLÓGICA COLOMBIANA

**Vol 23 No. 1 • SUPLEMENTO (1:1) • 2007 ISSN 0120-8748**

PUBLICACIÓN OFICIAL DE LA ASOCIACIÓN COLOMBIANA DE NEUROLOGÍA

Permiso Tarifa Postal Reducida Nº 738 de Adpostal





**Asociación Colombiana de Neurología**

Carrera. 11B No. 99-54 Oficina: 401
Teléfonos.: 611 2051 - 611 2474 - 236 3751
publicaciones@acnweb.org
informacion@acnweb.org
www.acnweb.org
Bogotá, D.C., Colombia


## CONTENS

## PRESENTACIÓN

Hasta hace algunos años el tratamiento de las enfermedades autoinmunes en neurología se limitaba al uso de inmunosupresores con sus efectos benéficos casi siempre tardíos para la urgencia del cuadro y con efectos secundarios que podían aumentar la morbilidad en el paciente.

El advenimiento de la inmunomodulación con la plasmaféresis y el uso de inmunoglobulina IV complementaron este arsenal terapéutico, con resultados más rápidos y mayor seguridad.

El uso de inmunoglobulina IV en el tratamiento del síndrome de Guillain Barré ha permitido controlar el cuadro agudo, disminuir la estancia hospitalaria en las unidades de cuidado crítico y mejorar el pronóstico funcional de estos pacientes. Sin embargo, este espectro terapéutico es potencialmente más amplio hacia otras enfermedades del sistema nervioso central, periférico e incluso en miopatías, cuya patogénesis involucra disfunción del sistema inmunológico.

El escaso número de pacientes que en muchas ocasiones acompaña el marco de estos estudios limita el poder estadístico de sus resultados y constituye un desafío para el análisis del tratamiento en enfermedades poco frecuentes como la neuropatía motora multifocal, la miastenia gravis, etc.

En Colombia y de acuerdo con el INVIMA la única indicación hoy aprobada para el uso de las inmunoglobulinas IV en neurología es el tratamiento del síndrome de Guillain Barré. La situación anterior limita el uso de este medicamento en otras enfermedades neurológicas mediadas inmunológicamente y da pie al sistema de auditoría médica a glosas indeclinables a pesar del beneficio que esta intervención puede producir en el paciente. Curiosamente con esta actuación el término glosa que significa nota o reparo que se pone en las cuentas a una o varias partidas de ellas, toma la acepción, también aceptada en castellano, de glosar como tomar o interpretar en mal sentido y con intención siniestra una palabra, una proposición o un acto.

Motivados por las quejas que algunos miembros de la Asociación Colombiana de Neurología hicieran de esta irregularidad, nos propusimos realizar una revisión sistematizada del uso de la inmunoglobulina IV en neurología y para ello comisionamos al Dr. Luis Morillo realizar un análisis del tema con técnicas de medicina basada en la evidencia. Este documento fue socializado en cada uno de los capítulos regionales de la ACN y posteriormente enviado a un Jurado constituido por los Doctores Pablo Lorenzana, Ángela María Gutiérrez y Federico Silva, quienes revisaron el documento inicial y las propuestas de modificación que en cada una de las regiones se hizo al respecto.

Una vez concluido el proceso anterior y basado en la buena evidencia que la literatura científica hoy nos aporta, el concepto de los neurólogos colombianos que fungieron como expertos en el tema y el debido consenso que aportó la socialización del mismo, elevamos ante el INVIMA una solicitud formal de ampliar el espectro terapéutico de las inmunoglobulinas IV en neurología.

Esperamos que con este esfuerzo de la ACN se beneficien los pacientes colombianos que padecen las enfermedades mencionadas y se disminuyan las trabas administrativas que hoy tienen los usos de medicamentos.

Finalmente la publicación de este consenso constituye una manifestación más de la alianza entre una institución del tercer sector como la ACN y el sector privado que en este caso fue Laboratorios Biotoscana a quienes damos también el debido reconocimiento.

**JAVIER TORRES ZAFRA, MD.**
**Presidente ACN.**

# Consenso Colombiano sobre la utilidad de la inmunoglobulina intravenosa (IgIV) en enfermedades del sistema nervioso central y periférico

## *Colombian consensus for the use of the intravenous immunoglobulin (IgIV) in central and peripheral nervous system diseases*

**Morillo LE, Díaz R, Gutiérrez AM, Lorenzana P, Pérez GE, Rodríguez JH, Silva F, Torres Zafra JF, Uribe CS, Vargas MJ. Por el Comité ad-hoc de la ACN para el análisis de la utilidad de la IgIV en las enfermedades neurológicas**

**RESUMEN**

**Introducción:** la inmunoglobulina G administrada vía intravenosa (IgIV) se ha introducido como alternativa en el tratamiento agudo de varias entidades del sistema nervioso central y periférico. La IgIV está disponible en nuestro medio y se requiere racionalizar su uso a aquellas entidades en las que se haya demostrado su eficacia.

**Objetivos:** desarrollar recomendaciones del uso de la IgIV basadas en evidencia proveniente de estudios clínicos controlados.

**Material y métodos:** se hizo una búsqueda sistemática sobre el uso de IgIV en neurología, se seleccionaron y analizaron los ensayos clínicos controlados en al menos cuatro colecciones (Medline, Ovid, Science Direct, Hinari) las revisiones de la librería Cochrane y se socializaron los hallazgos. Un total de 189 títulos resultaron de las búsqueda, un jurado revisó y sintetizó este trabajo.

**Resultados:** se analizaron en forma sistemática al menos 60 ensayos clínicos controlados en las cuales se utilizó la IgIV en afecciones del sistema nervioso central o periférico. Finalmente, 45 ensayos clínicos controlados y cinco revisiones Cochrane son la base para emitir las recomendaciones en un total de 11 entidades en las se ha probado como terapia la inmunoglobulina G intravenosa.

**Conclusiones:** existe beneficio de la IgIV comparada con el placebo y respaldado por evidencia obtenida de al menos dos estudios clínicos controlados con resultados similares para: Esclerosis múltiple con recurrencias y remisiones., Síndrome de Guillain Barre en niños, y Polineuropatía Inflamatoria Crónica desmielinizante. Bajo esta misma metodología, existe beneficio de la IgIV que es al menos tan eficaz como la plasmaférisis en el Síndrome de Guillain Barre en adultos. Adicionalmente, se discute el beneficio demostrado de la IgIV respaldado por evidencia obtenida de un solo estudio clínico controlado, el beneficio aparente de la IgIV por evidencia obtenida de estudios clínicos controlados con limitaciones metodológicas y la evidencia obtenida en uno o más estudios clínicos controlados en los que no hay un beneficio demostrado de la IgIV.

**Recibido: 13/10/06. Revisado: 19/10/06. Aceptado: 30/10/06.**

*Luis E. Morillo MD, MSc. Profesor Titular. Jefe Unidad de Neurología. Departamento de Neurociencias. Facultad de Medicina. Pontificia Universidad Javeriana. Ricardo Díaz Cabezas. Neurólogo Clínico. Profesor Asociado. Universidad de Caldas. Manizales, Caldas. Angela María Gutiérrez Alvarez MD. MSc. Profesora investigadora. Miembro grupos neURos e Investigación Clinica. Facultad de Medicina. Universidad del Rosario. Pablo Lorenzana Pombo. Profesor Asociado de Neurología. Coordinador División de apoyo especializado en Neurología. Facultad de Medicina. Universidad Nacional de Colombia, sede Bogotá. Germán E. Pérez. Médico internista. Especialista en neurología. Profesor Universidad Nacional de Colombia. Rodríguez JH. Neurólogo, neurofisiólogo. Jefe posgrado neurología. Universidad del Rosario. Fundación Cardio Infantil. Federico A. SIlva Sieger. Neurólogo Clínico. Fundación Cardiovascular de Colombia. Torres Zafra JF. Neurólogo, Clínica Shaio. Presidente Asociación Colombiana de Neurología. Uribe CS. Profesor de neurología. Facultad de medicina. Universidad de Antioquia. Expresidente de la ACN. Vargas MJ. Neurólogo clínico.*

*Correspondencia: lmorillo@javeriana.edu.co, acnacta@etb.net, geperezr@unal.edu.co*

**Palabras clave:** inmunoglobulina IV, esclerosis múltiple, síndrome de Guillain Barré, polineuropatía, neuropatía, miastenia gravis, síndrome de Lambert-Eaton, dermatomiositis, miositis de cuerpos de inclusión, síndrome de la persona rígida *(Acta Neurol Colomb 2007;23:S1-S72).*

## SUMMARY

**Introduction:** intravenous immunoglobulin (IVIg) has gained acceptance as an alternative treatment in several neurological diseases of the central and peripheral nervous system. Wherever available its' use should be rationalized to those diseases in which the clinical efficacy has been demonstrated.

**Objectives:** to generate evidence based recommendations from randomized clinical trials (RCT) for the use of IVIg.

**Methods:** a systematic search of RCTs was performed using Medline, Ovid, Science Direct, Hinari and Cochrane databases. A total of 189 titles were initially obtained from which pertinent RCTs where selected.

**Results.** sixty RCT's where systematically reviewed. At the end, 45 RCT's and 5 Cochrane systematic reviews where used to produce the present recommendations of IVIg use in 11 distinct neurological diseases.

**Conclusions:** the benefit of IVIg over placebo is supported by evidence provided by at least two RCTs with converging results in: Remitting and recurring multiple sclerosis, child Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy. The benefit of IVIg is at least as effective as plasma exchange in adult Guillain-Barré syndrome. The benefit of IVIg is also discussed for evidence based on single RCT results, RCTs with methodological drawbacks and RCTs with no demonstrable benefit.

**Keywords.** immunoglobulin IV, multiple sclerosis, Guillain-Barre syndrome, polyneuropathies, neuropathies, myasthenia gravis, Lambert-Eaton syndrome, dermatomyositis, myositis inclusion body, stiff-person syndrome *(Acta Neurol Colomb 2007;23:S1-S72).*

## INTRODUCCIÓN

Las afecciones neurológicas como la esclerosis múltiple, el síndrome de Guillain Barré, la miastenia gravis, entre otras, son enfermedades que a pesar de una baja prevalencia ocasionan gran morbilidad al paciente y desencadenan enormes esfuerzos a los servicios de salud generando costos significativos (1,10).

Por años el síndrome de Guillain Barré y la miastenia gravis se han tratado con plasmaféresis y la esclerosis múltiple con un inmunomoduladores (esteroides en especial); el advenimiento de la inmunoglobulina IV ha procurado una alternativa menos complicada para el terapeuta y quizás más segura para el paciente (11-20).

Con la intención de avalar la práctica de sus asociados, a veces glosada por las empresas aseguradoras del sector salud la Asociación Colombiana de Neurología solicitó a un grupo de expertos que obtuvieran y analizaran la mejor evidencia disponible sobre el uso de Ig IV en estas y otras enfermedades neurológicas.

El Dr. Morillo (neurólogo, neurofisiólogo y epidemiólogo clínico) obtuvo y analizó la evidencia, con esta información las diversas regionales de la Asociación discutieron y enriquecieron el análisis, material que se entregó a un jurado (neurólogos con formación en epidemiología clínica); en la fase final del trabajo se redacto por parte del cuerpo editorial de Acta Neurológica Colombiana el documento final (Anexos 1-6).

Este se presenta como Consenso Colombiano sobre la utilidad de la IgIV en enfermedades del sistema nervioso central y periférico.

Como siempre se privilegió el tratamiento útil para los pacientes, quienes con certeza soportan la mayor carga en lo personal, familiar, laboral y social cuando padecen una afección que si bien se expresa en el sistema nervioso involucra la personalidad, la vida de relación y por supuesto la afectividad del ser humano.

Como efecto apenas obvio la ACN ha utilizado esta información para solicitar la expansión de las indicaciones del uso de IgIV ante los entes gubernamentales pertinentes.

## MATERIAL Y MÉTODOS

Para realizar la búsqueda que comprendió desde el inicio de cada una de la colecciones hasta la fecha de la indagación, se consultaron las base de datos *Medline, Ovid, Science Direct* e *Hinari.*

Para efectos de presentar la evidencia más robusta de la efectividad de la inmunoglobulina G intravenosa como intervención, sólo se revisaron aquellos resultados que provenían de ensayos clínicos controlados. De esta manera, cualquier sesgo de asignación se anuló o por lo menos se disminuyó significativamente. Al seleccionar para la revisión este tipo de diseño metodológico, se emite con mayor certeza cualquier recomendación al respecto, basada en la validez de los resultados reportados. Muy esporádicamente, se complementó la revisión con los resultados de un estudio prospectivo no aleatorizado que contribuyó al contexto de la discusión. Se evitaron las cartas al editor. Otras revisiones sistemáticas publicadas sirvieron para identificar en la bibliografía referencias adicionales. Se consultó la base de datos de revisiones sistemáticas *The Cochrane Library* para detectar las referencias adicionales que no se hubieran identificado en las búsquedas. Con la anterior estrategia se incluyeron en la presente revisión sistemática 45 referencias que cubren el total de las 11 entidades en las cuales se ha probado en un ensayo clínico controlado la eficacia de la inmunoglobulina G intravenosa. La socialización del documento adiciono otras 20 referencias (Anexos 1-6).

Para facilitar la lectura, en la redacción se evitó atiborrar el contenido con resultados estadísticos. De tal manera que cuando se menciona que los resultados son estadísticamente significativos indica valores p menores de 0.05, y que los intervalos de confianza, en las pocas ocasiones que se reportaron, se ubicaron a un solo lado de la unidad o del limite de no diferencia entre grupos.

Los términos (MeSH terms) utilizados incluyeron los siguientes:

- Humans
- Child
- Randomized Controlled Trials
- Clinical Trials
- Placebos
- Double-Blind Method
- Immunoglobulins, Intravenous/*administration& dosage/adverse effects/therapeutic use
- Multiple Sclerosis/diagnosis/*drug therapy/ physiopathology
- Muscular Dystrophies/*drug therapy/physiopathology
- Miller Fisher Syndrome/physiopathology/*therapy
- Paraproteinemias/diagnosis
- Polyradiculoneuropathy, Chronic Inflammatory Demyelinatingldiagnosis/physiopathology/*therapy
- Muscle Weakness/diagnosis/*etiology
- Immunoglobulins, Intravenous/*therapeutic use Polyradiculopathy/etiology/*therapy
- Myasthenia Gravis/immunology/therapy
- Polyradiculoneuropathy/immunology/*therapy
- Polyradiculoneuropathy/*therapy
- Campylobacter jejuni/immunology
- Demyelinating Diseases/*drug therapy
- Nervous System Diseases/immunology/*therapy
- Guillain-Barre Syndrome/immunology/*therapy
- G(M1) Ganglioside/immunology
- Motor Neuron Diseaselblood/drug therapy/ immunology
- Motor Neuron Disease/physiopathology/*therapy
- Paraproteinemias/immunology/*therapy
- Paraproteinemias/therapy
- Paraproteins/administration & dosage
- Paraproteins/immunology
- Peripheral Nervous System Diseases/physiopathology/*therapy
- Polyneuropathies/physiopathology/*therapy
- Motor Skills/drug effects
- Recurrence
- Neural Conduction/physiology
- Neural Conduction
- Neural Conductionlphysiology
- Inflammationlimmunology/therapyMH -Electromyography

Los hallazgos se relacionan a continuación por entidades clínicas.

## RESULTADOS

### ESCLEROSISMÚLTIPLE

**Esclerosis múltiple con recurrencias y remisiones (EMRR)**

En dos ensayos clínicos controlados, se comparó la IgIV contra el placebo en un total de 167 pacientes con EMRR. Aleatoriamente se asignaron al tratamiento activo 107 sujetos y

al placebo un total de 90 personas. El criterio fundamental de inclusión contempló pacientes con EMRR clínicamente definitiva, ambulatorios y sin inmunosupresores, inmunomoduladores o esteroides en el momento de la inclusión.

Con una dosis de 0.2 g/kg o 0.4 g/kg aplicada mensualmente por un período de un año el puntaje de la discapacidad, obtenido en la escala expandida del estado de discapacidad (EDSS), fue significativamente menor en el grupo que recibió el tratamiento con IgIV independiente de las dosis o tiempo de aplicación en comparación con el placebo. La superioridad de la IgIV (0.15 a 0.2 g/kg) sobre el placebo se mantiene al analizar la proporción de pacientes que mejoran, se mantienen estables o empeoran (1).

Cuarenta pacientes con EMRR definitiva clínicamente confirmada con resonancia magnética (2) recibieron una dosis de carga de IgIV de 0.4 g/kg durante cinco días consecutivos y después fueron asignados en forma aleatoria para que durante dos años reciban una dosis igual cada dos meses o placebo. La menor tasa anual de exacerbación y el tiempo hasta la primera recaída fueron estadísticamente significativos en favor de la IgIV. La tasa anual de recaídas se redujo con la IgIV de un valor basal de 1.85 a 0.75 al año y a 0.42 después de dos años en comparación con el placebo que pasa de 1.55 a 1.8 al año y a 1.4 a los dos años. La mediana en días hasta la primera recaída fue de 233 con IgIV y de 82 con el placebo.

Por otra parte, la actividad de la enfermedad según se observa en resonancias magnéticas sucesivas fue menor en el grupo que recibió la IgIV. El volumen total en T2 o número de lesiones nuevas y que realzan con el gadolinio en T1 se reducen (3). Resultado de acuerdo con un ensayo clínico controlado y cruzado previo en el cual 26 pacientes con EMRR aleatorizados a 1 g/kg diario por dos días o placebo aplicado mensualmente durante periodos alternos de seis meses (4).

Después de un primer episodio desmielinizante que se presenta como un síndrome clínico aislado, la IgIV aumenta el tiempo transcurrido hasta la conversión a una esclerosis múltiple definitiva. Un total de 91 pacientes incluídos dentro las primeras seis semanas de los síntomas iniciales se aleatorizaron a una carga inicial de IgIV, 2g/kg o placebo y refuerzos cada seis semanas durante un año. La evolución clínica programada cada tres meses y una resonancia cerebral magnética al inicio y otra al finalizar el período de estudio sirvieron para establecer la incidencia de un segundo ataque desmielinizante y la actividad en el tiempo de la enfermedad. La probabilidad de conversión a esclerosis múltiple definitiva y el volumen lesional, el número de lesiones T2 y el volumen lesional que realza con el gadolinio son todos menor con la IgIV que con el placebo (5).

A diferencia de los anteriores resultados, la recuperación de la agudeza visual como resultado de una neuritis óptica en pacientes con esclerosis múltiple no es apropiada con IgIV ni demuestra ser superior al placebo. En 55 pacientes con perdida persistente de la agudeza visual que se aleatorizaron para recibir IgIV, 0.4 g/kg diarios por cinco días y cada mes durante tres meses o placebo no demostró beneficio alguno al cabo de l2 meses de seguimiento (6).

La efectividad de la IgIV se comparó con la del interferón beta 1-a IM, en un estudio clínico aleatorizado con un grupo de 80 pacientes con EMRR. Al seguir el grupo durante un año, ambos tratamientos fueron efectivos al reducir la tasa anual de recaídas, también se produjo una disminución del puntaje EDSS sin que existiera una diferencia significativa entre los efectos de estos dos tratamientos (7).

**Esclerosis múltiple secundariamente progresiva (EMSP)**

El estudio europeo de IgIV en esclerosis múltiple secundaria progresiva no demostró beneficio en la medida de desenlace primario de progresión de la discapacidad por EDSS. Un total de 318 pacientes asignados aleatoriamente a 1g/kg de IgIV mensual o placebo. En el período de 27 meses de seguimiento, las evaluaciones clínicas se efectuaron cada tres meses y la resonancia magnética cerebral a los 12 y 24 meses. En estos desenlaces el análisis por intención de tratar no indicó diferencias significativas entre grupos (6-9).

La IgIV fue superior al placebo al reducir la discapacidad en estudios cuyo seguimiento fue hasta de dos años. La tasa anual de recaídas disminuye y el tiempo hasta la siguiente recaída se

prolonga. La actividad de la enfermedad evaluada con resonancia magnética seriada disminuye paralelamente al efecto clínico. La evidencia proveniente de varias fuentes respalda el papel potencial de la IgIV en el tratamiento de la EMRR. Sin embargo, queda por establecer su efectividad en cuanto a la progresión de la discapacidad más allá de dos años. La IgIV no tiene indicación en el manejo de la EMSP o en la recuperación de la agudeza visual, secuela de la neuritis óptica (1-9).

## SINDROME DE GUILLAIN-BARRE (SGB)

Se ha demostrado, en al menos dos ensayos clínicos controlados internacionales multicéntricos que la IgIV en el tratamiento agudo de la polineuropatía desmielinizante aguda post infecciosa o síndrome de Guillain-Barré, es tan eficaz como la plasmaféresis (PF).

Los resultados publicados incluyen 529 pacientes con menos de dos semanas de evolución e incapacidad para caminar sin ayuda en uno o que requerían ayuda para hacerlo en el segundo (10, 11). Se utilizó una dosis de IgIV de 0.4 g/kg diarios por cinco días. Por otra parte, la duración de la plasmaférisis varió entre cinco y 13 días con recambios entre 50 ml/kg a 250 ml/kg. Los resultados indican que a las cuatro semanas el 35 por ciento de los pacientes tratados con PF y el 53 por ciento con IgIV habían mejorado al menos un punto en la escala funcional utilizada de siete puntos. Esta superioridad de la IgIV es estadísticamente significativa. Sin embargo, la mediana en días en la que se obtiene la mejoría predeterminada aunque menor con la IgIV que con la PF (27 días v*ersus* 41 días) no es estadísticamente significativa. De manera similar, la diferencia en el puntaje promedio de mejoría a las cuatro semanas en una escala de siete puntos, el tiempo hasta caminar sin asistencia y el tiempo en ventilador no son estadísticamente diferentes entre los grupos de tratamiento (12,13).

Los anteriores resultados son semejantes a los obtenidos en dos ensayos adicionales de menor escala y con un diseño similar. Diener *et al* en 79 pacientes y Bril *et al* en 50 pacientes con SGB no demostraron diferencias significativas con la PF al analizar los mismos desenlaces de recuperación (10,11).

La combinación de IgIV, 0.4 g/kg por cinco días, con metilprednisolona, 500 mg/día durante cinco días no demostró un beneficio adicional en el tratamiento agudo del GB (14). El estudio doble ciego controlado asignó aleatoriamente, en un término no superior a 48 horas luego de la primera dosis de IgIV, a 233 personas en dos grupos; metilprednisolona o placebo. Los puntajes a las cuatro semanas en la escala utilizada de discapacidad no fueron estadísticamente diferentes. Estos hallazgos están en contraposición a los obtenidos previamente y reportados por el *Dutch Guillain-Barre Study Group* en 1994 que sugieren una superioridad de la combinación con metilprednisolona sobre la IgIV en monoterapia. Sin embargo, hay que resaltar la limitación del diseño sobre los resultados que se derivaron de una comparación abierta en dos grupos no concurrentes (15).

Se reconoce que en 10-20 por ciento de pacientes con SGB está contraindicada la PF y en un 4-15 por ciento este procedimiento debe descontinuarse por distintas razones. En estas circunstancias particulares, un grupo de 39 sujetos con inestabilidad hemodinámica, hemostasis severa o sepsis se aleatorizaron a IgIV, 0.4 g/kg por tres días o seis días (16). No se documentó una diferencia significativa entre grupos en cuanto al tiempo requerido para restablecer marcha sin asistencia. Sin embargo, el tiempo en ventilador con seis días de tratamiento fue de 86 días versus 152 días con el esquema de tres días: una diferencia estadísticamente significativa.

En edad pediátrica la IgIV, 1 g/kg por dos días administrada en el curso temprano de la enfermedad cuando aún se mantiene la capacidad de caminar cinco metros sin asistencia, si bien no previene la progresión a un estado más severo parece ser que acelera el periodo de recuperación. De 21 niños, once perdieron la habilidad de caminar sin asistencia y seis quedaron limitados a cama. Estas diferencias no son estadísticamente significativas con respecto al grupo aleatorizado a ningún tratamiento. Por otra parte, diferir el inicio de la administración de IgIV hasta cuando se pierde la capacidad para caminar cinco metros sin asistencia, no influyó en 51 niños el tiempo requerido para restablecer la marcha sin asistencia. El hallazgo es independiente del esquema asignado al azar de 1 g/kg por dos días versus 0.4 g/kg por cinco días. Sin embargo, la

progresión transitoria hacia el deterioro ocurre más frecuentemente con el esquema de dos días (17). También se demostró la reducción del tiempo hasta la recuperación en el grupo de nueve niños aleatorizados a 1 g/kg día por dos días en comparación al mismo número de niños que no recibieron tratamiento específico precoz (18,19).

El tratamiento agudo del SGB en adultos con IgIV en es tan eficaz como la plasmaférisis en reducir de la discapacidad y el tiempo en ventilador. A diferencia de los estudios en adultos con SGB, en los que no existen ensayos clínicos comparados con ningún tratamiento o placebo, en niños se ha establecido la superioridad de la IgIV sobre no instaurar un tratamiento específico.

## POLINEUROPATÍAINFLAMATORIA CRÓNICA(CIDP)DESMIELINIZANTE

La efectividad superior de la IgIV sobre el placebo se ha demostrado en tres de cuatro ensayos clínicos controlados que totalizan 118 sujetos. En tres, el esquema de aplicación consistió en IgIV 0.4 g/kg durante cinco días consecutivos y en el estudio restante: IgIV 1 g/kg día por dos días consecutivos y una dosis adicional a los 21 días.

El diseño de grupos paralelos se utilizó en dos ensayos de calidad similar. El de mayor tamaño de muestra (n=53), favoreció la IgIV (20) mientras que el que utilizó un menor tamaño de muestra (n=28) no demostró diferencias significativas con el placebo (21). En el primero, el desenlace principal del puntaje muscular promedio (*Average Muscle Score*) fue comparable en ambos grupos. La mejoría estadísticamente significativa fue detectable a los 10 días de seguimiento con IgIV. El grupo placebo, por el contrario perdió fuerza muscular en el mismo intervalo. Adicionalmente, ninguno de los pacientes que recibió IgIV perdió fuerza. Los parámetros electrofisiológicos investigados que mejoran con la IgIV incluyen: latencia motora distal del cubital; amplitud del potencial motor compuesto del nervio tibial y la velocidad de conducción del peroneo. En contraposición, Vermuelen et al no demostraron una diferencia significativa con el placebo tanto en las mediciones clínicas como en las electrofisiológicas.

La eficacia de la IgIV de mejorar las medidas clínicas de fuerza muscular, discapacidad y parámetros electrofisiológicos se replicó en dos estudios aleatorizados cruzados con 30 y siete sujetos respectivamente (22,23).

Un ensayo clínico controlado cruzado evaluó en 24 sujetos con CIDP, prednisolona oral, iniciada con 60 mg día seguida de una disminución gradual durante el período de estudio de seis semanas, mientras que el otro grupo recibió IgIV 2.0 g/kg día administrados en uno a dos días. Si bien hay una tendencia de mejoría en favor de la IgIV, ambos tratamientos producen un beneficio según los valores obtenidos en la escala de discapacidad utilizada o el tiempo requerido para caminar 10 metros en la evaluación efectuada a las dos semanas después de la aleatorización. A las seis semanas tampoco se observó una diferencia significativa entre tratamientos (24).

La plasmaféresis (PF), que ha demostrado ser eficaz en el tratamiento agudo de síndrome de Gullain-Barre se probó en 20 pacientes con CIDP. Períodos de tres semanas de IgIV 0.4 g/kg semana seguidas de 0.2 g/kg semanal se compararon con PF dos recambios semanales por tres semanas seguidos de un recambio semanal por tres semanas adicionales. Al completar las seis semanas y luego de un período de lavado, se cruzaron los tratamientos. A pesar de que durante el periodo de lavado sucedió un deterioro en ambos grupos, no se demostraron diferencias significativas en las medidas de desenlace clínicos de discapacidad y fuerza muscular o parámetros electrofisiológicos al completarse los periodos de estudio (25).

La IgIV es superior al placebo para obtener la recuperación clínica de la fuerza muscular. Las respuestas electrofisiológicas previamente ausentes o de amplitud disminuida son evocables y de mayor amplitud después del tratamiento; fenómeno que ocurre en paralelo con la recuperación clínica. Estos efectos clínicos y electrofisiológicos son indistinguibles de los que resultan de utilizar prednisolona oral o plasmaférisis (25,26).

## NEUROPATÍAMOTORAMULTIFOCAL (NMM)

La pérdida progresiva y asimétrica de fuerza que resulta del compromiso de la motoneurona inferior y el bloqueo de conducción característico de esta entidad, responden de manera no bien definida a la IgIV. El número reducido de pacientes incluidos en los reportes discutidos a continuación, obedece a la rara ocurrencia de la misma.

Dieciséis pacientes con NMM se asignaron aleatoriamente en un diseño cruzado a placebo o IgIV, 0.4 g/k día durante cinco días consecutivos. La evaluación a los 28 días demostró una mejoría clasificada como dramática o muy buena en nueve sujetos con la IgIV y no con el placebo. La discapacidad neurológica, la fuerza de prensión y el bloqueo de conducción mejoraron con la IgIV y se empeoraron con el placebo (27).

Por otra parte, en un ensayo aleatorizado con placebo, 19 sujetos que nunca habían recibido IgIV según la respuesta inicial, tuvieron la opción de recibir el tratamiento alterno. Los efectos del placebo o la IgIV 0.5 g/kg día por cinco días consecutivos administrados mensualmente y durante tres meses se evaluaron al cuarto mes. Los respondedores permanecieron con el mismo tratamiento mientras que los no respondedores cambiaron al tratamiento alterno. Clínicamente, el análisis del total de pacientes indicó una diferencia estadísticamente significativa en siete de los nueve pacientes que recibieron IgIV inicialmente y mejoraron al cuarto mes en comparación con dos en un mismo número de pacientes que recibió placebo. En el momento de evaluación, los parámetros electrofisiológicos no fueron estadísticamente diferentes entre grupos (28).

Un pequeño grupo, cada uno de cinco pacientes que recibieron IgIV mejoró en 50 por ciento la fuerza muscular en comparación con su estado inicial. Ninguno de los que recibió placebo lo hizo (29). Seis sujetos en un estudio abierto con IgIV respondieron satisfactoriamente (30). La mejoría inicial de la fuerza muscular, no se sostuvo más allá de 12 semanas y una reducida proporción de sujetos empeoró discretamente con la IgIV de mantenimiento. El bloqueo de conducción múltiple que también desaparece, durante el tratamiento de mantenimiento aparece en nervios previamente indemnes (31).

La evidencia de la eficacia de la IgIV está limitada a ensayos clínicos con tamaño reducido de muestra. La respuesta inicial clínica y electrofisiológica favorable no parece sostenerse en el tiempo aún con dosis de mantenimiento (32).

## MIASTENIA GRAVIS (MG)

La IgIV se evaluó en un grupo reducido de pacientes con MG estable. El estudio aleatorizado se suspendió tempranamente por falta de disponibilidad de la IgIV. No se demostró una diferencia estadísticamente significativa con relación a los sujetos que se asignaron aleatoreamente al placebo. Aquí, una carga inicial de 2 g/kg y otra a las tres semanas de 1 g/kg no fue superior al placebo (33). Por otra parte, un grupo de 12 pacientes con MG moderada a severa en fase estable aleatorizados en un diseño cruzado a IgIV 0.4 g/kg en cinco días consecutivos y 16 semanas después cinco recambios de plasmaféresis (PF). El grupo control se sometió inicialmente a los recambios de PF, seguidos a las 16 semanas de la IgIV. El puntaje clínico cuantificado de MG mejoró en ambos grupos sin que se demuestre una diferencia estadísticamente significativa entre los dos esquemas de tratamiento medidos a la semana y a las cuatro semanas (34).

La IgIV en la exacerbación aguda de la MG es al menos tan eficaz como el manejo con PF. Un primer ensayo clínico aleatorizó a 87 pacientes a IgIV 0.4 g/kg diarios durante 3-5 días consecutivos o tres recambios consecutivos de PF. El desenlace primario se basó en la cuantificación del cambio en el puntaje muscular entre la aleatorización y el día 15. La eficacia de la IgIV fue discretamente menor que la PF sin que esta diferencia fuera estadísticamente significativa. Posteriormente, en un ensayo que recolectó 187 pacientes aleatorizadas, las dosis de 1g/kg por un día resultan igualmente efectivas en la crisis miasténica. La mejoría a las dos semanas en la escala muscular cuantificada para MG es similar con ambas dosis sin una diferencia estadísticamente significativa (35,36).

La IgIV es al menos tan eficaz como la PF tanto en el manejo de la MG estable o en el manejo de la exacerbación aguda. La mejor tolerancia y menor incidencia de efectos secundarios con la IgIV permiten considerarla como una alternativa de manejo (37).

## SINDROME DE LAMBERT-EATON (SLE)

La evaluación de los efectos de la IgIV en el SLE se limita a un ensayo clínico aleatorizado con un total de nueve pacientes en períodos cruzados de tratamiento de ocho semanas. Se compararon los índices de fuerza muscular, respiratorio y bulbar entre IgIV, 1 g/kg en dos días consecutivos o placebo. En las medidas clínicas seleccionadas, la IgIV produjo una mejoría estadísiticamente significativa sobre el placebo. El pico de la mejoría ocurrió entre las dos a cuatro semanas y disminuyó a las ocho semanas (38).

## NEUROPATIA DESMIELINIZANTE ASOCIADA A PARAPROTEINEMIA

La polineuropatía desmielinizante asociada a anticuerpos monoclonales IgM responde modestamente a la IgIV. Un ensayo clínico aleatorizó 22 pacientes a IgIV 2.0 g/kg o placebo administrados en uno a dos días consecutivos. La IgIV fue más eficaz que el placebo en reducir las medidas de discapacidad a las cuatro semanas. Con la IgIV, 10 mejoraron, uno empeoró y el resto se mantuvieron estables. A su vez durante la administración de placebo; cuatro mejoraron, cuatro empeoraron y 14 se mantuvieron estables. La diferencia fue estadísticamente significativa a las cuatro semanas más no en la evaluación a las dos semanas. Adicionalmente se apreció una mejoría significativa en desenlaces secundarios que incluyeron la escala de Rankin, el tiempo requerido para caminar 10 metros, la fuerza de prensión palmar y los síntomas sensoriales (39). Previamente, en un ensayo clínico en 11 pacientes, con diseño cruzado similar y un esquema de IgIV o placebo mensual durante tres meses, los resultados obtenidos no fueron significativos. Hubo mejoría en dos pacientes en la escala de discapacidad después de tres meses de la aplicación de IgIV que declinó durante el período en placebo (40).

El interferon alfa es superior a la IgIV para disminuir el puntaje de discapacidad después de seis meses de tratamiento. Veinte sujetos se asignaron de manera aleatoria a IgIV 2 g/kg iniciales seguidos de 1 g/kg cada tres semanas o interferón alfa 3MU/m2 subcutáneos tres veces a la semana. El puntaje en la escala de discapacidad clínica mejoró con IgIV en tan sólo uno de los pacientes mientras ocho de 10 pacientes lo hicieron con el interferón. La diferencia significativa persistió después de 12 meses de seguimiento y se debió principalmente a la mejoría de los síntomas sensoriales más que al componente motor de la neuropatía. Los parámetros electrofisiológicos no demostraron cambios significativos de mejoría en el tiempo (41).

La evidencia del modesto beneficio de la IgIV es limitada a dos estudios con resultados disímiles aunque con esquemas distintos de aplicación. El interferón alfa resulta superior a la IgIV para reducir especialmente los componentes sensoriales de la polinueropatía desmielinizante asociada a la paraproteinemia IgM (42, 43).

## DERMATOMIOSITIS

Con la IgIV, la discapacidad severa, la fuerza muscular, los síntomas neuromusculares y las alteraciones características de la piel, responden de una manera impactante hasta la recuperación normal de la funcionalidad. El único ensayo clínico controlado cruzado disponible, demuestró un efecto útil en 15 pacientes resistentes al tratamiento convencional. Con una infusión de IgIV inicial de 2 g/kg mensual durante tres meses, de 12 pacientes en total, nueve lograron una recuperación óptima en los desenlaces preestablecidos. Durante el período de tres meses en el cual se aplicó placebo no hubo mejoría significativa y cinco se deterioraron. Las biopsias musculares repetidas en cinco pacientes cuya fuerza muscular alcanzó niveles normales, evidenciaron un aumento tanto del diámetro de las fibras musculares como del número de capilares. Así mismo los complejos antigénicos disminuyeron (44,45).

## MIOSITIS DE CUERPOS DE INCLUSIÓN (MCI)

La IgIV se ha probado como tratamiento en la MCI con el propósito de detener la progresión de la enfermedad y aliviar los síntomas clínicos. En al menos tres ensayos clínicos controlados y cruzados los resultados han sido decepcionantes con mejoría mínima o nula. Un grupo de 22 pacientes, con 5.6 ± 3.6 años en promedio

de duración de la enfermedad recibieron una infusión de IgIV 2 g/kg o placebo mensual durante seis meses. Después de esto, los grupos se cruzaron al tratamiento alterno por un período igual. En 90 por ciento de los pacientes, la progresión de la enfermedad se detuvo a pesar de que la mejoría de los síntomas neuromusculares fue mínima (46). Otro ensayo con 19 pacientes, con 5.6 a 7.4 años en promedio de duración de la enfermedad se asignaron aleatoriamente o bien a IgIV, 2 g/kg mensualmente durante tres meses o a placebo para luego recibir el tratamiento alterno. Las medidas pre-aleatorización de fuerza muscular, contracción máxima voluntaria y los puntajes de discapacidad y síntomas neuromusculares se compararon al finalizar cada uno los períodos de tratamiento. En un tercio de los pacientes con IgIV la tendencia fue hacia la mejoría. Las ganancias menores y las diferencias obtuvieron una significancia estadística (47).

La MCI, confirmada por biopsia, no se beneficia al agregar prednisolona a la IgIV mensual por tres meses. Comparativamente con el placebo la fuerza muscular al segundo, tercer o cuarto meses después de haberse iniciado el tratamiento combinado no demuestró cambios significativos (48).

El efecto de la IgIV en la recuperación de la fuerza muscular y de la mejoría de los síntomas neuromuscualres fue escaso y muy leve cuando se logró y no es significativamente diferente del efecto del placebo. No existe una aparente sinergia con la predinisolona al utilizar la combinación.

## SINDROME DE LA PERSONA RIGIDA (SPR)

La evidencia existente de la efectividad de la IgIV en el SPR se limita a un ensayo clínico controlado cruzado de un reducido grupo de 16 pacientes con títulos altos de anticuerpos anti-GAD positivos. Durante períodos alternos de tres meses los pacientes recibieron IgIV o placebo. El puntaje de rigidez al primer mes y al cuarto mes se redujo significativemente con la IgIV y aumentó al compasarse con el placebo. El efecto en los once pacientes que recobran la marcha con o sin asistencia tuvo una duración variable entre las seis semanas a un año. Paralelamente los títulos de anticuerpos anti-GAD se redujeron con la IgIV (49).

## SINDROME POSTPOLIO (SPP)

El aumento o desarrollo de nuevos síntomas en pacientes con secuelas de poliomielitis ocurrida décadas antes se conoce como el SPP. Un reciente ensayo clínico controlado en 142 pacientes aplicó según una asignación aleatoria a 90 gramos totales de IgIV administrados en tres días consecutivos y repetidos a los tres meses o placebo bajo el mismo esquema. Los desenlaces principales fueron fuerza muscular y calidad de vida medida con el cuestionario SF36. El promedio de la fuerza muscular favoreció a la IgIV. La ligera diferencia clínica obtenida fue del 8.3 por ciento con respecto al placebo que es estadísticamente significativa. Las medidas de calidad de vida no alcanzaron una diferencia significativa (50).

## OTROS USOS DE LA IgIV

**Síndrome de Rasmusen** (Encefalitis crónica y epilepsia). Es un trastorno progresivo de etiología desconocida que produce epilepsia focal, hemiparesia y deterioro intelectual. El tratamiento con Ig- IV y altas dosis de esteroides o ambos, controla las convulsiones y mejoran la enfermedad. Hart *et al* (62) en 19 niños utilizó IgIV; altas dosis de esteroides o ambos para controlar las convulsiones. Con IgV 0.4 g/k/día por tres días sucesivos, seguido de una infusión mensual de 0.4 g/k de IgIV observa mejoría. En ésta serie, 10 de 17 pacientes que recibieron esteroides y ocho de nueve pacientes que recibieron inmunoglobulina tuvieron alguna reducción de la frecuencia de la crisis en corto plazo. Los casos que no tuvieron mejoría, se aplicó inicialmente metilprednisolona 400 mg/m2 en tres infusiones en día alternos.

Carabello y col (63) informaron una detención de la progresión del deterioro neurológico y control de crisis convulsivas en 55 por ciento de sus 12 pacientes con encefalitis de Rasmusen con IglV y Leach y col (64) informan mejoría notoria en el control de las convulsiones y de la cognición en adultos para la adultez, tratados con IgIV.

No hay un tratamiento establecido para la encefalomielitis aguda diseminada aparte del tratamiento de soporte, se usaron con frecuencia la IgIV y la plasmaferesis en los casos severos que no tuvieron respuesta a los esteroides (1).

**Síndrome de West (espasmos infantiles) y Lennox Gastaut.** Las IgIV no parecen producir efectos terapéuticos valiosos, aún en casos recién diagnosticados, en los cuales el promedio de respuesta no excede el 10 por ciento de mejoría. Sin embargo, es de anotar que la IgIV se ha utilizado como coadyuvantes en el tratamiento de síndromes epilépticos de difícil control, tales como el síndrome de West y Lennox - Gastaut con mejoría parcial o total, con un máximo efecto a los 90 días de iniciado el tratamiento. Espinoza Zacarías *et al* (3) usó 0.5 g/k/día por cinco días consecutivos, seguidos de una dosis cada dos semanas hasta completar tres meses de tratamiento (3).

## DISCUSIÓN

En la EMRR los estudios de Fasekas (1) y Achiron indican que disminuyen los períodos de recurrencia al menos con seguimiento de hasta dos años. Este es un corto periodo de seguimiento para esta enfermedad, lo que limita la recomendación de la IgIV como tratamiento de elección aunque podria considerarse como una alternativa viable (1,5).

En la forma de EM secundariamente progresiva (EMSP), los estudios no son concluyentes así como para el caso de la neuritis óptica y la recuperación de la agudeza visual (6,9), de tal forma que no puede emitirse una recomendación del uso de la IgIV en estos casos.

El estudio de Kalanie col (7) que comparó pacientes con Interteron Beta - 1 A intramuscular (IM) vs. inmunoglobulina IV en un grupo de 80 pacientes con EMRR por espacio de un año; demostró que ambos tratamientos eran efectivos en reducir la tasa anual de recaídas así como el puntaje de la escala EDDSS sin que existiera diferencia significativa entre los dos tratamientos. Sin embargo el periodo de seguimiento es corto y el número de pacientes reducido (80 pacientes). Aunque la IglV es superior al placebo reduciendo la discapacidad en estudios de seguimiento de hasta dos años, disminuyendo la tasa anual de recaídas y aún la actividad de la enfermedad apoyada con resonancia magnética seriada, no se han conducido estudios que establezcan su efectividad después de dos años.

En el embarazo, hay contraindicación para el uso de los interferones en la EM. En el post-parto inmediato es útil el empleo de la IgIV para evitar recaídas, como lo confirma el estudio PRIMS (51). Achiron *et al* (2) sugieren la administrar de 0.4 g/kg/día de IgIV por cinco días, en la primera, sexta y décima segunda semana después del parto a aquellas mujeres con recaídas post-parto en embarazos previos.

Achiron (5) sugiere la coveniencia de la IgIV desde el comienzo del embarazo. Ciento ocho mujeres seguidas durante el embarazo y en el período post-parto se analizaron retrospectivamente. Se dividieron en tres grupos: grupo I; no recibió tratamiento, el grupo II recibió IgIV 0.4 g/kg/día por cinco días a la primera semana y por un día, en las semanas sexta y 12 después del parto; el grupo III recibió IgIV desde el comienzo del embarazo (semana 6 -8) con un refuerzo de 0.4 kg/día cada seis semanas hasta la semana 12 post-parto. El promedio de recaída en el primer trimestre post-parto, fué significativamente más bajo en el grupo tratado comparado con el grupo no tratado, el promedio de recaída durante el embarazo fue más bajo para el grupo III. No hubo eventos adversos serios de un total de 649 infusiones de IgIV (51-53). Estos hallazgos están sustentados adicionalmente por otros autores (7,8). En resumen, durante el embarazo y el post-parto, los pacientes con EM y en riesgo de recaida, deben considerarse y tratarse como enfermedad activa con IgIV (5).

En el síndrome de Guillain-Barré (GB) en adultos ambos tratamientos, plasmaféresis (PF) e IgIV son eficaces en el periodo agudo de la enfermedad. Esto lo confirman tres trabajos comparativos entre IgIV y plasmaféresis (PF) (11-13) y lo corrobora el informe del subcomité de estándares de calidades de la Academia Americana de Neurología (54).

Es necesario aclarar que el tratamiento con IgIV se recomienda con suficiente apoyo en pacientes hospitalizados, dentro de las dos semanas de comienzo de los síntomas de

neuropatía (4) y tiene los mismos niveles de evidencia de la plasmaféresis (PF) para reducir la discapacidad y el tiempo en ventilador.

La evidencia disponible indica que la IgIV puede inicarse hasta en la cuarta semana de la enfermedad aguda. Cuando se hace en las dos primeras su eficacia es comparable a la plasmaferesis. En niños también puede usarse la IgIV en la fase aguda de la enfermedad.

La dosis recomendada de IglV por la mayoría de autores es de 0.4 g/kg/día por cinco días. El promedio de recaída en GS es significativamente más alto para los que usan IglV (10.8%) comparado con el grupo de PF (4.3%) (1, 8-10). No existen datos que determinen si un curso mayor a cinco días de IglV sea más benéfico para evitar recaídas (55-59).

Si bien es cierto que en la CIDP el uso de la IglV es superior al placebo según tres trabajos, existen también informes con prednisona 60 a 100 mg/kg/día, para adultos y 1.5 mg/kg/día en niños, con un tiempo promedio de inicio de la respuesta de dos meses. También se ha usado plasmaféresis (PF) agregada al tratamiento inicial de prednisona.

Hughes *et al* (54) evaluaron en 24 pacientes con diagnóstico de CIDP, la prednisona oral a dosis de 60 mg día por seis semanas y otro grupo con IgIV 2.0 g/kg/día en uno o dos días, a las seis semanas no se observó diferencia significativa entre los dos tratamientos.

La IgIV es superior al placebo, pero los efectos de mejoría clínica y electrofisiológica son indistinguibles en quienes usan prednisona oral o plasmaféreis. Sin embargo por los efectos colaterales adversos que producen los esteroides, se recomienda la lgIV como alternativa en la polineuropatía crónica inflamatoria desmielinizante.

Van Doom *et al* (1) documentó que los pacientes con corta duración de los síntomas, igual debilidad en las extremidades superiores e inferiores, arreflexia de miembros superiores y velocidades de conducción disminuidas fueron los que mejor responden a la IgIV (60).

El uso de la IglV en la NMM indica que en un grupo reducido de pacientes puede ser efectiva. Un estudio abierto no controlado produjo mejoría significativa en un periodo entre 3-6 meses (61).

En los períodos de exacerbación aguda (crisis miasténica) y en la miastenia severa la IglV es tan eficaz como la plasmaféresis (PF). La mejor tolerancia y menor incidencia de efectos secundarios con IglV permiten considerarla como una alternativa de manejo. Se recomienda seguir la clasificación modificada de Osserman y hacer diagnóstico diferencial con la miastenia moderada o severa.

En cuanto al uso de la IglV en el manejo de la MG estable, la evidencia no muestra resultados favorables La dosis recomendada es de 2 g/kg en infusión por espacio de 2-5 días (33,62,63).

En el síndrome de Lambert Eaton (SLE), el tratamiento de ocho semanas, con IgIV a la dosis de 1 g/kg, pero en dos días consecutivos, produjo una mejoría estadísticamente significativa sobre el placebo. Otro estudio que reportó el uso de IglV en el síndrome de Lambert Eaton, mostró eficacia comparable a la plasmaféresis (38,64).

En la neuropatía desmielinizante asociada a paraproteinemia los beneficios son modestos y no se justifica usarla, pues en algunos casos los resultados pueden ser mejores con el interferon alfa al menos para reducir o mejorar los componentes sensoriales de la enfermedad (42,43).

En la dermatomiositis el uso de la IgIV, fue muy útil según el único trabajo controlado analizado de Dalakas *et al*. La mejoría se obtuvo en la fuerza muscular, en los síntomas neuromusculares, en las alteraciones de la piel, hasta llegar a la recuperación normal de la funcionalidad, el trabajo fue controlado con placebo y se usó dosis de 2g/kg de IglV mensual durante tres meses.

En la miositis de cuerpos de inclusión no existe evidencia suficiente para recomendar el uso de IgIV (44-45).

La IgIV en el síndrome de la persona rígida, produce una buena respuesta clínica y de laboratorio (49), con beneficio de la IglV en un grupo de 16 pacientes con títulos altos de anticuerpos anti- GAD. Dos estudios adicionales con muestras reducidas respaldan también esta observación de mejoría funcional con IgIV (2,3).

Aunque no existe tratamiento específico para el SPP esta entidad (1) puede usarse la IglV apoyándose en el trabajo de González (50).

## CONCLUSIONES

**A. Beneficio demostrado de la IgIV respaldado por evidencia obtenida de al menos dos estudios clínicos controlados con resultados similares.**

***Comparación contra PLACEBO o NINGÚN TRATAMIENTO***

1. Esclerosis múltiple con recurrencias y remisiones. La IgIV es superior al placebo en disminuir el grado de discapacidad al año, la tasa anual de recaídas medida hasta los dos años, el tiempo hasta la primera recaída y actividad de la enfermedad según criterios de resonancia magnética cerebral. Su indicación a largo plazo es incierta con base en los estudios hasta ahora reportados (1-4).
2. Síndrome de Guillian Barre. En niños la IgIV es superior a ningún tratamiento específico en reducir el tiempo hasta la recuperación de la marcha (18,19). El efecto es independiente de la iniciación precoz o no de la IgIV (17).
3. Polineuropatía Inflamatoria Crónica desmielinizante. La IgIV es superior al placebo en la mejoría de los parámetros de discapacidad, fuerza muscular y electrofisiológicos (20-23).

***Comparación contra otro TRATAMIENTO ACTIVO***

4. Síndrome de Guillian Barre. La IgIV es tan eficaz como la plasmaferesis en aumentar la escala de funcionabilidad a las cuatro semanas en sujetos que han desarrollado en el transcurso de dos semanas incapacidad para caminar sin ayuda o de requerir ayuda para hacerlo (10-13). La IgIV en combinación con metilprednisolona no es superior a la IgIV combinada con placebo al medir la discapacidad a las cuatro semanas (14).

**B. Beneficio demostrado de la IgIV respaldado por evidencia obtenida de un solo estudio clínico controlado.**

***Comparación contra PLACEBO***

5. Síndrome Neurológico Aislado. En comparación con el placebo la IgIV prolonga el tiempo hasta la conversión a esclerosis múltiple definitiva y así mismo reduce el número de lesiones observadas en la resonancia magnética cerebral (5).

***Comparación contra otro TRATAMIENTO ACTIVO***

6. Esclerosis múltiple con recurrencias y remisiones. En el seguimiento a un año la IgIV es tan eficaz como el interferón beta 1-a en reducir la tasa anual de recaídas y el puntaje de discapacidad (7).
7. Polineuropatía Inflamatoria Crónica desmielinizante. La IgIV es tan eficaz como la prednisolona oral en reducir la discapacidad y el tiempo requerido para restablecer la marcha a las dos o seis semanas (24). Por otra parte la IgIV es tan eficaz como la plasmaferesis en reducir la discapacidad, fuerza muscular o parámetros electrofisiológicos (25).

**C. Beneficio no conclusivo aunque aparente de la IgIV por evidencia obtenida de estudios clínicos controlados con limitaciones metodológicas.**

8. Neuropatía Motora Multifocal. La IgIV produce una mejoría clínica significativamente superior al placebo aunque no parece sostenerse en el tiempo. Estudios clínicos controlados con tamaño de muestra reducidos (27-29)
9. Miastenia Gravis Estable. La IgIV es tan eficaz como la plasmaferesis en la mejoría clínica medida a la semana o a las cuatro semanas de sujetos con enfermedad moderada a severa de su enfermedad. Estudio clínico controlado con tamaño de muestra reducido (34).

10. Síndrome de Eaton Lambert. La IgIV es superior al placebo en mejorar los índices de fuerza muscular, respiratorio y bulbar medidos a las ocho semanas. Estudio clínico controlado con tamaño de muestra reducido (38).
11. Neuropatía Desmielinizante Asociada a Paraproteinemia. La IgIV reduce en un estudio, modestamente las medidas de discapacidad a las cuatro semanas comparativamente con el placebo (39). Los hallazgos que no se habían demostrado en un estudio previo similar (40). Estudios clínicos controlados con tamaño de muestra reducidos
12. Dermatomiositis. La IgIV tiene un efecto aparentemente impactante y superior al placebo sobre las alteraciones de la piel, la funcionalidad y el efecto demostrable en la biopsia muscular. Estudio clínico controlado con tamaño de muestra reducido (44).
13. Síndrome de la Persona Rígida. La IgIV es superior al placebo en lograr la recuperación de la marcha y la disminución de la rigidez. El efecto se sostiene por espacio variable entre seis meses a un año. Estudio clínico controlado con tamaño de muestra reducido (49).
14. Síndrome Post Polio. La IgIV es superior al placebo en aumentar ligeramente la fuerza muscular mas no la calidad de vida (50).

**D. Sin beneficio demostrado de la IgIV respaldado por evidencia obtenida en uno o más estudios clínicos controlados.**

15. Neuritis Óptica. La IgIV no es superior al placebo en la recuperación de la agudeza visual por neuritis óptica en sujetos con esclerosis múltiple (6).
16. Esclerosis Múltiple Secundariamente Progresiva. En 27 meses de seguimiento la IgIV no es superior al placebo en disminuir la discapacidad o la actividad de la enfermedad medida por resonancia magnética cerebral (8).
17. Miastenia Gravis Estable. La IgIV no es superior al placebo en el control del paciente con miastenia gravis estable (33).
18. Neuropatía Desmielinizante Asociada a Paraproteinemia. La IgIV es inferior al interferón alfa con peores puntajes en la escala de discapacidad utilizada. Efecto que se sostiene por 12 meses (41).
19. Miositis de Cuerpos de Inclusión. La IgIV no es superior al placebo demostrando un efecto mínimo en el control de los sintomas neuromusculares y recuperación de la fuerza muscular (46,47). El escaso efecto de la IgIV no se potencializa combinándola con prednisolona (48).

## REFERENCIAS


**1. Fazekas F, Strasser-Fuchs S, Nahler G, Marmoli B for the Austrian Immunoglobulin in Multiple Sclerosis.** Randomized placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis. *Lancet* 1997;349(9052):589-93.

**2. Achiron A, Gabbay U, Gilad R, et al.** Intravenous immunoglobulin treatment in multiple sclerosis. Effect on relapses. *Neurology* 1998; 50: 398-402.

**3. Lewanska M, Siger-Zajdel M, Selmaj K.** No difference in efficacy of two different doses of intravenous immunoglobulins in MS: clinical and MRI assessment. *Eur J Neurol* 2002; 9: 565-572..

**4. Sorensen PS, Wanscher B, Jensen CV, et al.** Intravenous immunoglobulin G reduces MRI activity in relapsing multiple sclerosis. *Neurology* 1998; 50: 1273-1281.

**5. Achiron A, Kishner I, Sarova-Pinhas I, Raz H, Faibel M, Stern Y, Lavie M, Gurevich M, Dolev M, Magalashvili D,** Barak Y. Intravenous immunoglobulin treatment following the first demyelinating event suggestive of multiple sclerosis: a randomized, double-blind, placebo-controlled trial. *Arch Neurol* 2004;61(10):**1515-20.**

**6. Noseworthy JH, O'Brien PC, Petterson TM, Weis J, Stevens L, Peterson WK, Sneve D, Cross SA, Leavitt JA, Auger RG, Weinshenker BG, Dodick DW, Wingerchuk DM, Rod**riguez M. A randomized trial of intravenous immunoglobulin in inflammatory demyelinating optic neuritis. *Neurology* 2001;56(11):1514-22.

**7. Kalanie H, Gharagozli K, Hemmatie A, Ghorbanie M, Kalanie AR.** Interferon Beta-1a and intravenous immunoglobulin treatment for multiple sclerosis in Iran. *Eur Neurol* 1906; 52: **202-206.**

**8. Hommes OR, Sorensen PS, Fazekas F, Enriquez MM, Koelmel HW, Fernandez O, Pozzilli C, O'**Connor P. Intravenous immunoglobulin in secondary progressive multiple sclerosis: randomised placebo-controlled trial. *Lancet* 2004:364(9440):**1149-56.**

**9. Gray OM, McDonnell GV,** Forbes RB. Intravenous immunoglobulin for multiple sclerosis (Cochrane Review). In The Cochrane Library, Issue 1, 2006. Oxford: Update Software.

**10. van der Meche FG, Schmitz PI.** A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barre syndrome. Dutch Guillain-Barre Study Group. *N Engl J Med* 1992; 326: 1123-1129.

**11.** Anonymous Randomized trial of plasma exchange, intravenous immunoglobulin, and combined treatments in

Guillain-Barre syndrome. Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group. *Lancet* 1997; 349: 225-230.

**12. Diener HC, Haupt WF, Kloss TM, et al.** A preliminary, randomized, multicenter study comparing intravenous immunoglobulin, plasma exchange, and immune adsorption in Guillain-Barre syndrome. *Eur Neurol* 2001; 46: 107-109.

**13. Bril V, WK Ilse, R Pearce, A Dhanani, D Sutton and K Kong** Pilot trial of immunoglobulin versus plasma exchange in patients with Guillain-Barre syndrome. Neurology, Vol 46, Issue 1 100-103.

**14. van Koningsveld R, Schmitz PI, Meche FG, Visser LH, Meulstee J, van Doorn PA.** Effect of methylprednisolone when added to standard treatment with intravenous immunoglobulin for Guillain-Barre syndrome: randomised trial. *Lancet* 2004; 363: 192-196.

**15.** Anonymous Treatment of Guillain-Barre syndrome with high-dose immune globulins combined with methylprednisolone: a pilot study. The Dutch Guillain-Barre Study Group. *Ann Neurol* 1994; 35: 749-752.

**16. Raphael JC, Chevret S, Harboun M, Jars-Guincestre MC.** Intravenous immune globulins in patients with Guillain-Barre syndrome and contraindications to plasma exchange: 3 days versus 6 days. *J Neurol Neurosurg Psychiatry* 2001; 71: 235-238.

**17. Korinthenberg R, Schessl J, Kirschner J, Monting JS.** Intravenously administered immunoglobulin in the treatment of childhood Guillain-Barre syndrome: a randomized trial. *Pediatrics* 2005; 116: 8-14.

**18. Gurses N, Uysal S, Cetinkaya F, Islek I, Kalayci AG.** Intravenous immunoglobulin treatment in children with Guillain-Barre syndrome. *Scand J Infect Dis* 1995; 27: 241-243.

**19. Hughes RAC, Raphaël J-C, Swan AV, van Doorn PA.** Intravenous immunoglobulin for Guillain-Barré syndrome (Cochrane Review). In The Cochrane Library, Issue 1, 2006. Oxford: Update Software.

**20. Mendell JR, Barohn RJ, Freimer ML, et al.** Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology* 2001; 56: 445-449.

**21. Vermeulen M, PA van Doorn, A Brand, PF Strengers, FG Jennekens and HF Busch.** Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy: a double blind, placebo controlled study Journal of Neurology, Neurosurgery, and Psychiatry, 1993, Vol 56, 36-39.

**22. Hahn AF, Bolton CF, Zochodne D, Feasby TE.** Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy. A double-blind, placebo-controlled, cross-over study. *Brain* 1996; 119: 1067-1077.

**23. Thompson N, Choudhary P, Hughes RA, Quinlivan RM.** A novel trial design to study the effect of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol* 1996; 243: 280-285.

**24. Hughes R, Bensa S, Willison H, et al.** Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 2001; 50: 195-201

**25. Dyck PJ, Litchy WJ, Kratz KM, et al.** A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 1994; 36: 838-845.

**26. van Schaik IN, Winer JB, de Haan R, Vermeulen M.** Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy (Cochrane Review). In The Cochrane Library, Issue 1, 2006. Oxford: Update Software.

**27. Federico P, Zochodne DW, Hahn AF, Brown WF, Feasby TE.** Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study. *Neurology* 2000; 55: 1256-1262.

**28. Leger JM, Chassande B, Musset L, Meininger V, Bouche P, Baumann N. Int**ravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. *Brain* 2001; 124: 145-153.

**29. Azulay JP, Blin O, Pouget J, Boucraut J, Billé-Turc F, Carles G, et al.** Intravenous immunoglobulin treatment in patients with motor neuron syndromes associated with anti-GM1 antibodies: a double-blind, placebo-controlled study. *Neurology 199*4; 44: 429-432.

**30. van den Berg LH, Kerkhoff H, Oey PL, et al.** Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study. *J Neurol Neurosurg Psychiatry* 1995; 59: 248-252.

**31. van den Berg LH, Franssen H, Wokke JH.** The long-term effect of intravenous immunoglobulin treatment in multifocal motor neuropathy. *Brain* 1998; 121: 421-428.

**32. Van Schaik IN, va der Berg LH, de Haan R, Vermeulen M.** Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy (Cochrane Review). In The Cochrane Library, Issue 1, 2006. Oxford: Update Software.

**33. Wolfe GI, Barohn RJ, Foster BM, Jackson CE, Kissel JT, Day JW, Thornton CA, Nations SP, Bryan WW, Amato AA, Freimer ML, Parry GJ.** Myasthenia Gravis-IVIG Study Group. Randomized, controlled trial of intravenous immunoglobulin in myasthenia gravis. *Muscle Nerve* 2002;26:549-52.

**34. Ronager J, Ravnborg M, Hermansen I, Vorstrup S.** Immunoglobulin treatment versus plasma exchange in patients with chronic moderate to severe myasthenia gravis. *Artif Organs* 2001; 25:967-73.

**35. Gajdos P, Chevret S, Clair B, Tranchant C, Chastang C.** Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Myasthenia Gravis Clinical Study Group. *Ann Neurol* 1997;41:789-96.

**36. Gajdos P, Tranchant C, Clair B, Bolgert F, Eymard B, Stojkovic T, Attarian S, Chevret S.** Myasthenia Gravis Clinical Study Group. Treatment of myasthenia gravis exacerbation with intravenous immunoglobulin: a randomized double-blind clinical trial. *Arch Neurol* 2005;62:1689-93.

**37. Gajdos P, Chevret S, Toyka K.** Intravenous immunoglobulin for myasthenia gravis (Cochrane Review). In The Cochrane Library, Issue 1, 2006. Oxford: Update Software.

**38. Bain PG, Motomura M, Newsom-Davis J, et al.** Effects of intravenous immunoglobulin on muscle weakness and calcium-channel autoantibodies in the Lambert-Eaton myasthenic syndrome. *Neurology* 1996;

**39. Comi G, Roveri L, Swan A, et al.** A randomised controlled trial of intravenous immunoglobulin in IgM paraprotein associated demyelinating neuropathy. *J Neurol* 2002; 249: 1370-1377.

**40. Dalakas MC, Quarles RH, Farrer RG, Dambrosia**

**J, Soueidan S, Stein DP, Cupler E, Sekul EA, Otero C.** A controlled study of intravenous immunoglobulin in demyelinating neuropathy with IgM gammopathy. *Ann Neurol* 1996; 40:792-5.

**41. Mariette X, Chastang C, Clavelou P, Louboutin JP, Leger JM, Brouet JC.** A randomised clinical trial comparing interferon-alpha and intravenous immunoglobulin in polyneuropathy associated with monoclonal IgM. The IgM-associated Polyneuropathy Study Group. *J Neurol Neurosurg Psychiatry* 1997; 63: 28-34.

**42. Lunn MPT, Nobile-Orazio E.** Intravenous immunoglobulin for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies (Cochrane Review). In The Cochrane Library, Issue 1, 2006. Oxford: Update Software.

**44. Dalakas MC, Illa I, Dambrosia JM, et al.** A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med* 1993; 329: 1993-2000.

**45. Choy EH, Hoogendijk JE, Lecky B, Winer JB.** Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis (Cochrane Review). In: The Cochrane Library, Issue 1, 2006.Oxford: Update Software.

**46. Walter MC, Lochmuller H, Toepfer M, et al.** High-dose immunoglobulin therapy in sporadic inclusion body myositis: a double-blind, placebo-controlled study. *J Neurol* 2000; 247: 22-28.

**47. Dalakas MC, Sonies B, Dambrosia J, Sekul E, Cupler E, Sivakumar K.** Treatment of inclusion-body myositis with IVIg: a double-blind, placebo-controlled study. *Neurology* 1997; 48: 712-716.

**48. Dalakas MC, Koffman B, Fujii M, Spector S, Sivakumar K, Cupler E.** A controlled study of intravenous immunoglobulin combined with prednisone in the treatment of IBM. *Neurology* 2001; 56: 323-327.

**49. Dalakas MC, Fujii M, Li M, Lutfi B, Kyhos J, McElroy B.** High-dose intravenous immune globulin for stiff-person syndrome. *N Engl J Med* 2001 Dec 27; 345:1870-6.

**50. Gonzalez H, Stibrant Sunnerhagen K, Sjoberg I, Kaponides G, Olsson T, Borg K.** Intravenous immunoglobulin for post-polio syndrome: a randomised controlled trial. *Lancet Neurol.* 2006;5:493-500.

**51. Vukusic S, Confavreux C.** pregnancy and multiple sclerosis: The children of PRIMS. *Clinical Neurology and Neurosurgery* 2006;108:266-270.

**52. Confevreux C.** Intravenous inmunoglobulins, pregnancy and multiple sclerosis. *J Neurol* 2004; 251: 1138 -1 139.

**53. Ferrero S, Pretta S, Ragn N.** Multiple sclerosis: management issues during pregnancy. European Joumal of Obstetrics and Gynecology and Reproduction Biology 2004; 115: 3 - 9.

**54. Hugles RAC, Wijdicks EFM, Barohn R.et al.** Practice parameter: Immunotherapy for Guillain - Barré syndrome. Report of the Quality standards subcommittee of the American Academy of Neurology. *Neurology* 2003; 61: 736-740.

**55. Lamont P J, Johnston H M, Berdoukas VA.** Plasmapheresis in children with Guillain- Barré Syndrome *Neurology* 1991; 41: 1928 - 1931.

**56. Abd - Allah SA, Jansen PW, Ashwal S, Perkin RM .** Intravenous immunoglobulin as therapy for pediatric Guillain - Barré syndrome *J Child Neurol* 1997; 12: 376 -380.

**57. GreenDM**. Weaknessin tIle ICU,Guillain- Barré syndrome Myasthenia gravis and critical iIIness Poly neuropathy I myopathy *The Neurologist* 2005; 11:338 -347.

**58.** The Guillain - Barré syndrome Study Group. Plasmapheresis and acute Guillain -Barré syndrome. N*eurology* 1985; 35: 1096 -1104.

**59.** French Cooperative Group on Plasma Exchange in Guillain -Barré syndrome Role of replacement fluids. *Ann Neurol* 1987; 22:753 - 761.

**60. Van Doom, Vermenlen M, Brand E, et al.** Intravenosis immunoglobulin treatment in patients with chronic inflammatory demyelinatig polyneuropathy. Clinical and laboratory characteristics associated with improvemnet. *Arch Neuro1* 1991; 48: 217.

**61. Chaudry V, Corse AM, Comblath A, et al.** Multifocal Motor Neuropathy: response to human immune globulin *Ann Neurol* 1993; 33: 237 - 242.

**62. Cosi V, Lonbardi M, Piccolo G et al.** Treatment of myasthenia gravis with high dose intravenosis immunoglobulin. *Acta Neurol Scand* 1991; 84: 81- 84.

**62. Hart YM, Cortez M, Anderman F, Hwang P, Fish DR, Dulac O, Silver IL, et al.** Medical treatment of Rasmusen's syndrome (chonic encephalitis and epilepsy): effect of high - dose steroids or immunoglobulins in 19 patients. Neurology 1994; 44: 1030 -1036.

**63. Pascuazzi RM.** Pearls and Pitfalls in the Diagnosis and Management of Neuromuscular Junction Disease. *Seminars in Neurology* 2001; 21:425 -439.

**63. Carabello R. Tenembaum S, Cerosimo R et al.** Rasmusen's syndrome. *Rev Neurol (Madrid)* 1998; 26:978- 983.

**64. Leach JP, Chadwick DW, Miles JB, Hart JK.** Improvement in adult onset Rasmusen's encephalitis with long - term immunomodulatory therapy. *Neurology* 1999; 52 738 - 742.

**64. Bird SJ.** Clinical and electrophysiologicimprovement in the Lambert - Eaton syndrome wiyh intravenous immunoglobulin therapy. *Neurology* 42: 1422, 1992.

**65. Miller AE, Cogle PK.** Clínical Jeatures J Multiple Sclerosis. Contínuum, Multiple Sclerosis. 2004; 10:64.

**66. Espinoza - Zacarias, Gutierrez - Modezuma. J Villegas- Peña H, Olmos G de Alba G.** Tratamiento intravenoso con inmunoglobulina en síndromes epilépticos de difícil control. *Rev Neurol* 2002; 34: 816 -9.

## ANEXO 1

Bogotá, 21 de septiembre de 2006

Doctor
**Javier Torres Zafra**
Presidente
Asociación Colombiana de Neurología
Ciudad

Señor Presidente:

Con base en el material desarrollado por el doctor Luis Morillo Z, y los aportes de los capítulos regionales en relación con la utilidad de la inmunoglobulina intravenosa en enfermedades del sistema nervioso central y periférico, para uso intra hospitalario podemos concluir lo siguiente:

Hay suficiente evidencia basada en revisiones sistemáticas y ensayos clínicos aleatorizados para recomendar el uso de la inmunoglobulina intravenosa en las siguientes patologías:

- Síndrome de Guillain Barre o neuropatía desmielinizante aguda
- Esclerosis múltiple tipo remisiones y recaídas (EMRR), particularmente durante el embarazo
- Neuropatía desmielinazante crónica
- Crisis miasténica

Hay evidencia basada en estudios clínicos aleatorizados con muestra pequeña que sugieren que puede ser beneficiosa la inmunogloblina intravenosa en:

- Dermatomiositis y polimiositis
- Neuropatía motora multifocal
- Síndrome de Lambert Eaton
- En la miastenia grave estable moderada o severa

Hay evidencia en un solo estudio clínico aleatorizado en:

- Síndrome post polio
- Síndrome de la persona rígida

No se recomienda en:

- Miositis de cuerpos de inclusión
- En las neuropatías asociadas a paraproteinemias
- En la esclerosis múltiple secundaria progresiva

Hay información basada en series de casos aislados en:

- Encefalomielitis aguda diseminada tanto en adultos como en niños
- Algunos síndromes epilépticos como la encefalitis de Rasmusen
- Síndrome de Lennox Gastaut
- Síndrome de Landau Klefnner
- Síndrome de West o espasmos infantiles
- Algunas vasculitis sistémicas con compromiso de sistema nervioso central o periférico: lupus eritematoso sistémico, Sjogren, granulomatosis de Wegener, Churg-Strauss y panarteritis nodosa.
- Vasculitis aisladas del sistema nervioso central o periférico

Es importante tener en cuenta estudios de costo efectividad en intervenciones en salud. Esto no quiere decir que hay que preferir "tratamientos baratos" a "tratamientos caros". Hay que examinar los resultados finales de invertir dinero, que en salud siempre es limitado en un escenario comparado con otro. Un tratamiento costoso puede producir mejores desenlaces y por ello ser considerado costo efectivo. Adicionalmente un tratamiento que aparenta ser costoso puede reducir costos mas adelante en sistemas de salud.

Es importante resaltar la baja incidencia de efectos secundarios serios en la terapia de inmunoglobulina intravenosa en comparación con la terapia con esteroides, inmunosupresores o plasmaféresis.

Hay que destacar que para algunas de las patologías anteriormente descritas hay

un bajo nivel de evidencia, por el hecho de que corresponden a patologías de muy baja prevalencia, lo cual dificulta el poder contar con estudios de mejor poder y validez. Representan además patología compleja y de alta morbimortalidad, lo cual da validez a los reportes y series de casos.

Como puede verse por lo anterior estas indicaciones están basadas en un trabajo colectivo nacional que ha incluido a miembros de la Asociación Colombiana de Neurología, sus capítulos y expertos que utilizaron una metodología reconocida en la investigación clínica permitiendo llegar a conclusiones objetivas que sólo pretenden mejorar el ejercicio de la neurología en beneficio de los pacientes.

Reciba un cordial saludo, atentamente,

**PABLO LORENZANA POMBO**
**FEDERICO SILVA SIEGER**
**ANGELA M. GUTIERREZ ALVAREZ**

## ANEXO 2

### ACTA NO. 03-06

Los Médicos Neurólogos, miembros del capitulo Costa Atlántica de la ASOCIACION COLOMBIANA DE NEUROLOGÍA, reunidos en sesión ordinaria el día 19 de Agosto del presente año, para analizar la investigación realizada por el Dr. Luís Morillo consistente en demostrar, basado en la evidencia, la efectividad de la gammaglobulina humana en el tratamiento de varias enfermedades neurológicas que pueden causar gran discapacidad o la muerte a las personas que las padezcan, concluyen por consenso:

Que están de acuerdo en toda su extensión con la efectividad del medicamento en todas las patologías Neurológicas que allí aparecen que la evidencia es contundente cuando se revisa la extensa bibliografía aportada, y que se hace imperativo que los neurólogos y la Asociación Colombiana de Neurología, cumplan con lo ordenado en la Constitución de la Republica de Colombia, en la Ley 100/93 y en los estatutos, que no es otra que la de brindar una atención de calidad y siempre con los últimos avances de la neurología.

En constancia se firma en Barranquilla a los 19 días del mes de agosto de 2006, por el Presidente del Capitulo Costa Atlántica de la Asociación Colombiana de Neurología, después de haber sido aprobada por unanimidad esta acta por los miembros asistentes, quienes conformaron Quórum.

**JOSE VARGAS**
**Presidente Capítulo Costa Atlántica**

## ANEXO 3

Bogota 31 de Julio del 2006

Doctor
**Javier Torres Zafra**
Presidente
Asociación Colombiana de Neurología

Estimado Doctor:

De acuerdo a sus instrucciones se llevo acabo la difusión de la revisión sistemática de la bibliografía acerca del uso de las Inmunoglobulinas en enfermedades Neurológicas.

Dicha difusión se realizó por vía Email a los integrantes de la Asociación Colombiana de Neurología región Bogotá y que participan en la reunión de Neurofisiología. La cual se realizo el día 28 de Julio del 2006 en la clínica Marly y entre los asistentes se realizaron las siguientes recomendaciones:

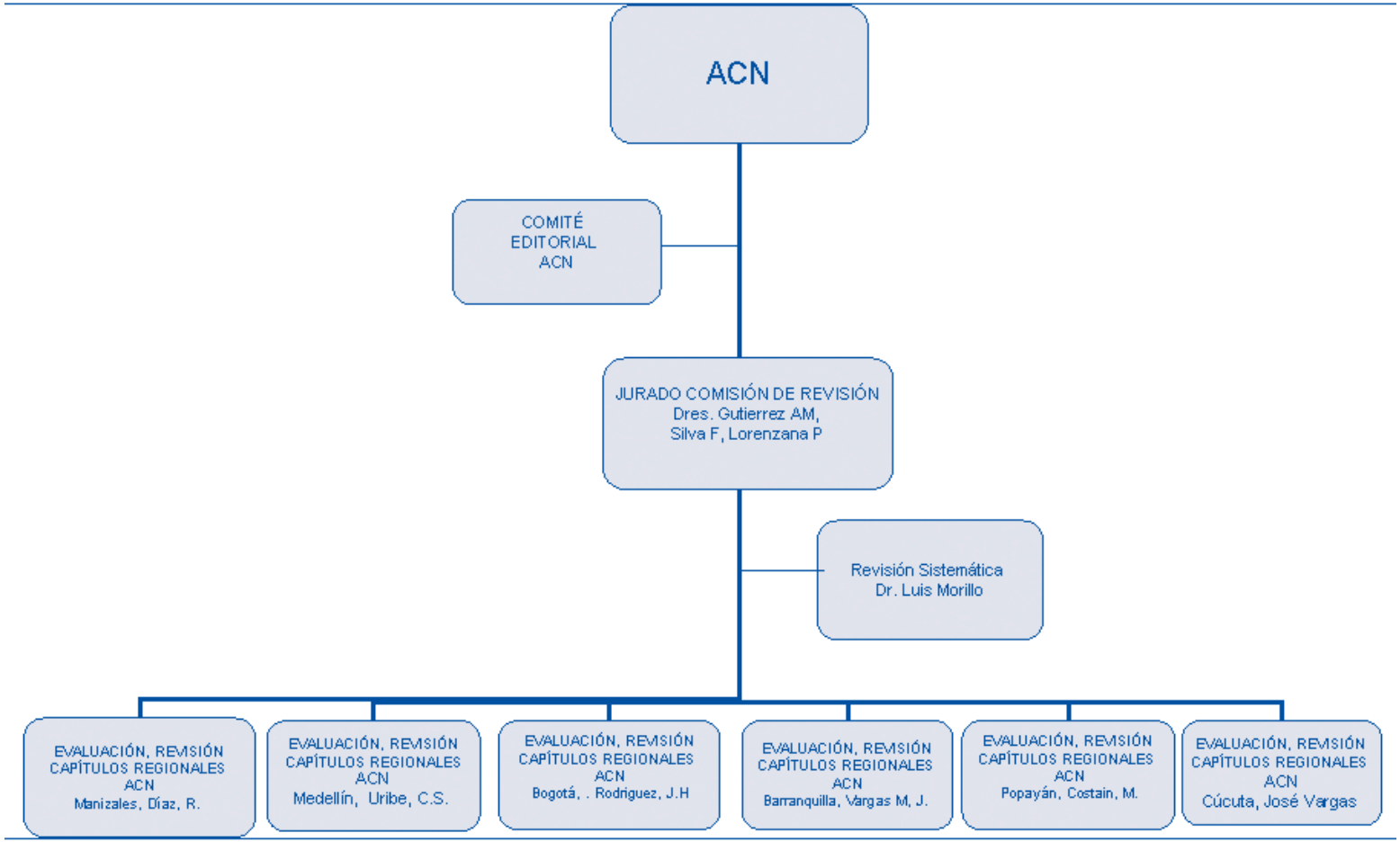
1. No se recomienda colocar en el documento final al INVIMA el nivel de evidencia ya que esto podría fortalecer el uso de inmunoglobulinas en algunas patologías pero debilitaría su uso en otras en donde por lo infrecuente de las enfermedades y series cortas, podría perjudicar a los médicos neurólogos que acudieran a el uso de estos medicamentos ante las EPS.
2. El uso de las inmunoglobulinas en patologías neurológicas por su ventaja como relativos bajos efectos secundarios y riesgos de uso frente a otras alternativas terapéuticas debe quedar resaltada especialmente en aquellos casos en que los pacientes puedan correr el riego de tener un aumento de la morbimorta1idad con las otras alternativas.
3. El uso de inmunoglobulinas siempre debe ser intrahospitalario, bajo la monitoria o supervisión de un médico neurólogo/ neuropediatra
4. Se debe incluir dentro de las indicaciones el uso de la inmunoglobulina en la encefalitis aguda diseminada, patología con buen nivel de evidencia en neuropediatria

Además anexo los comentarios enviados por el Dr. Lorenzana quien los envió por escrito y listado de asistentes con sus firmas.

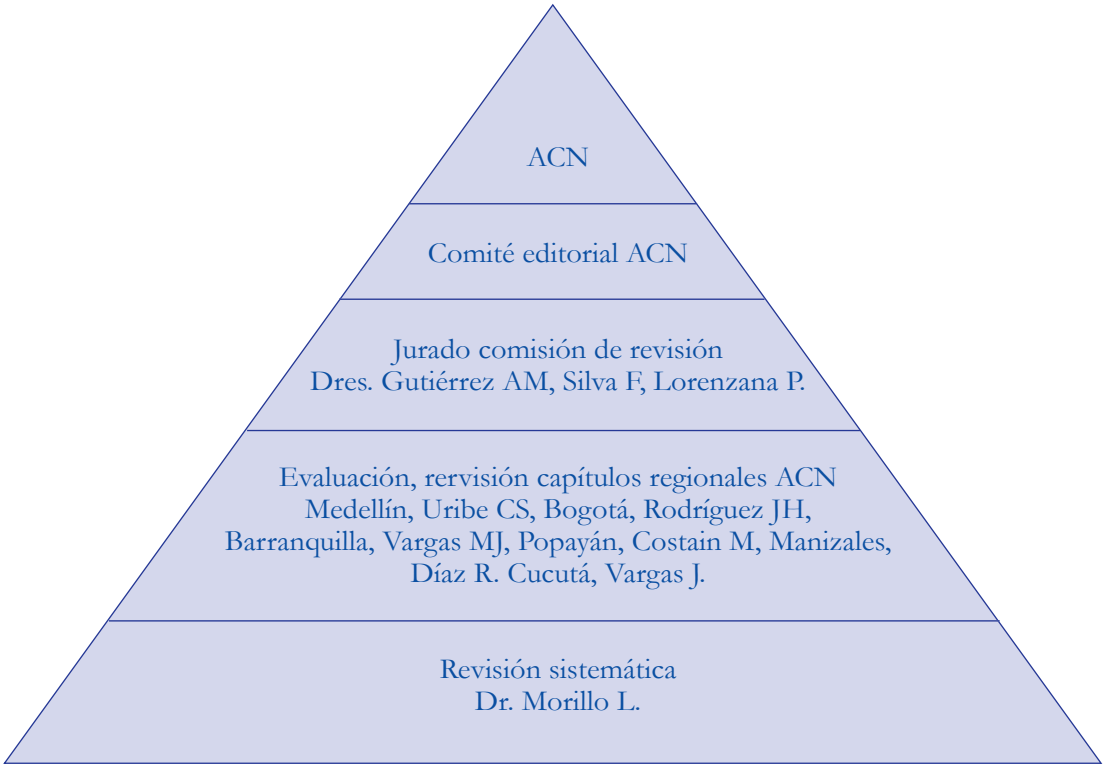
Espero haber podido cumplir con las expectativas de su encargo,

**Jesús Hernán Rodríguez Q. MD.**
**Neurólogo, Neurofisiólogo**

## ANEXO 4.
## Esquema de trabajo sobre la utilidad de la inmunoglobulina intravenosa (IgIV) en enfermedades del sistema nervioso central y periférico: revisión sistemática de la literatura.



**ANEXO 5.**
**Propuesta de difusión y análisis de la información sobre la utilidad de la inmunoglobulina intravenosa (IgIV) en enfermedades del sistema nervioso central y periférico: revisión sistemática de la literatura.**



## ANEXO 6.

### Bibliografía obtenida en la búsqueda sistemática


• **Achiron A.** Complications of intravenous immune globulin treatment in neurologic disease. *Neurology* 1997; 49: 899-900.

• **Achiron A, Gabbay U, Gilad R, et al.** Intravenous immunoglobulin treatment in multiple sclerosis. Effect on relapses. *Neurology* 1998; 50: 398-402.

**Abstract:** We conducted a double-blind, placebo-controlled study of 40 patients (aged 19 to 60 years) with clinical definite relapsing remitting (RR) MS and brain MRI confirmed. Patients were randomly assigned to receive a loading dose of immunoglobulin IgG (0.4 g/kg/body weight per day for 5 consecutive days), followed by single booster doses (0.4 g/kg/body weight) or placebo once every 2 months for 2 years. The primary outcome measures were change in the yearly exacerbation rate (YER), proportion of exacerbation-free patients, and time until first exacerbation. Neurologic disability, exacerbation severity, and changes in brain MRI lesion score were the secondary outcome measures, all determined at baseline, 1 year, and on completion. Treated patients showed a reduction in YER from 1.85 to 0.75 after 1 year and 0.42 after 2 years versus 1.55 to 1.8 after 1 year and to 1.4 after 2 years in the placebo group ($p = 0.0006$, overall), reflecting a 38.6% reduction in relapse rate. Six patients in the IVIg group were exacerbation free throughout the 2-year period of the study, whereas none were exacerbation free in the placebo group. The median time to first exacerbation was 233 days in the IVIg group versus 82 days in the placebo group ($p = 0.003$). Neurologic disability as measured by the Expanded Disability Status Scale (EDSS score) decreased by 0.3 in the IVIg group and increased by 0.15 in the placebo group. Total lesion score evaluated by brain MRI did not show a significant difference between groups. Side effects were minor and occurred in only 19 of 630 (3.0%) infusions administered in both groups. Our results suggest that IVIg may be safe and effective in reducing the frequency of exacerbations in RR-MS.

• **Achiron A, Kishner I, Sarova-Pinhas I, et al.** Intravenous immunoglobulin treatment following the first demyelinating event suggestive of multiple sclerosis: a randomized, double-blind, placebo-controlled trial. *Arch Neurol* 2004; 61: 1515-1520.

**Abstract: BACKGROUND:** Intravenous immunoglobulin (IVIg) has been reported to reduce disease activity in patients with relapsing-remitting multiple sclerosis. We assessed the effect of IVIg treatment in patients after the first neurological event suggestive of demyelinative disease and evaluated the occurrence of a second attack and dissemination in time demonstrated by brain magnetic resonance imaging within the first year from onset. **METHODS**: We conducted a randomized, placebo-controlled, double-blind study in 91 eligible patients enrolled within the first 6 weeks of neurological symptoms. Patients were randomly assigned to receive IVIg treatment (2-g/kg loading dose) or placebo, with boosters (0.4 g/kg) given once every 6 weeks for 1 year. Neurological and clinical assessments were done every 3 months, and brain magnetic resonance imaging was performed at baseline and the end of the study. **RESULTS:** The cumulative probability of developing clinically definite multiple sclerosis was significantly lower in the IVIg treatment group compared with the placebo group (rate ratio, 0.36 [95% confidence interval, 0.15-0.88]; $P = .03$). Patients in the IVIg treatment group had a significant reduction in the volume and number of T2-weighted lesions and in the volume of gadolinium-enhancing lesions as compared with the placebo group ($P = .01$, $P = .01$, and $P = .03$, respectively). Treatment was well tolerated, compliance was high, and incidence of adverse effects did not differ significantly between groups. **CONCLUSIONS:** Intravenous immunoglobulin treatment for the first year from onset of the first neurological event suggestive of demyelinative disease significantly lowers the incidence of a second attack and reduces disease activity as measured by brain magnetic resonance imaging.

• **Ahn SY, Kim DS.** Treatment of intravenous immunoglobulin-resistant Kawasaki disease with methotrexate. *Scand J Rheumatol* 2005; 34: 136-139.

**Abstract: OBJECTIVE:** To evaluate the effect of low-dose oral methotrexate (MTX) as treatment for patients with Kawasaki disease (KD) resistant to intravenous immunoglobulin (IVIG). METHODS: The subjects were four patients with KD, aged 8 months to 8 years old, who showed persistent disease after treatment with high-dose IVIG (2 g/kg) and aspirin (100 mg/kg). These patients were re-treated with IVIG and were also treated with

IV dexamethasone (0.3 mg/kg). IV dexamethasone induced defervescence in three patients, but fever recurred upon discontinuing the steroid. One patient showed no response to either IVIG or dexamethasone. All patients were subsequently treated weekly with low-dose oral MTX [10 mg/body surface area (BSA)]. **RESULTS:** MTX treatment resulted in rapid defervescence, improvement in clinical symptoms, and normalization of acute-phase reactants in all patients. There was no progression of coronary artery dilatation and MTX was discontinued with no recurrence of fever. No adverse effects of MTX were observed. **CONCLUSION:** Low-dose oral MTX is an effective treatment for refractory KD.

• **Allos BM.** Association between Campylobacter infection and Guillain-Barre syndrome. *J Infect Dis* 1997; 176 Suppl 2: S125-S128

**Abstract:** Guillain-Barre syndrome (GBS), a neurologic disease that produces ascending paralysis, affects people all over the world. Acute infectious illnesses precede 50%-75% of the GBS cases. Although many infectious agents have been associated with GBS, the strongest documented association is with Campylobacter infection. The first line of evidence supporting Campylobacter infection as a trigger of GBS is anecdotal reports. The second line of evidence is serologic surveys, which have demonstrated that sera from GBS patients contain anti-Campylobacter jejuni antibodies, consistent with recent infection. Finally, culture studies have proven that a high proportion of GBS patients have C. jejuni in their stools at the time of onset of neurologic symptoms. Neurologic symptoms are more severe and more likely to be irreversible when GBS is preceded by C. jejuni infection. One of every 1058 Campylobacter infections results in GBS, and 1 of 158 Campylobacter type O:19 infections results in GBS.

• **Anonymous.** Plasma exchange in Guillain-Barre syndrome: one-year follow-up. French Cooperative Group on Plasma Exchange in Guillain-Barre Syndrome. *Ann Neurol* 1992; 32: 94-97.

**Abstract:** We report the one-year assessment of plasma exchange (PE) versus control in Guillain-Barre syndrome (GBS), based on a randomized multicenter clinical trial of 220 patients with GBS. Treated patients received four PEs, with either albumin or fresh frozen plasma (FFP) as replacement fluid. This study completes the short-term analysis previously published (Ann Neurol 1987;22: 753-761). Long-term benefit from PE was observed, as demonstrated by full muscular strength recovery at one year: 71% in the PE group versus 52% in the control group ($p = 0.007$), confirmed after adjustment for four prognostic factors. FFP showed no additional benefit compared with albumin (77% full recovery in the FFP group versus 65% in the albumin group; $p = 0.22$). PE did not affect the incidence of severe motor disability (11% in both groups).

• **Anonymous.** Double-blind trial of intravenous methylprednisolone in Guillain-Barre syndrome. Guillain-Barre Syndrome Steroid Trial Group. *Lancet* 1993; 341: 586-590.

**Abstract:** Steroids have been beneficial in the treatment of demyelinating diseases with features similar to those of Guillain-Barre syndrome (GBS). However, steroid treatment of GBS has been disappointing; in an earlier trial oral prednisolone was ineffective, although the dose was low and the sample small. We assessed the benefit of a high-dose steroid regimen in a large sample of patients with GBS in a multicentre, randomised, double-blind trial. 242 adult patients were randomised to receive intravenous methylprednisolone (IVMP) 500 mg (124 patients) or a placebo (118) daily for 5 days. Patients were diagnosed by standard clinical criteria and entered the trial within 15 days of onset of neurological symptoms. All patients were too weak to run. Some patients received plasma exchange depending on the practice of their centre. Disability was graded on a scale from 0 (healthy) to 6 (dead) at intervals for 48 weeks. There was no significant difference in any outcome variable between patients treated with IVMP and those given placebo. The most important outcome was the difference between the groups in disability grade 4 weeks after randomisation, which was only a 0.06 grade (95% Cl -0.23 to 0.36) greater improvement in the IVMP than the placebo group. The 39 patients in the IVMP group who required ventilation did so for a median of 18 days, 9 days fewer than the 44 patients who had a placebo and required ventilation (95% Cl -9.6 to 27.6). Median time to walk unaided was 38 days in the IVMP patients and 50 days in the placebo patients (difference 12 days, (95% Cl -21.3 to 45.3). A short course of high-dose IVMP given early in GBS is ineffective.

• **Anonymous.** Treatment of Guillain-Barre syndrome with high-dose immune globulins combined with methylprednisolone: a pilot study. The Dutch Guillain-Barre Study Group. *Ann Neurol* 1994; 35: 749-752.

**Abstract:** In an open study 25 patients with Guillain-Barre syndrome were treated for 5 days with intravenous immune globulins in a dose of 0.4 gm/kg of body weight/day and 0.5 gm of methylprednisolone intravenously per day. The results of this combined treatment were compared with the results from a group of 74 patients who were treated with immune globulins only in a recent Dutch Guillain-Barre trial. In the methylprednisolone-immune globulin treatment group, 19 of 25 patients (76%) improved by one or more functional grades after 4 weeks, as compared with 39 (53%) of 74 patients treated with immune globulin alone ($p = 0.04$). Also the median time required to the stage of walking independently was reduced in the methylprednisolone-immune globulin treatment group. This pilot study suggests that combined treatment with methylprednisolone and immune globulins in patients with the Guillain-Barre syndrome is more effective than treatment with immune globulins alone; a randomized clinical trial might confirm this.

- **Anonymous.** Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barre syndrome. Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group. *Lancet* 1997; 349: 225-230.

**Abstract: BACKGROUND:** The relative efficacy of plasma exchange (PE) and intravenous immunoglobulin (IVIg) for the treatment of Guillain-Barre syndrome has not been established. We compared PE with IVIg, and with a combined regimen of PE followed by IVIg, in an international, multicentre, randomised trial of 383 adult patients with Guillain-Barre syndrome. **METHODS:** The patients were randomly assigned PE (five 50 mL/kg exchanges over 8-13 days), IVIg (Sandoglobulin, 0.4 g/kg daily for 5 days), or the PE course immediately followed by the IVIg course. The inclusion criteria were severe disease (aid needed for walking) and onset of neuropathic symptoms within the previous 14 days. Patients were followed up for 48 weeks. **FINDINGS:** Four patients were excluded because they did not meet the randomisation criteria. All the remaining 379 patients were assessed for the major outcome criterion-change on a seven-point disability grade scale-by an observer unaware of treatment assignment, 4 weeks after randomisation. At that time, the mean improvement was 0.9 (SD 1.3) in the 121 PE-group patients, 0.8 (1.3) in the 130 IVIg-group patients, and 1.1 (1.4) in the 128 patients who received both treatments (intention-to-treat analysis). None of the differences between the groups for this major outcome criterion was significant. The difference between PE alone and IVIg alone was so small that a 0.5 grade difference was excluded at the 95% level of confidence. There was no significant difference between any of the treatment groups in the secondary outcome measures: time to recovery of unaided walking, time to discontinuation of ventilation, and trend describing the recovery from disability up to 48 weeks. There was a non-significant trend towards a more favourable outcome on some outcome measures with combined treatment. **INTERPRETATION:** In treatment of severe Guillain-Barre syndrome during the first 2 weeks after onset of neuropathic symptoms, PE and IVIg had equivalent efficacy. The combination of PE with IVIg did not confer a significant advantage.

- **Anonymous.** Appropriate number of plasma exchanges in Guillain-Barre syndrome. The French Cooperative Group on Plasma Exchange in Guillain-Barre Syndrome. *Ann Neurol* 1997; 41: 298-306.

**Abstract:** Plasma exchange (PE) is the standard treatment in Guillain-Barre syndrome (GBS) patients who have lost the ability to walk. The effect of exchanges before this stage and the optimal number of exchanges for the other patients are still unknown. We randomized 556 GBS patients according to severity and number of exchanges as follows: Zero versus 2 PEs for patients who could walk-with or without aid-but not run, or who could stand up unaided (mild group); 2 versus 4 PEs for patients who could not stand up unaided (moderate group); and 4 versus 6 PEs for mechanically ventilated patients (severe group). In the mild group, 2 PEs were more effective than none for time to onset of motor recovery (median, 4 vs 8 days, respectively). In the moderate group, 4 PEs were more beneficial than 2 for time to walk with assistance (median, 20 vs 24 days) and for 1-year full muscle-strength recovery rate (64% vs 46%). Six PEs were no more beneficial than 4 in the severe cases. Patients with mild GBS on admission should receive 2 PEs. Patients with moderate and severe forms should benefit from 2 further exchanges.

- **Aries PM, Hellmich B, Gross WL.** Intravenous immunoglobulin therapy in vasculitis: speculation or evidence? *Clin Rev Allergy Immunol 2005; 29: 237-245.*

**Abstract:** Initially, intravenous immunoglobulins (IVIgs) were used as replacement therapy in primary and secondary antibody-deficiency syndromes. The

clinical use of IVIg has been extended during the past decade to a wide variety of clinical conditions, such as infectious processes, neuroimmunological diseases, and different systemic autoimmune diseases. The mode of action of IVIg is complex, involving modulation of the Fc receptors, interference with the complement and cytokine network, and effects on the activation and differentiation of T and B-cells. Kawasaki disease (KD) was one of the first diseases within the group of primary vasculitides in which IVIg were used. Today, there is a clear evidence of benefit for IVIg in the treatment of coronary artery abnormalities related to KD. Subsequently, various reports have suggested a beneficial effect in other vasculitides; however, there are few data from controlled studies. For antineutrophil cytoplasmic antibody-associated vasculitis (AAV) one placebo-controlled and several open-label studies have shown a beneficial effect on the disease activity in patients with Wegener's granulomatosis or microscopic polyangiitis refractory to standard therapy with prednisone and cyclophosphamide. For other vasculitides, such as polyarteritis nodosa or Henoch-Schonlein purpura, only case reports have described an inhibition of a disease progression by IVIg so far. However, the effect was partly only temporary. In conclusion, KD and AAV are the only vasculitides with a definite beneficial use of IVIg. For other vasculitides, the efficacy of IVIg has not been proven properly but may be useful in single cases.

• **Ayusawa M, Sonobe T, Uemura S, et al.** Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). *Pediatr Int* 2005; 47: 232-234.

**Abstract:** Diagnostic guidelines for Kawasaki Disease was revised to meet the present situation in 2002. This issue intends to explain new guidelines and their backgrounds. Major alterations are interpretation of cases with 4 or fewer febrile days shortened by early intravenous immunoglobulin treatment, and the clinical importance of atypical (incomplete, or suspected) cases.

• **Bain PG, Motomura M, Newsom-Davis J, et al.** Effects of intravenous immunoglobulin on muscle weakness and calcium-channel autoantibodies in the Lambert-Eaton myasthenic syndrome. *Neurology* 1996; 47: 678-683.

**Abstract:** Intravenous immunoglobulin improves many antibody-mediated autoimmune disorders, but its mode of action is unknown. We investigated its effects on muscle strength and on the serum titer of the calcium-channel autoantibodies that are likely to be pathogenic in the Lambert-Eaton myasthenic syndrome (LEMS). In a randomized, double-blind, placebo-controlled crossover trial, serial indices of limb, respiratory, and bulbar muscle strength and the serum titer of calcium-channel antibodies in nine patients were compared over an 8-week period, using the area-under-the-curve approach, following infusion on two consecutive days of immunoglobulin at 1 g/kg body weight/day (total dose 2.0 g/kg body weight) or placebo (equivalent volume of 0.3% albumin). Calcium-channel antibodies were measured by radioimmunoassay using 125I-omega-conotoxin MVIIC. Direct anti-idiotypic actions of immunoglobulin were tested in this assay. Immunoglobulin infusion was followed by significant improvements in the three strength measures ($p = 0.017$ to 0.038) associated with a significant decline in serum calcium-channel antibody titers ($p = 0.028$). Improvement peaked at 2 to 4 weeks and was declining by 8 weeks. Mean serum titers were unchanged at 1 week, however, and direct anti-idiotypic neutralization by immunoglobulin was not demonstrable in vitro. We conclude that immunoglobulin causes a short-term improvement in muscle strength in LEMS that probably results from the induced reduction in calcium-channel autoantibodies. The reduction is not due to a direct neutralizing action of the immunoglobulin, but a delayed anti-idiotypic action cannot be excluded. Improvement following intravenous immunoglobulin in other autoantibody-mediated disorders may similarly be associated with decline in levels of pathogenic autoantibodies.

• **Bensa S, Hadden RD, Hahn A, Hughes RA, Willison HJ.** Randomized controlled trial of brain-derived neurotrophic factor in Guillain-Barre syndrome: a pilot study. *Eur J Neurol* 2000; 7: 423-426.

**Abstract:** Brain-derived neurotrophic factor (BDNF) has the theoretical potential to protect neurones from axonal degeneration. The objective of this study was to discover whether brain-derived neurotrophic factor is safe in Guillain-Barre syndrome, and to make preliminary observations of its efficacy. This was a parallel group randomized controlled trial of subcutaneous brain-derived neurotrophic factor 25 microg/kg daily compared with placebo for up to 24 weeks or until patients could walk without aid. Six patients received brain-derived neurotrophic factor, of whom three had serious adverse events including one death. Four patients received placebo, of whom two had serious adverse events including one death.

The rate and extent of recovery were similar in the two groups. This pilot study did not detect any serious adverse events attributed to brain-derived neurotrophic factor treatment

• **Boman S, Ballen JL, Seggev JS.** Dramatic responses to intravenous immunoglobulin in vasculitis. *J Intern Med* 1995; 238: 375-377.

**Abstract:** Intravenous immunoglobulin (IVIG) has been successfully used to treat autoimmune diseases. We report dramatic, rapid and sustained responses to its use in two cases of vasculitis: a patient with primary angitis of the central nervous system: and a patient with hepatitis-B-antigen-related polyarteritis nodosa, who failed treatment with corticosteroids. Improvement in gait and a marked decrease in serum creatinine, respectively, were observed within 24 h of the first dose of IVIG. Both patients remained stable for several months. We conclude that IVIG should be considered in patients with vasculitis who fail corticosteroids, or when a rapid response is required.

• **Bouget J, Chevret S, Chastang C, Raphael JC.** Plasma exchange morbidity in Guillain-Barre syndrome: results from the French prospective, randomized, multicenter study. The French Cooperative Group. *Crit Care Med* 1993; 21: 651-658.

**Abstract: OBJECTIVES:** To describe all adverse events occurring during plasma exchange sessions in adult patients with the Guillain-Barre syndrome. To analyze these events with regard to the technical modalities and biological changes induced by sessions, and to try to identify a population at high risk for adverse events. **DESIGN:** Double-blind, randomized, prospective, multicenter trial. **SETTING:** A total of 28 French and Swiss intensive care units. **PATIENTS:** The study is based on 220 patients allocated either to plasma exchange (n = 109) or not (n = 111). This study focused on 105 patients who received at least one plasma exchange, with replacement fluid secondly allocated by randomization to albumin, or fresh frozen plasma. A total of 105 patients underwent 390 plasma exchanges. Fifty-five patients received albumin (208 sessions) as replacement fluid, and 50 patients received fresh frozen plasma (182 sessions). **INTERVENTIONS:** Prospective monitoring of patients for each session including technical modalities, adverse effects, and biological parameters. **MEASUREMENTS AND MAIN RESULTS:** A total of 253 adverse incidents were recorded. At least one adverse incident occurred in 39% of plasma exchange sessions among 80 (76%) patients. In 15 patients, plasma exchange treatment had to be discontinued because of severe intolerance (six patients, including three patients with severe bradycardias), intercurrent complications, mainly infections (four patients), and technical difficulties. One patient with pneumococcal septicemia and pneumonia died during the second plasma exchange session. Fresh frozen plasma was associated with more adverse incidents than albumin (135 vs. 118, p = .008). The occurrence of adverse events was also related to the preplasma exchange hemoglobin level assessed before the session (p = .04). Otherwise, the frequency of adverse effects did not depend on technical modalities (type of equipment, anticoagulation). Age, sex, previous history, neurologic severity, and the need for mechanical ventilation, as assessed on inclusion in the study, did not modify the risk of adverse effects. Finally, occurrence of bradycardia did not rely on initial neurologic severity. **CONCLUSIONS:** These results confirm that fresh frozen plasma should be abandoned as replacement fluid in plasma exchanges of Guillain-Barre syndrome patients. They also underline the need for close monitoring of patients during sessions and, especially, the respect of treatment contraindications. Some adverse incidents could be attributed to the underlying disease rather than to the plasma exchange session.

• **Bril V, Ilse WK, Pearce R, Dhanani A, Sutton D, Kong K.** Pilot trial of immunoglobulin versus plasma exchange in patients with Guillain-Barre syndrome. *Neurology* 1996; 46: 100-103.

**Abstract:** We compared intravenous immunoglobulin (IVIG) and plasma exchange (PLEX) in the treatment of 50 patients with Guillain-Barre syndrome (GBS). Standard outcome measures did not differ for the two groups. Sixty-one percent of the PLEX-treated group and 69% of the IVIG-treated group improved by one disability grade at 1 month. The complication rate was higher in the PLEX-treated group. We conclude that the efficacy of IVIG in the treatment of GBS is comparable with that of PLEX and that it can be used safely, although we had a small number of patients. We did not observe a higher relapse rate with IVIG. The usefulness of combination therapy is unknown at this time

• **Bril V, Allenby K, Midroni G, O'Connor PW, Vajsar J.** IGIV in neurology--evidence and recommendations. *Can J Neurol Sci* 1999; 26: 139-152.

**Abstract: OBJECTIVE:** To summarize the evidence for neurologic uses of immunoglobulin, intravenous (IGIV) in light of present-day clinical usage. This summary guided the development of practice recommendations for the effective and efficient use of IGIV in Neurology. **METHODS: MEDLINE** was searched to identify pertinent English-language review articles and original reports (n = 231) on the use of IGIV in neurology (excluding editorials, letters, and comments) published before March 1998. Evidence on alternative therapies was only included as compared to IGIV. The relevant original reports and review articles and older classic studies (n = 92) were synthesized into an information foundation. Extracted data included laboratory and clinical findings, objective measures, and clinical impressions. Clinical recommendations were based on evidence quality, graded by study design, clinical experiences of IGIV in Neurology Advisory Board members, and the conditions of IGIV use in therapy. **RESULTS AND CONCLUSIONS:** In neurology, many disorders are poorly understood, and the mechanisms behind beneficial regimens even less so. As a result, it is fairly common for best-practice decisions to rest on weaker evidence. The usefulness of IGIV in neurology can be described by a "combined score" based on evidence quality and strength of impact. Combined scores ranged from A+ (strongly recommended) to C (recommended as a last resort). The following clinical recommendations are made: IGIV is: strongly recommended for the treatment of Guillain-Barre syndrome (A+); favorably recommended for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy, dermatomyositis, and multifocal motor neuropathy (A); recommended as a second resort for the treatment of multiple sclerosis and myasthenia gravis (B); and recommended as a last resort for the treatment of polymyositis, inclusion-body myositis, intractable epilepsies, and stiff-man syndrome (C).

• **Brinar VV, Poser CM, Basic S, Petelin Z.** Sudden onset aphasic hemiplegia: an unusual manifestation of disseminated encephalomyelitis. *Clin Neurol Neurosurg* 2004; 106: 187-196.

**Abstract:** The association of the sudden onset of aphasia with hemiplegia, hemisenosry defect, and facial palsy, with MRI evidence of white matter lesions, requires differentiation between multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM). We have observed eight patients with such a syndrome, all of whom were originally diagnosed as multiple sclerosis, but who, on closer examination, turned out to be instances of disseminated encephalomyelitis. The patterns of demyelination seen in T2-weighted MRI are quite different in both conditions. In two of our patients, MRI reverted to normal after the treatment; in others, the images remained unchanged. A review of the reported cases of multiple sclerosis presenting with the acute onset of aphasia, reveals that the majority of them are, in reality, instances of acute disseminated encephalomyelitis with a much better prognosis. Most of these cases are monophasic and immunomodulatory treatment is inappropriate.

• **Bushra JS.** Miller Fisher syndrome: an uncommon acute neuropathy. *J Emerg Med* 2000; 18: 427-430.

**Abstract:** The syndrome of ophthalmoplegia, ataxia, and areflexia was first described in 1956 by Miller Fisher. This syndrome has long been believed to be a variant of Guillain-Barre syndrome (GBS), mainly because of its areflexia, cerebrospinal fluid findings, and its postinfectious presentation. The case of an 11-year-old male with Miller Fisher syndrome (MFS) is described. MFS differs from GBS in several key clinical features and presents an extensive and challenging differential diagnosis. It is useful to recognize MFS as both a variant of GBS and a distinct entity with its own therapeutic considerations.

• **Calabrese LH.** Clinical management issues in vasculitis. Angiographically defined angiitis of the central nervous system: diagnostic and therapeutic dilemmas. *Clin Exp Rheumatol* 2003; 21: S127-S130.

**Abstract:** A case of acute neurologic deficit accompanied by a cerebral angiogram consistent with CNS vasculitis is presented. The differential diagnosis and diagnostic decision process generated in this type of evaluation is illustrated

• **Caldemeyer KS, Smith RR, Harris TM, Edwards MK.** MRI in acute disseminated encephalomyelitis. *Neuroradiology* 1994; 36: 216-220.

**Abstract:** A retrospective analysis of CT and MRI studies in 12 patients with a clinical diagnosis of acute disseminated encephalomyelitis (ADEM) was performed. MRI was the definitive modality for the assessment of the lesions of ADEM: all patients had abnormalities consistent with the clinical diagnosis. Ten had abnormalities in the brain, three spinal cord lesions, and three showed evidence of optic neuritis.

CT was normal in 6 of the 7 patients in which it was performed.

- **Canhao H, Fonseca JE, Rosa A.** Intravenous gammaglobulin in the treatment of central nervous system vasculitis associated with Sjogren's syndrome. *J Rheumatol* 2000; 27: 1102-1103.

- **Choy EH, Hoogendijk JE, Lecky B, Winer JB.** Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis. *Cochrane Database Syst Rev* 1906; CD003643.

**Abstract: BACKGROUND:** Idiopathic inflammatory myopathies are chronic skeletal diseases with significant mortality and morbidity despite treatment by corticosteroids. Immunosuppressive agents and immunomodulatory therapy are used to improve disease control and reduce the long-term side effects of corticosteroids. While these treatments are used commonly in routine clinical practice, the optimal therapeutic regimen remains unclear. **OBJECTIVES:** To systematically review the evidence for the effectiveness of immunosuppressants and immunomodulatory treatments for dermatomyositis and polymyositis. **SEARCH STRATEGY:** We searched the Cochrane Neuromuscular Disease Group trials register (searched February 2002 and updated in November 2003) and MEDLINE (January 1966 to December 2002). We checked bibliographies of identified trials and wrote to disease experts. **SELECTION CRITERIA:** Randomised or quasi-randomised controlled trials including patients with probable or definite dermatomyositis and polymyositis as defined by the criteria of Bohan and Peter or definite, probable or mild/early by the criteria of Dalakas. Patients with inclusion body myositis should have been excluded by muscle biopsies. Any immunosuppressant or immunomodulatory treatment including corticosteroids, azathioprine, methotrexate, ciclosporin, chlorambucil, cyclophosphamide, intravenous immunoglobulin, interferon and plasma exchange was considered. Primary outcome was assessment of muscle strength after at least six months. Other outcomes were: change in disability, number of relapses and time to relapse, number of patients in remission and time-to-remission, cumulative corticosteroid dose and serious adverse effects. **DATA COLLECTION AND ANALYSIS:** Two authors (EC and JH) independently selected trials for inclusion in the review. Four authors independently assessed each study. Methodological criteria and the results of each study were recorded on data extraction forms. **MAIN RESULTS:** Seven potentially relevant randomised controlled trials were identified. One trial was excluded. Three studies compared immunosuppressant with placebo control, one trial compared one immunosuppressant (methotrexate) with another (azathioprine), another trial compared ciclosporin A with methotrexate and the final trial compared intramuscular methotrexate with oral methotrexate plus azathioprine. The study comparing intravenous immunoglobulin with placebo concluded that the former was superior. Two randomised placebo-controlled trials assessing plasma exchange, leukapheresis and azathioprine produced negative results. The fourth study compared azathioprine with methotrexate and found azathioprine and methotrexate equally effective but methotrexate had a better side effect profile. The fifth study comparing ciclosporin A with methotrexate and the sixth study comparing intramuscular methotrexate with oral methotrexate plus azathioprine found no statistically significant differences between the treatment groups. Immunosuppressants are associated with significant side effects. **AUTHORS' CONCLUSIONS:** This systematic review highlights the lack of high quality randomised controlled trials that assess the efficacy and toxicity of immunosuppressants in inflammatory myositis.

- **Choy EH, Isenberg DA.** Treatment of dermatomyositis and polymyositis. *Rheumatology* (Oxford) 2002; 41: 7-13.

**Abstract:** Since idiopathic inflammatory myositis is relatively uncommon, randomized placebo controlled trials are rare. Although corticosteroids have not been tested in randomized controlled trials, general clinical consensus among physicians has accepted it as effective therapy. However, corticosteroid toxicity leads to significant disability in many patients. For patients with refractory dermatomyositis, intravenous immunoglobulin is an effective short-term treatment but its long-term effect remains unknown. Immunosuppressants are commonly used in refractory inflammatory myositis; evidence for their efficacy, with very few exceptions, has been derived from case reports and open studies with small numbers of patients. Even in randomized trials, the lack of validated and generally accepted outcome measures makes it difficult to compare the effect of interventions in different studies. Although the balance of evidence suggests that immunosuppressants are equally effective in dermatomyositis and polymyositis, there are no randomized controlled trials to show if any of these drugs, individually or in combination, is best. For

uncommon diseases, such as inflammatory myositis, only multicentre randomized controlled trials involving rheumatologists and neurologists will define the optimal therapy.

• **Colsky AS.** Intravenous immunoglobulin in autoimmune and inflammatory dermatoses. A review of proposed mechanisms of action and therapeutic applications. *Dermatol Clin* 2000; 18: 447-57, ix.

**Abstract:** Off-label use of intravenous immunoglobulin (IVIG) at high doses has resulted in numerous anecdotal reports of its effectiveness in a variety of autoimmune and inflammatory conditions. Despite its growing acceptance as a viable therapeutic option in the management of several such disorders, the poorly defined mechanism of action of IVIG has stifled its rational therapeutic application. The lack of carefully designed prospective randomized clinical trials has further fueled controversy and mitigates against optimal application of this burgeoning therapy. Nevertheless, some standardization of IVIG therapy is slowly advancing that promises to support the use of this treatment for a growing number of autoimmune and inflammatory dermatoses.

• **Comi G, Roveri L, Swan A, et al.** A randomised controlled trial of intravenous immunoglobulin in IgM paraprotein associated demyelinating neuropathy. *J Neurol* 2002; 249: 1370-1377.

**Abstract:** This multicentre randomised double blind crossover trial tested the short term efficacy of intravenous immunoglobulin (IVIg) 2.0 g/kg given over 24 or 48 hours in patients with paraproteinaemic demyelinating neuropathy (PDN). Twenty-two patients were randomised and completed the trial. After 2 weeks, the overall disability grade decreased during both IVIg treatment and placebo but neither change was significant nor was the mean difference between the treatment effects. After 4 weeks the overall disability decreased by a mean of 0.55 [0.67] grades during the IVIg period ($p = 0.001$) while it was substantially unmodified during the placebo period. The mean difference between the treatment effects was significant ($p = 0.05$). Overall during the IVIg period 10 patients improved and 11 were stable and one got worse. During the placebo period 4 patients improved, 4 deteriorated and 14 were stable. Many secondary outcome measures, including Rankin scale, time to walk 10 metres, grip strength, sensory symptoms score were significantly better during IVIg treatment. Two serious adverse events occurred during the trial, both during placebo treatment. In conclusion the trial showed some short-term benefit of IVIg in about half of the patients confirming previous observation.

• **Cook SD, Troiano R, Rohowsky-Kochan C, et al.** Intravenous gamma globulin in progressive MS. *Acta Neurol Scand* 1992; 86: 171-175.

**Abstract:** In an attempt to prevent disease exacerbations, intravenous gamma globulin (500 mg to 2 g/kg) plus methylprednisolone was administered monthly to 14 patients with progressive multiple sclerosis, 11 of whom were steroid dependent. Seventeen exacerbations of disease activity were seen in 11 patients over a mean follow-up period of 7.8 months. Four exacerbations occurred in 3 patients within one month of receiving 1.6 to 2.0 g/kg of intravenous gamma globulin (IVGG). Most exacerbations occurred within 2 weeks of steroids being tapered; thus a steroid sparing effect of IVGG could not be demonstrated. We conclude that IVGG plus methylprednisolone can be given safely at monthly intervals for a prolonged period but in the dosage administered did not prevent exacerbations in 80% of patients with progressive multiple sclerosis.

• **Dalakas MC, Illa I, Dambrosia JM, et al.** A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med* 1993; 329: 1993-2000.

**Abstract: BACKGROUND.** Dermatomyositis is a clinically distinct myopathy characterized by rash and a complement-mediated microangiopathy that results in the destruction of muscle fibers. In some patients the condition becomes resistant to therapy and causes severe physical disabilities. **METHODS.** We conducted a double-blind, placebo-controlled study of 15 patients (age, 18 to 55 years) with biopsy-proved, treatment-resistant dermatomyositis. The patients continued to receive prednisone (mean daily dose, 25 mg) and were randomly assigned to receive one infusion of immune globulin (2 g per kilogram of body weight) or placebo per month for three months, with the option of crossing over to the alternative therapy for three more months. Clinical response was gauged by assessing muscle strength, neuromuscular symptoms, and changes in the rash. Changes in immune-mediated muscle abnormalities were determined by repeated muscle biopsies.

**RESULTS.** The eight patients assigned to immune globulin had a significant improvement in sores of muscle strength ($P < 0.018$) and neuromuscular symptoms ($P < 0.035$), whereas the seven patients assigned to placebo did not. With crossovers a total of 12 patients received immune globulin. Of these, nine with severe disabilities had a major improvement to nearly normal function. Their mean muscle-strength scores increased from 74.5 to 84.7, and their neuromuscular symptoms improved. Two of the other three patients had mild improvement, and one had no change in his condition. Of 11 placebo-treated patients, none had a major improvement, 3 had mild improvement, 3 had no change in their condition, and 5 had worsening of their condition. Repeated biopsies in five patients of muscles whose strength improved to almost normal showed an increase in muscle-fiber diameter ($P < 0.04$), an increase in the number and a decrease in the diameter of capillaries ($P < 0.01$), resolution of complement deposits on capillaries, and a reduction in the expression of intercellular adhesion molecule 1 and major-histocompatibility-complex class I antigens. **CONCLUSIONS.** High-dose intravenous immune globulin is a safe and effective treatment for refractory dermatomyositis.

• **Dalakas MC, Quarles RH, Farrer RG, et al.** A controlled study of intravenous immunoglobulin in demyelinating neuropathy with IgM gammopathy. *Ann Neurol* 1996; 40: 792-795.

**Abstract:** Eleven patients with demyelinating polyneuropathy associated with monoclonal IgM antibodies were randomized to receive IVIg or placebo, monthly, for 3 months in a double-blind study. After a washout period, they crossed over to the alternate therapy. Response was gauged by evaluating muscle strength, sensation, and neuromuscular symptoms at baseline, after 3 months, and at treatment's end. After IVIg therapy, the strength improved in only 2 of 11 patients, by 28 and 38.5 points from baseline, and declined after placebo. In 1 other patient, the sensory score improved by 13 points. Antibody titers to MAG/SGPG or gangliosides did not appreciably change. We conclude that IVIg has only a modest benefit to not more than 18% of patients with IgM paraproteinemic demyelinating neuropathy.

• **Dalakas MC, Sonies B, Dambrosia J, Sekul E, Cupler E, Sivakumar K.** Treatment of inclusion-body myositis with IVIg: a double-blind, placebo-controlled study. *Neurology* 1997; 48: 712-716.

**Abstract:** We randomized 19 patients with inclusion-body myositis (IBM) to a double-blind, placebo-controlled, crossover study using monthly infusions of 2 g/kg intravenous immunoglobulin (IVIg) or placebo for 3 months. Patients crossed over to the alternate treatment after a washout period. We evaluated responses at baseline and at the end of each treatment period using expanded (0-10) MRC scales, the Maximum Voluntary Isometric Contraction (MVIC) method, symptom and disability scores, and quantitative swallowing studies. We calculated the differences in scores between IVIg and placebo from baseline to end of treatment. Of the 19 patients, 9 (mean age, 61.2 years; mean disease duration, 5.6 years) were randomized to IVIg and 10 (mean age, 66.1 years; mean disease duration, 7.4 years) to placebo. During IVIg the patients gained a mean of 4.2 (-16 to +39.8) MRC points, and during placebo lost 2.7 (-10 to +8) points ($p < 0.1$). These gains were not significant. Similar results were obtained with the MRC and MVIC scores when the patients crossed to the alternate treatment. Six patients had a functionally important improvement by more than 10 MRC points that declined when crossed over to placebo. Limb-by-limb analysis demonstrated that during IVIg the muscle strength in 39% of the lower extremity limbs significantly increased compared with placebo ($p < 0.05$), while a simultaneous decrease in 28% of other limbs was detected. The clinical importance of these minor gains is unclear. The duration of swallowing functions measured in seconds with ultrasound improved statistically in the IVIg-randomized patients ($p < 0.05$) compared with placebo. Although the study did not establish efficacy of IVIg, possibly because of the small sample size, the drug induced functionally important improvement in 6 (28%) of the 19 patients. Whether the modest gains noted in certain muscle groups justify the high cost of trying IVIg in IBM patients at a given stage of the disease remains unclear.

• **Dalakas MC, Fujii M, Li M, McElroy B.** The clinical spectrum of anti-GAD antibody-positive patients with stiff-person syndrome. *Neurology* 2000; 55: 1531-1535.

**Abstract: OBJECTIVE:** To evaluate the clinical spectrum of anti-GAD-positive patients with stiff-person syndrome (SPS) and provide reproducible means of assessing stiffness. **BACKGROUND:** SPS can be difficult to diagnose. Delineation of the clinical spectrum in a well defined population will increase diagnostic sensitivity. **METHODS**: In 20 anti-GAD-positive patients with SPS (six men, 14 women), screened among 38 referred patients, the authors

assessed symptoms and signs, degree of disability, associated conditions, and immunogenetic markers. Degree of bending, distribution of stiff areas, timed activities, and magnitude of heightened sensitivity were examined monthly for 4 months in five patients. **RESULTS:** Average age at symptom onset was 41.2 years. Time to diagnosis was delayed from 1 to 18 years (mean 6.2). Stiffness with superimposed episodic spasms and co-contractures of the abdominal and thoracic paraspinal muscles were characteristic. All had stiff gait and palpable stiffness in the paraspinal muscles. Stiffness was asymmetric or prominent in one leg in 15 patients (stiff-leg syndrome) and involved facial muscles in 13. In one patient spasms lasted for days (status spasticus). Twelve patients needed a cane and seven a walker due to truncal stiffness and frequent falls (average three to four per month). Distribution of stiffness and degree of heightened sensitivity were two reproducible indices of stiffness and spasms. Autoimmune diseases or autoantibodies were noted in 80% and an association of with DRss(1) 0301 allele in 70%. **CONCLUSIONS:** SPS is 1) frequently misdiagnosed due to multifaceted presentations and asymmetric signs, 2) disabling if untreated, and 3) associated with other autoimmune conditions.

- **Dalakas MC, Koffman B, Fujii M, Spector S, Sivakumar K, Cupler E.** A controlled study of intravenous immunoglobulin combined with prednisone in the treatment of IBM. *Neurology* 2001; 56: 323-327.

**Abstract: OBJECTIVE:** To investigate whether the combination of intravenous immunoglobulin (IVIg) with prednisone improves muscle strength and alters endomysial inflammation in patients with sporadic inclusion body myositis (s-IBM). **BACKGROUND:** In a previous controlled trial in s-IBM, IVIg did not significantly improve strength in spite of modest benefits in some muscle groups. The possibility that prednisone may have a synergistic effect with IVIg prompted another controlled trial. **METHODS:** Thirty-six patients with biopsy-proven IBM were randomized to receive IVIg or placebo monthly for 3 months. Before infusions, all patients were started on high-dose prednisone for 3 months. Primary outcome measures were differences in the 1) Quantitative Muscle Strength (QMT) testing; and 2) modified Medical Research Council (MRC) scores, between the patients randomized to IVIg + prednisone compared with those randomized to placebo + prednisone. Repeated open muscle biopsies were performed at random in 24 patients to determine changes in the number of autoinvasive T cells and necrotic muscle fibers. **RESULTS:** Nineteen patients were randomized to IVIg + prednisone and 17 to placebo + prednisone. No significant change was noted in muscle strength, assessed by QMT and MRC, from baseline to the 2nd, 3rd, or 4th month after treatment between the two groups. The number of necrotic fibers was reduced in the IVIg randomized group ($p < 0.01$), and the mean number of CD2+ cells was significantly decreased in both groups ($p < 0.0001$), denoting a steroid effect. **CONCLUSION:** IVIg combined with prednisone for a 3-month period was not effective in IBM. Endomysial inflammation was significantly reduced after treatment, but the reduction was not of clinical significance.

- **Dalakas MC, Fujii M, Li M, Lutfi B, Kyhos J, McElroy B.** High-dose intravenous immune globulin for stiff-person syndrome. *N Engl J Med* 2001; 345: 1870-1876.

**Abstract: BACKGROUND:** Stiff-person syndrome is a disabling central nervous system disorder with no satisfactory treatment that is characterized by muscle rigidity, episodic muscle spasms, high titers of antibodies against glutamic acid decarboxylase (GAD65), and a frequent association with autoimmune disorders. Because stiff-person syndrome is most likely immune-mediated, we evaluated the efficacy of intravenous immune globulin. **METHODS:** We assigned 16 patients who had stiff-person syndrome and anti-GAD65 antibodies, in random order, to receive intravenous immune globulin or placebo for three months, followed by a one-month washout period and then by three months of therapy with the alternative agent. Efficacy was judged by improvements in scores on the distribution-of-stiffness index and heightened-sensitivity scale from base line (month 1) to the second and third month of each treatment phase. Direct and carryover effects of treatment were compared in the two groups. **RESULTS:** Among patients who received immune globulin first, stiffness scores decreased significantly ($P=0.02$) and heightened-sensitivity scores decreased substantially during immune globulin therapy but rebounded during placebo administration. In contrast, the scores in the group that received placebo first remained constant during placebo administration but dropped significantly during immune globulin therapy ($P=0.01$). When the data were analyzed for a direct and a first-order carryover effect, there was a significant difference in stiffness scores ($P=0.01$ and $P<0.001$, respectively) between the immune globulin and placebo groups, and immune globulin therapy had a significant direct treatment effect on sensitivity scores ($P=0.03$). Eleven patients who received immune globulin became able to walk more easily or without

assistance, their frequency of falls decreased, and they were able to perform work-related or household tasks. The duration of the beneficial effects of immune globulin varied from six weeks to one year. Anti-GAD65 antibody titers declined after immune globulin therapy but not after placebo administration. **CONCLUSIONS:** Intravenous immune globulin is a well-tolerated and effective, albeit costly, therapy for patients with stiff-person syndrome and anti-GAD65 antibodies.

- **Dalakas MC.** Intravenous immunoglobulin in autoimmune neuromuscular diseases. *JAMA* 2004; 291: 2367-2375.

**Abstract: CONTEXT:** Intravenous immunoglobulin (IVIG) enhances immune homeostasis by modulating expression and function of Fc receptors, interfering with activation of complement and production of cytokines, providing anti-idiotypic antibodies, and affecting the activation and effector functions of T and B cells. These mechanisms may explain the effectiveness of IVIG in autoimmune neuromuscular disorders. **OBJECTIVE:** To systematically review the current status of the treatment of autoimmune neuromuscular diseases with IVIG, with emphasis on controlled trials. **DATA SOURCES:** Peer-reviewed publications identified through MEDLINE (1966-2003), EMBASE (1974-2003), and references from bibliographies of pertinent articles. Each autoimmune neuromuscular disease term was searched in combination with the term intravenous immunoglobulin. **STUDY SELECTION AND DATA EXTRACTION:** Criteria for selection of studies included controlled study design, English language, and clinical pertinence. Data quality was based on venue of publication and relevance to clinical care. **DATA SYNTHESIS:** Outcomes of controlled trials indicate that IVIG at a total dose of 2 g/kg is effective as first-line therapy in Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy and as second-line therapy in stiff-person syndrome, dermatomyositis, myasthenia gravis, and Lambert-Eaton myasthenic syndrome. In other controlled studies, IVIG produced a modest, variable, and transient but not statistically significant benefit in patients with inclusion body myositis and paraproteinemic anti-myelin-associated glycoprotein antibody demyelinating polyneuropathy. Intravenous immunoglobulin is not effective in patients with multiple sclerosis who have established weakness or optic neuritis. In myasthenia gravis, it should be reserved for difficult cases or before thymectomy in lieu of plasma exchange. **CONCLUSION:** Intravenous immunoglobulin is effective in many autoimmune neurologic diseases, but its spectrum of efficacy, especially as first-line therapy, and the appropriate dose for long-term maintenance therapy are not fully established. Further controlled studies of IVIG, combined with a dose-finding effect, pharmacoeconomics, and quality-of-life assessments, are warranted to improve the evidence base for clinical practice.

- **Dalakas MC.** Intravenous immunoglobulin in patients with anti-GAD antibody-associated neurological diseases and patients with inflammatory myopathies: effects on clinicopathological features and immunoregulatory genes. *Clin Rev Allergy Immunol* 2005; 29: 255-269.

**Abstract:** Controlled trials with intravenous immunoglobulin (IVIg) were conducted in patients with Stiff-Person Syndrome (SPS) and dermatomyositis (DM), two humorally mediated neurological disorders, and in inclusion body myositis (IBM), a T-cell-mediated inflammatory myopathy. The clinical efficacy was compared with alterations on tissue expression of complement, cytokines, chemokines, adhesion molecules, and immunoregulatory genes. The following patients were randomized in three separate trials to receive IVIg or placebo for 3 mo: (a) 16 patients with anti-GAD antibody-positive SPS; (b) 15 patients with DM resistant to therapies; and (c) 19 patients with IBM. After a washout, they crossed to the alternative therapy for another 3 mo. Efficacy was based on the difference in the respective disease scores from baseline to the second and third month of the infusions. In patients with SPS and DM, the scores changed positively and significantly from months 1 through 3, but returned to baseline when the patients crossed to placebo. In contrast, the scores in the placebo-randomized group remained constant or worsened from months 1 to 3, but improved significantly after crossing to IVIg. The muscle scores of patients with IBM did not significantly change between IVIg or placebo. In SPS, the anti-GAD65 antibody titers declined after IVIg but not after placebo. In DM, there was reduction of complement consumption, interception of membranolytic attack complex formation, downregulation of inflammation, fibrosis, cytokines, chemokines and adhesion molecules, and alterations in thousands of immunoregulatory genes. We conclude that IVIg is a safe and effective therapy for patients with SPS and DM unresponsive to other agents. In tissues, IVIg restores tissue cytoarchitecture by suppressing the inflammatory mediators at the protein, mRNA, and gene level.

• **Dalakas MC.** The role of IVIg in the treatment of patients with stiff person syndrome and other neurological diseases associated with anti-GAD antibodies. *J Neurol* 2005; 252 Suppl 1: I19-I25.

**Abstract: INTRODUCTION:** High-titre anti-GAD antibodies are characteristically seen in patients with stiff person syndrome (SPS). Other CNS disorders, rarely associated with high anti-GAD antibody titres, include: a) SPS-plus, a syndrome characterised by SPS and cerebellar ataxia; b) Batten's disease; and c) rare patients with epilepsy and idiopathic cerebellar ataxia. Currently, high-titre anti- GAD antibodies serve only as markers of an autoimmune process within the CNS because their pathogenic role in the aforementioned disorders has not been established. In SPS, there is evidence of autoimmune pathogenesis based on: the association of the disease with other autoimmune disorders or autoantibodies; immunogenetic background; presence of oligoclonal IgG bands in the CSF with increased intrathecal anti-GAD antibody synthesis and response to immunotherapies. SPS is the only GAD-positive CNS disease where a controlled study with immunotherapy has been conducted. **METHODS:** Sixteen anti-GAD antibody-positive patients were randomised to receive IVIg or placebo for 3 months. After a washout, they crossed to the alternative therapy for another three months. Efficacy was based on the difference in scores of the distribution of stiffness index and heightened sensitivity (spasms) from baseline to the second and third month of the infusions. Direct treatment and carry-over effect were compared for both groups. **RESULTS:** The stiffness scores in the IVIg-randomised patients declined significantly from month 1 through 4, but rebounded when they crossed to placebo. In contrast, the scores in the placebo-randomised group remained constant from month 1-4 but dropped significantly after crossing to IVIg. Eleven patients who received IVIg became able to walk unassisted, stopped falling and assumed household or work duties. The duration of benefit varied from 6-12 weeks or up to a year. The anti-GAD(65) antibody titres declined after IVIg, but not after placebo. **CONCLUSION:** Based on a controlled study, IVIg is a safe and effective therapy for SPS in patients unresponsive to other agents. Whether IVIg has a role in the other GAD-positive patients with neurological disease, or in SPS patients without GAD antibodies, remains unknown.

• **Danieli MG, Cappelli M, Malcangi G, Logullo F, Salvi A, Danieli G.** Long term effectiveness of intravenous immunoglobulin in Churg-Strauss syndrome. *Ann Rheum Dis* 2004; 63: 1649-1654.

**Abstract: OBJECTIVE:** To study the long term effectiveness of intravenous immunoglobulin and plasmapheresis associated with prednisone and cyclophosphamide in Churg-Strauss syndrome. **SUBJECTS:** and methods: We studied 18 subjects with new onset Churg-Strauss syndrome. All received the "standard" treatment based on prednisone (1 mg/kg/day for 1 month and then slowly tapered) and cyclophosphamide (2 mg/kg/day for 6 months in severe cases). In nine patients, synchronised cycles with plasmapheresis and intravenous immunoglobulin (2 g/kg) were repeated monthly for 6 months and every other month for a further three cycles. Clinical (disease activity monitored by Birmingham vasculitis activity score (BVAS) and damage index (modified Rankin score)) and functional (C reactive protein, blood eosinophil count, and electromyogram-electoneurogram) parameters were collected during treatment and the 3 year follow up period. **RESULTS:** After 12 months, all patients in the treatment group and four (44%) in the control group were in remission. At the end of the 3 year follow up period, we documented significant differences in BVAS ($p<0.01$), global damage ($p<0.02$), modified Rankin score ($p<0.04$), and the daily maintenance prednisone dose ($p<0.002$) between the two groups. We found a tendency towards lower frequency of relapse and incidence of osteoporosis in the treatment group. **CONCLUSION:** Complete clinical and functional recovery with a long term stable remission and a low incidence of side effects can be achieved by intravenous immunoglobulin associated with plasmapheresis in patients with Churg-Strauss syndrome.

• **de Groot K, Schmidt DK, Arlt AC, Gross WL, Reinhold-Keller E.** Standardized neurologic evaluations of 128 patients with Wegener granulomatosis. *Arch Neurol* 2001; 58: 1215-1221.

**Abstract: OBJECTIVE:** To assess the frequency and type of neurologic involvement in a cohort of patients with generalized Wegener granulomatosis (WG). **PATIENTS AND METHODS:** In a prospective analysis the clinical, electrophysiologic, radiological, and serologic data of 128 patients have been studied over a median observation period of 19 months (range, 1-60 months). **RESULTS**: Sixty-four patients (50%) revealed central or peripheral nervous system involvement. Peripheral neuropathy (PN) affected 56 patients, in 9 cases the central nervous system was involved, and in 6 cases the cranial nerves were involved. Thirty-one patients showed a distal

symmetrical polyneuropathy, 25 a mononeuritis multiplex. Within the first 2 years of the disease course 47 of the 56 patients had developed their PN, sometimes as the initial symptom of WG. Patients with PN were significantly more often male (34 of 65 patients) than female (22 of 63 patients, P =.04), were significantly older at the onset of WG (median age, 53 vs 44 years; P =.001), had a significantly larger disease extent (P =.001), and had higher classic antineutrophil cytoplasmic antibody titers (P =.002) than neurologically unaffected patients. Response to immunosuppression was moderate concerning peripheral nervous system manifestations. **CONCLUSIONS:** Peripheral neuropathy is frequent in generalized WG, occurring early in the disease course. As PN can be the first and sole symptom of a beginning systemic vasculitis, it is important that in cases of PN of an unclear origin, interdisciplinary investigations are initiated to detect, treat, and closely follow-up a possible underlying WG, especially as these patients seem to have a more severe disease course.

- **Diener HC, Haupt WF, Kloss TM, et al.** A preliminary, randomized, multicenter study comparing intravenous immunoglobulin, plasma exchange, and immune adsorption in Guillain-Barre syndrome. *Eur Neurol* 1906; 46: 107-109.

- **Donofrio PD.** Immunotherapy of idiopathic inflammatory neuropathies. *Muscle Nerve* 2003; 28: 273-292.

**Abstract:** Evaluation of peripheral neuropathy is a common reason for referral to a neurologist. Recent advances in immunology have identified an inflammatory component in many neuropathies and have led to treatment trials using agents that attenuate this response. This article reviews the clinical presentation and treatment of the most common subacute inflammatory neuropathies, Guillain-Barre syndrome (GBS) and Fisher syndrome, and describes the lack of response to corticosteroids and the efficacy of treatment with plasma exchange and intravenous immunoglobulin (IVIG). Chronic inflammatory demyelinating polyneuropathy, although sharing some clinical, electrodiagnostic, and pathologic similarities to GBS, improves after treatment with plasma exchange and IVIG and numerous immunomodulatory agents. Controlled trials in multifocal motor neuropathy have shown benefit after treatment with IVIG and cyclophosphamide. Also discussed is the treatment of less common inflammatory neuropathies whose pathophysiology involves monoclonal proteins or antibodies directed against myelin-associated glycoprotein or sulfatide. Little treatment data exist to direct the clinician to proper management of rare inflammatory neuropathies resulting from osteosclerotic myeloma; POEMS syndrome; vasculitis; Sjogren's syndrome; and neoplasia (paraneoplastic neuropathy).

- **Durelli L, Ricci A, Verdun E.** Immunoglobulin treatment of multiple sclerosis: future prospects. *Neurol Sci* 2003; 24 Suppl 4: S234-S238.

**Abstract:** In one of the most frequent MS demyelination patterns, IgG and complement are demonstrable on myelin surface. It is, probably, an antibody-mediated pattern of myelin damage, usually associated with acute MS, but, at times, observed even in chronic cases. This pattern of myelin damage is extremely similar to that observed in acute demyelinating inflammatory polineuropathies, such as Guillain-Barre syndrome, and in acute disseminated encephalomyelitis (ADEM), a rare demyelinating disease usually occurring after a viral infection or vaccination. These pathologies response well to IgG treatment. Although hyperacute severe cases of MS seem to respond well to IgG treatment, this does not seem the case for other cases of relapses in relapsing-remitting MS. Several trials failed to provide clear evidence of clinical and MRI efficacy of high-dose IgG parenteral treatment in relapsing-remitting multiple sclerosis (MS). The study of Confavreux and the PRIMS study showed that the relapse rate decreases significantly during pregnancy in MS patients, while increases after delivery. IgG is not a cytostatic drug and therefore it has been tested to see whether it reduces relapse occurrence after delivery. In pregnant MS patients treated with high dose, Haas' study and our experience noted a slight increase relapse rate during the six month after delivery but lower than that showed in Confavreux and PRIMS studies in untreated pregnant MS women.

- **Dyck PJ, Litchy WJ, Kratz KM, et al.** A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 1994; 36: 838-845.

**Abstract:** Chronic inflammatory demyelinating polyradiculoneuropathy is a paralytic syndrome, causing considerable disability and even death. In controlled clinical trials, plasma exchange prevented

or ameliorated neurological deficits, but the efficacy of immune globulin infusion remains unproved. Also unknown is whether immune globulin infusion is as effective, or more effective, than plasma exchange and what dosages and frequencies are best. In this observer-blinded study, using some objective end points not subject to bias (e.g., summated compound muscle action potential), 20 patients with progressive or static polyneuropathy were randomly assigned to receive either of the two treatments for 6 weeks, followed by a washout period, and then were assigned to receive the other treatment. Plasma exchange (twice a week for 3 weeks then once a week for 3 weeks) and immune globulin infusion (0.4 gm/kg once a week for 3 weeks, then 0.2 gm/kg once a week for the next 3 weeks) were used. End points assessed before and after treatment schedules were neurological disability score; muscle weakness of the neurological disability score; summated compound muscle action potentials of ulnar, median, and peroneal nerves; summated sensory nerve action potentials of ulnar and sural nerves; and vibratory detection threshold of the great toe using CASE IV. Observers were masked as to treatment used. Of 20 patients, 13 received both treatments whereas 4 did not worsen sufficiently to receive the second treatment--1 patient left the study during and 2 after the first treatment to receive unscheduled treatment elsewhere. (ABSTRACT TRUNCATED AT 250 WORDS)

• **Enayati PJ, Papadakis KA.** Association of anti-tumor necrosis factor therapy with the development of multiple sclerosis. *J Clin Gastroenterol* 2005; 39: 303-306.

**Abstract:** A 35-year-old woman with a history of indeterminate colitis developed symptoms of multiple sclerosis after treatment with infliximab. Neurologic examination confirmed upper and lower extremity motor and sensory deficits. MRI showed multiple enhancing white matter lesions distributed throughout her brain as well as her thoracic spine. There may be a link between inflammatory demyelinating disease of the central nervous system and anti-tumor necrosis-alpha therapy. This case report describes the onset or worsening of a demyelinating process after the initiation of infliximab therapy in a patient with indeterminate colitis.

• **Esperou H, Jars-Guincestre MC, Bolgert F, Raphael JC, Durand-Zaleski I.** Cost analysis of plasma-exchange therapy for the treatment of Guillain-Barre syndrome. French Cooperative Group on Plasma Exchange in Guillain-Barre Syndrome. *Intensive Care Med* 2000; 26: 1094-1100.

**Abstract: OBJECTIVE:** To undertake a cost analysis of therapeutic strategies with plasma exchange (PE) for the treatment of patients with Guillain-Barre syndrome. **DESIGN:** A randomized clinical trial including 556 patients with Guillain-Barre syndrome. We demonstrated that in the group with mild disease (walking possible) two PEs were more effective than none in shortening the time to beginning motor recovery. In the groups with moderate disease (walking impossible) and or severe disease (mechanically ventilated patients) four sessions were more effective than two and no more effective than six in shortening the time to recovery of walking with assistance and for the recovery rate of full muscle strength within 1 year. Data on outcomes and costs was collected. Complete cost data were available on 546 from the 556 patients of the trial. Costs were estimated from the viewpoint of the healthcare system and computed over a 1-year period. Because the analysis of medical outcomes did not show any difference regarding mortality but only on intermediate short-term and long-term outcomes, we carried out a cost minimization analysis. **RESULTS:** In two groups a dominant strategy appeared, with greater efficacy and lower costs in the two-PE arm for the mild group: 21,353 euros vs. 38,753 euros and in the four-PE arm in the moderate group: 59,480 euros vs. 80,737 euros. In the severe group four PEs were as efficient and somewhat less expensive than six: 57,621 vs. 61,056 euros. **CONCLUSION:** The treatment of Guillain-Barre syndrome by PE at the onset of disease appears to have medical justification. The least expensive strategies are either more or equally efficient as more expensive strategies.

• **Farcas P, Avnun L, Frisher S, Herishanu YO, Wirguin I.** Efficacy of repeated intravenous immunoglobulin in severe unresponsive Guillain-Barre syndrome. *Lancet* 1997; 350: 1747-Farcas, P.

• **Farkkila M, Penttila P.** Plasma exchange therapy reduces the nursing care needed in Guillain-Barre syndrome. *J Adv Nurs* 1992; 17: 672-675.

**Abstract:** The authors compared the effect of plasma exchange therapy on the need for nursing care for 26 patients with acute idiopathic Guillain-Barre syndrome. The patients were randomized either to a plasma exchange (PE) or conservative treatment

group. The need for nursing care and the need for specialist nursing services was assessed daily by the nurses at the Department of Neurology. At first, the average need for care was the same for the two groups of patients, but the pattern of care over time was different, with the PE group needing more care at the beginning and then very much less care, whilst the conservative group needed a more uniform amount of care over the entire stay at hospital. In the PE group the need for specialist nursing services increased markedly, and the need for nursing care decreased rapidly after the first 2 weeks to a level lower than that needed by control group patients, probably because PE increased muscle forces of patients. This study suggests that PE treatment is useful in reducing patients' needs for nursing care, especially after the first 2 weeks following the treatment.

• **Fazekas F, Strasser-Fuchs S, Hartung HP.** [Intravenous immunoglobulins in therapy of intermittent multiple sclerosis. An update]. *Nervenarzt* 1998; 69: 361-365.

**Abstract:** Experimental studies and open clinical trials have suggested intravenous immunoglobulin (i.v.Ig) as a potentially effective treatment of multiple sclerosis (MS). The Austrian Immunoglobulin in Multiple Sclerosis (AIMS) study tested this assumption by examining 148 patients with relapsing-remitting MS in a randomized, double-blind, placebo controlled fashion (75 i.v.Ig, 73 placebo). Monthly administration of i.v.Ig in a dosage of 0.15-0.20 g/kg over a period of 2 years slowed the progression of or even reversed disability as evident in a total of 24% of patients and almost halved the number of relapses in comparison to placebo treatment. Therapeutic efficacy was noted within the first 6 months of treatment and was not correlated to the severity of disability (mild neurological signs without disability to ambulatory with assistance) at study entry. Overall the magnitude of treatment effects of i.v.Ig was comparable to that reported for beta-interferon and copolymer 1. Further ongoing studies will have to clarify the future role of i.v.Ig in the treatment of MS, in particular in the progressive forms of the disease.

• **Fazekas F, Sorensen PS, Filippi M, et al.** MRI results from the European Study on Intravenous Immunoglobulin in Secondary Progressive Multiple Sclerosis (ESIMS). *Mult Scler* 2005; 11: 433-440.

**Abstract: BACKGROUND:** Monthly application of high-dose intravenous immunoglobulin (IVIG) to patients with secondary progressive multiple sclerosis (MS) showed no clinical benefit in the European Study on Immunoglobulin in MS (ESIMS). Magnetic resonance imaging (MRI) results may provide insights into the morphologic consequences of such treatment. **METHODS:** A total of 318 patients (mean age 44 +/- 7 years) were enrolled in 31 European and Canadian centres and treated monthly with 1 g/kg body weight of IVIG or equivalent amounts of albumin 0.1% for 27 months. MRI was performed at baseline and after 12 and 24 months and comprised of conventional dual-echo T2-weighted and T1-weighted scans before and after application of 0.1 mmol/kg Gd-DTPA. **RESULTS:** Similar to clinical variables, MRI measures at baseline were well comparable between treatment groups except for a somewhat lower mean number of contrast-enhancing lesions and number of active scans in IVIG-treated patients. Over the trial period there was almost no change of the T2-lesion load and the 'black hole' volume in both treatment groups and the cumulative number of contrast-enhancing lesions were similar. There was only a trend for fewer new or enlarged T2-lesions in IVIG patients, which disappeared after correction for the imbalance in the number of contrast-enhancing lesions at baseline. Brain volume in terms of a partial cerebral fraction decreased significantly less with IVIG than placebo treatment (final visit: -0.62 -/+ 0.88% versus -0.88 +/- 0.91%; P=0.009). This difference remained statistically significant with correction for active lesions at baseline (P=0.02) and was seen primarily in male patients and those with an Expanded Disability Status Scale score > or = 6 and no relapses in the two years before the study. **CONCLUSION:** The absence of significant differences in conventional MRI measures between both treatment groups parallels the negative clinical results of ESIMS. The causes for and possible long-term clinical effects of a lower rate of brain volume loss in IVIG patients should be explored further.

• **Federico P, Zochodne DW, Hahn AF, Brown WF, Feasby TE.** Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study. *Neurology* 2000; 55: 1256-1262.

**Abstract: OBJECTIVE:** To determine the effect of IV immunoglobulin (IVIg) on neurologic function and electrophysiologic studies in multifocal motor neuropathy with conduction block (MMN). **BACKGROUND:** MMN is characterized by progressive, asymmetric, lower motor neuron weakness and is probably immune-mediated. IVIg treatment has been shown to have beneficial effects in several open-label studies and in one small controlled trial. However,

larger randomized controlled studies are lacking. **METHODS:** The authors recruited 16 patients with MMN. All subjects were given each of two treatments (IVIg [0.4 g/kg/d for 5 consecutive days] or placebo [dextrose or saline]) that were assigned according to a randomized, crossover design under double-blind conditions. Patients were evaluated before and about 28 days after trial treatment for subjective functional improvement, neurologic disability score, grip strength, distal and proximal compound muscle action potential amplitude, and conduction block. **RESULTS:** Subjective functional improvement with IVIg treatment was rated as dramatic or very good in nine patients, moderate in one, mild in one, and absent in five patients. This improvement was absent after placebo. The neurologic disability score improved by 6.7+/-3.3 points with IVIg treatment, whereas it decreased by 2.1+/-3.0 with placebo ($p = 0.038$). Grip strength on the weaker side was increased by 6.4+/-1.9 kg with IVIg treatment; it decreased by 1.0+/-0.8 kg with placebo ($p = 0.0021$). Conduction block worsened by 12.98+/-6.52 % with placebo, but improved by 12.68+/-5.62 % with IVIg treatment ($p = 0.037$). Conduction block was reversed in five patients with IVIg but not placebo. **CONCLUSION:** IVIg improved conduction block as well as subjective and objective clinical measures of function in patients with MMN.

- **Fergusson D, Hutton B, Sharma M, et al.** Use of intravenous immunoglobulin for treatment of neurologic conditions: a systematic review. *Transfusion* 2005; 45: 1640-1657.

**Abstract: BACKGROUND:** Given the increasing use of intravenous immunoglobulin (IVIG) for various neurologic conditions and uncertainty pertaining to its benefits and harms, a systematic review was conducted of randomized controlled trials (RCTs) evaluating IVIG for all neurologic indications for which there was at least one published trial. **STUDY DESIGN AND METHODS:** For this systematic review, a systematic search strategy was applied to MEDLINE (1966-June 2003) and the Cochrane Register of Controlled Trials (June 2003) to identify potentially eligible RCTs comparing IVIG to placebo or an active control. All dosage regimens were considered. Abstracts were excluded, and no restriction was placed on language of publication. Two investigators independently performed data extraction with a standardized form. Measures of effect were calculated for each trial independently, and studies were pooled based on clinical and methodologic judgment as to its appropriateness. Where pooling of trials was inappropriate, a qualitative discussion of findings is provided. **RESULTS AND CONCLUSIONS:** Thirty-seven trials representing 14 conditions were identified. IVIG is more effective than placebo for treatment of relapsing-remitting multiple sclerosis and idiopathic chronic inflammatory demyelinating polyneuropathy. There is also potential benefit for treatment of multifocal motor neuropathy, myasthenia gravis, dermatomyositis, stiff-person syndrome, and Lambert-Eaton myasthenic syndrome. There was insufficient evidence to determine whether IVIG therapy was more effective than plasma exchange for Guillain-Barre syndrome. There was also insufficient evidence regarding paraprotein-associated polyneuropathy. No evidence of benefit was observed for secondary progressive multiple sclerosis or inclusion body myositis.

- **Finsterer J, Grass R, Stollberger C, Mamoli B**. Immunoglobulins in acute, parainfectious, disseminated encephalo-myelitis. *Clin Neuropharmacol* 1998; 21: 258-261.

**Abstract:** Acute, parainfectious, disseminated encephalo-myelitis (ADEM) is usually treated with corticosteroids. Intravenous immunoglobulins have not been applied to patients with ADEM. This article describes a 22-year old woman who developed progressive paraparesis, ascending sensory dysfunction, and urinary incontinence one week after tonsillitis. Guillain-Barre syndrome was diagnosed initially, and intravenous immunoglobulins (0.4 g/kg daily) were begun. Symptoms deteriorated after the first and second applications, but after the third application the patient's sensory level declined. After the fourth application, the deterioration of symptoms stopped and cerebrospinal fluid (CSF) abnormalities improved. Because of diffuse spinal cord swelling, intramedullary edema, and hyperintense white and grey matter lesions in the basal ganglia and the corpus callosum on MRI scans, the diagnosis was corrected to ADEM. It is concluded that initial administration of intravenous immunoglobulins might be of therapeutic value in patients with ADEM.

- **Fox RJ, Bethoux F, Goldman MD, Cohen JA.** Multiple sclerosis: advances in understanding, diagnosing, and treating the underlying disease. *Cleve Clin J Med* 2006; 73: 91-102.

**Abstract:** Recent advances in our understanding of the diagnosis, imaging, pathology, and clinical monitoring of multiple sclerosis (MS) have significantly increased our ability to successfully treat this often

perplexing neurologic disorder. Magnetic resonance imaging (MRI) is now integral to the diagnostic process. Treatment of MS can be considered as three parallel pathways: treatment of relapses, symptom management, and long-term prevention of tissue injury.

• **Gabis LV, Panasci DJ, Andriola MR, Huang W.** Acute disseminated encephalomyelitis: an MRI/MRS longitudinal study. *Pediatr Neurol* 2004; 30: 324-329.

**Abstract:** A clinical and radiologic diagnosis of acute disseminated encephalomyelitis was made in two children: a 6-month-old female who presented with focal seizures and thalamic and cerebral white matter lesions, and a 4.5-year-old male who presented with tremor and dystonia and had bilateral basal ganglia lesions, without evidence of active brain infection. Serial clinical and laboratory evaluations were supplemented by neuroimaging including routine magnetic resonance imaging and (1) H magnetic resonance spectroscopy. They were treated symptomatically, without using steroids or intravenous immunoglobulin, and both children recovered. Single voxel (1) H magnetic resonance spectroscopy data were acquired from the involved areas and from normal-appearing white matter. Abnormalities in N-acetyl-aspartate, choline, and lactate peaks were evident during the symptomatic phase, and persistence of low N-acetyl-aspartate was observed during recovery. These spectroscopic findings are consistent with neuropathologic findings of neuronal dysfunction, cellular membrane turnover, cellular infiltration, and metabolic stress in the acute phase, and with neuronal loss in the chronic phase.

• **Gajdos P, Chevret S, Clair B, Tranchant C, Chastang C.** Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Myasthenia Gravis Clinical Study Group. *Ann Neurol* 1997; 41: 789-796.

**Abstract:** We have conducted a trial to randomly assess the efficacy and tolerance of intravenous immunoglobulin (i.v.Ig) or plasma exchange (PE) in myasthenia gravis (MG) exacerbation and to compare two doses of i.v.Ig. Eighty-seven patients with MG exacerbation were randomized to receive either three PE (n = 41), or i.v.Ig (n = 46) 0.4 gm/kg daily further allocated to 3 (n = 23) or 5 days (n = 23). The main end point was the variation of a myasthenic muscular score (MSS) between randomization and day 15. The MSS variation was similar in both groups (median value, +18 in the PE group and +15.5 in the i.v.Ig group, p = 0.65). Similar efficacy, although slightly reduced in the 5-day group was observed with both i.v.Ig schedules. The tolerance of i.v.Ig was better than that of PE with a total of 14 side effects observed in 9 patients, 8 in the PE group and 1 in the i.v.Ig group (p = 0.01). Although our trial failed to show a pronounced difference in the efficacy of both treatments, it exhibited a very limited risk for i.v.Ig. i.v.Ig is an alternative for the treatment of myasthenic crisis. The small sample sizes in our trial, however, could explain why a difference in efficacy was not observed. Further studies are needed to compare PE with i.v.Ig and to determine the optimal dosage of i.v.Ig.

• **Gajdos P, Tranchant C, Clair B, et al.** Treatment of myasthenia gravis exacerbation with intravenous immunoglobulin: a randomized double-blind clinical trial. *Arch Neurol* 2005; 62: 1689-1693.

**Abstract: BACKGROUND:** The optimal dose of intravenous immunoglobulin (IVIG) in acute exacerbation of myasthenia gravis remains unknown. Increasing the treatment duration might provide added efficacy. **OBJECTIVE:** To determine the optimal dose of IVIG for treating myasthenia gravis exacerbation. **DESIGN:** Randomized double-blind placebo-controlled multicenter trial designed to demonstrate superiority of the 2 g/kg dose over the 1 g/kg dose of IVIG, conducted between November 13, 1996, and October 26, 2002. **PARTICIPANTS:** One hundred seventy-three patients aged 15 to 85 years with acute exacerbation of myasthenia gravis. **INTERVENTION:** Participants were randomly assigned to receive 1 g/kg of IVIG on day 1 and placebo on day 2 (group 1) vs 1 g/kg of IVIG on 2 consecutive days (group 2). **MAIN OUTCOME MEASURE:** Improvement in the myasthenic muscular score after 2 weeks. **RESULTS:** The mean improvements in the myasthenic muscular scores after 2 weeks were 15.49 points (95% confidence interval, 12.09-18.90 points) in group 1 and 19.33 points (95% confidence interval, 15.82-22.85 points) in group 2. However, the difference between the 2 groups was not significant (effect size, 3.84 [95% confidence interval, -1.03 to 8.71]; P = .12). **CONCLUSION:** This trial found no significant superiority of 2 g/kg over 1 g/kg of IVIG in the treatment of myasthenia gravis exacerbation.

• **Garg RK.** Acute disseminated encephalomyelitis. *Postgrad Med J* 2003; 79: 11-17.

**Abstract:** Acute disseminated encephalomyelitis (ADEM) is an acute demyelinating disorder of the central nervous system, and is characterised by multifocal white matter involvement. Diffuse neurological signs along with multifocal lesions in brain and spinal cord characterise the disease. Possibly, a T cell mediated autoimmune response to myelin basic protein, triggered by an infection or vaccination, underlies its pathogenesis. ADEM is a monophasic illness with favourable long term prognosis. The differentiation of ADEM from a first attack of multiple sclerosis has prognostic and therapeutic implications; this distinction is often difficult. Most patients with ADEM improve with methylprednisolone. If that fails immunoglobulins, plasmapheresis, or cytotoxic drugs can be given. Recent literature suggests that a significant proportion of patients with ADEM will later develop multiple sclerosis; however, follow up experience from developing countries does not support this view.

• **Ghezzi A.** Childhood-juvenile multiple sclerosis: clinical characteristics and treatment. *Expert Rev Neurother* 2005; 5: 403-411.

**Abstract:** The characteristics of multiple sclerosis with onset during childhood or adolescence are presented in this review. The clinical findings are similar to those of the adult form, but some aspects are peculiar: the high female to male ratio, occurrence of hyperacute forms, occurrence of encephalopatic symptoms and high relapse rate. The evolution is relapsing-progressive in most cases. Mild and severe disability are reached after a longer interval than in the adult form but, in spite of this, at a given age disability is higher. A high relapse rate, short interval between first and second attack and high disability after the first year are negative prognostic factors. Magnetic resonance imaging and cerebrospinal fluid data are discussed, with particular reference to differential diagnosis from acute disseminated encephalomyelitis. Currently, there are no controlled trials concerning subjects aged under 16 years. Some observations demonstrate that immunomodulatory drugs are well tolerated and have a beneficial effect, reducing the relapse rate and progression of the disease.

• **Gonzalez H, Stibrant SK, Sjoberg I, Kaponides G, Olsson T, Borg K.** Intravenous immunoglobulin for post-polio syndrome: a randomised controlled trial. *Lancet Neurol* 2006; 5: 493-500.

**Abstract: BACKGROUND:** Survivors of poliomyelitis often develop increased or new symptoms decades after the acute infection, known as post-polio syndrome. Production of proinflammatory cytokines within the CNS indicates an underlying inflammatory process, accessible for immunomodulatory treatment. We did a multicentre, randomised, double-blind, placebo-controlled study of intravenous immunoglobulin in post-polio syndrome. **METHODS:** 142 patients at four university clinics were randomly assigned infusion of either 90 g in total of intravenous immunoglobulin (n=73) or placebo (n=69) during 3 consecutive days, repeated after 3 months. Seven patients were withdrawn from the study. Thus, 135 patients were assessed per protocol. Primary endpoints were muscle strength in a selected study muscle and quality of life as measured with the SF-36 questionnaire (SF-36 PCS). Secondary endpoints were 6-minute walk test (6MWT), timed up and go (TUG), muscle strength in muscles not chosen as the study muscle, physical activity scale of the elderly (PASE), visual analogue scale (VAS) for pain, multidimensional fatigue inventory (MFI-20), balance, and sleep quality. Outcome tests were done immediately before the first infusion and 3 months after the second infusion. This study is registered with , number NCT00160082. **FINDINGS:** Compared with baseline, median muscle strength differed by 8.3% between patients receiving intravenous immunoglobulin and placebo, in favour of the treatment group (p=0.029). SF-36 PCS did not differ significantly between the groups after treatment (p=0.321). Differences in the subscale vitality score (p=0.042) and PASE (p=0.018) favoured the active treatment group. MFI-20, TUG, muscle strength in the muscles not chosen as the study muscle, 6MWT, balance, and sleep quality did not differ between groups. For the whole study population there was no significant change in pain, as determined by VAS. Nevertheless, patients who reported pain at the study start improved in the intervention group but not in the placebo group (p=0.037). Intravenous immunoglobulin was well tolerated. **INTERPRETATION:** Intravenous immunoglobulin could be a supportive treatment option for subgroups of patients with post-polio syndrome. Further studies on responding subgroups, long-term effects, and dosing schedules are needed.

• **Goodman SN, Sladky JT.** A Bayesian approach to randomized controlled trials in children utilizing information from adults: the case of Guillain-Barre syndrome. *Clin Trials* 1906; 2: 305-310.

**Abstract: BACKGROUND**: Guillain-Barre syndrome (GBS) is a rare neurologic disease that occurs at all ages, causing a progressive, ascending paralysis

that usually resolves over weeks or months. The disease appears to be identical in children and adults, except that children recover more quickly, with fewer residua. For patients who lose the ability to walk independently, the main treatment options are plasmapheresis or intravenous immune globulin (IVIg), treatments that have shown to have identical effectiveness in adults in two large RCTs involving 388 patients. The effectiveness of the treatments in children has only been studied in small, poorly controlled studies. If one could capture all eligible patients in the United States, only about 100-300 children would be available for a trial annually. **METHODS:** The goal of this case was to demonstrate how Bayesian methods could be used to incorporate prior information on treatment efficacy from adults to design a randomized noninferiority trial of IVIg versus plasmapheresis in children. A Bayesian normal-normal model on the hazard ratio of time to independent walking was implemented. **RESULTS:** An evidence-based prior was constructed that was equivalent to 72 children showing exact equivalence between the therapies. A design was constructed based on a Bayesian normal-normal model on the hazard ratio, yielding a sample size of 160 children, with a preposterior analysis demonstrating a "Type I" error rate of 5% and a power of 77%. **CONCLUSIONS:** This case study illustrates a rational approach to constructing an evidence-based prior that would allow information from adults to formally augment data from children to minimize unnecessary pediatric experimentation. The frequentist properties of a Bayesian design can be evaluated and reported as they would be for a standard design. Discussion of the appropriate prior for such designs is both a necessary and desirable feature of Bayesian trials.

- **Gorson KC.** Clinical features, evaluation, and treatment of patients with polyneuropathy associated with monoclonal gammopathy of undetermined significance (MGUS). *J Clin Apher* 1999; 14: 149-153.

**Abstract:** A number of common disorders of the peripheral nervous system are closely linked to a monoclonal gammopathy. In a minority of patients, the neuropathy represents the sentinel feature of a malignant plasma cell dyscrasia, such as multiple myeloma or its osteosclerotic variant, Waldenstrom's disease, amyloidosis, cryoglobulinemia or lymphoma; the vast majority have so-called "monoclonal gammopathy of undetermined significance" (MGUS). Sensory symptoms predominate with paresthesias, numbness, imbalance, and gait ataxia. Electrodiagnostic studies show mixed demyelinating and axonal features and often may be indistinguishable from findings in chronic inflammatory demyelinating polyneuropathy. Some have a pure axonal polyneuropathy, and in these patients the relationship to the paraprotein is less certain. With limited success, correlations have been made between the immunoglobulin type (IgM, IgG, or IgA) and the clinical and electromyographic characteristics of the neuropathy. The treatment of MGUS neuropathies poses a considerable challenge. Patients with IgG/IgA-MGUS have improved with corticosteroids or intravenous immune globulin. Only the benefit of plasma exchange has been substantiated in a controlled trial. The IgM neuropathies tend to be more refractory but often improve with similar regimens, particularly if cytotoxic agents are added in doses sufficient to reduce the amount of the M-protein. In addition to plasma exchange, chlorambucil, and cyclophosphamide, interferon-alpha is a novel therapy that holds promise for patients with IgM neuropathies associated with anti-myelin associated antibodies.

- **Greenhouse JB, Seltman H.** Using prior distributions to synthesize historical evidence: comments on the Goodman-Sladky case study of IVIg in Guillain-Barre syndrome. *Clin Trials* 1906; 2: 311-318.

**Abstract:** One feature of the Bayesian approach is that it provides methods for synthesizing what is known about a question of interest and provides a formalism based on the laws of probability for incorporating this auxiliary knowledge into the planning and the analysis of the next study. In this comment, we use elements of the Goodman-Sladky case study to illustrate (1) the use of Bayesian methods to quantify historical information about an intervention through the specification of a prior distribution, (2) an approach to the analysis of the sensitivity of the conclusions of a Bayesian analysis to the specification of the prior distribution, and (3) we comment on the role of research synthesis for combining information about an intervention from different data sources as a tool to help summarize evidence about the intervention.

- **Gurses N, Uysal S, Cetinkaya F, Islek I, Kalayci AG.** Intravenous immunoglobulin treatment in children with Guillain-Barre syndrome. *Scand J Infect Dis* 1995; 27: 241-243.

**Abstract:** Guillain-Barre syndrome is an acquired demyelinating polyneuropathy that is presumed to be immune-mediated. On the basis of this assumption,

intravenous immunoglobulin (IVIG) has been used in the treatment of Guillain-Barre syndrome in recent years and found to be effective. To test this we performed a randomized study in patients with Guillain-Barre syndrome by giving IVIG (1 g/kg body weight per day over 2 consecutive days) in 9 children who were compared with 9 patients who were observed but not given specific therapy. We concluded that intravenous immunoglobulin is a safe and effective treatment for childhood Guillain-Barre syndrome which shortens the time to recovery.

• **Gurses N, Uysal S, Cetinkaya F, Islek I, Kalayci AG.** Intravenous immunoglobulin treatment in children with Guillain-Barre syndrome. *Scand J Infect Dis* 1995; 27: 241-243.

**Abstract:** Guillain-Barre syndrome is an acquired demyelinating polyneuropathy that is presumed to be immune-mediated. On the basis of this assumption, intravenous immunoglobulin (IVIG) has been used in the treatment of Guillain-Barre syndrome in recent years and found to be effective. To test this we performed a randomized study in patients with Guillain-Barre syndrome by giving IVIG (1 g/kg body weight per day over 2 consecutive days) in 9 children who were compared with 9 patients who were observed but not given specific therapy. We concluded that intravenous immunoglobulin is a safe and effective treatment for childhood Guillain-Barre syndrome which shortens the time to recovery.

• **Hadden R.** European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *J Peripher Nerv Syst* 2006; 11: 9-19.

**Abstract: BACKGROUND:** Paraprotein-associated neuropathies have heterogeneous clinical, neurophysiological, neuropathological, and hematological features. **OBJECTIVES:** The aim of this guideline was to prepare evidence-based and consensus guidelines on the clinical management of patients with both a demyelinating neuropathy and a paraprotein [paraproteinemic demyelinating neuropathy (PDN)]. **METHODS:** Disease experts and a representative of patients considered references retrieved from MEDLINE and the Cochrane Library and prepared statements that were agreed in an iterative fashion. **RECOMMENDATIONS:** In the absence of adequate data, evidence-based recommendations were not possible, but the Task Force agreed on the following good practice points: (1) patients with PDN should be investigated for a malignant plasma cell dyscrasia; (2) the paraprotein is more likely to be causing the neuropathy if the paraprotein is immunoglobulin M (IgM), antibodies are present in serum or on biopsy, or the clinical phenotype is chronic distal sensory neuropathy; (3) patients with IgM PDN usually have predominantly distal and sensory impairment, with prolonged distal motor latencies, and often anti-myelin-associated glycoprotein antibodies; (4) IgM PDN sometimes responds to immunotherapies. Their potential benefit should be balanced against their possible side effects and the usually slow disease progression; (5) IgG and IgA PDN may be indistinguishable from chronic inflammatory demyelinating polyradiculoneuropathy clinically, electrophysiologically, and in response to treatment; and (6) for POEMS syndrome, local irradiation or resection of an isolated plasmacytoma, or melphalan with or without corticosteroids, should be considered, with hemato-oncology advice.

• **Hadden RD, Cornblath DR, Hughes RA, et al.** Electrophysiological classification of Guillain-Barre syndrome: clinical associations and outcome. Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group. *Ann Neurol* 1998; 44: 780-788.

**Abstract:** We performed electrophysiological and serological testing within 15 days of symptom onset on 369 patients with Guillain-Barre Syndrome (GBS) enrolled in a trial comparing plasma exchange, intravenous immunoglobulin, and both treatments. Patients were classified into five groups by motor nerve conduction criteria; 69% were demyelinating, 3% axonal, 3% inexcitable, 2% normal, and 23% equivocal. Six of 10 (60%) patients with axonal neurophysiology had had a preceding diarrheal illness compared with 71 of 359 (20%) in other groups. Antiganglioside GM1 antibodies were present in a higher proportion of patients with axonal physiology or inexcitable nerves than other patients. The number dead or unable to walk unaided at 48 weeks was greater in the group with initially inexcitable nerves (6 of 12, 50%) compared with the rest (52 of 357, 15%), but was not significantly different between the axonal (1 of 10, 10%) and demyelinating (44 of 254, 17%) groups. Sensory action potentials and clinical sensory examination were both normal in 53 of 342 (16%) patients, and these "pure motor GBS" patients were more likely than other GBS patients to have IgG antiganglioside GM1 antibodies and to have had preceding diarrhea but had a similar outcome. The axonal group was more likely than

other groups to have normal sensory action potentials. The outcomes in response to the three treatments did not differ in any subgroup (including patients with pure motor GBS or preceding diarrhea) or any neurophysiological category.

• **Hadden RD, Hughes RA.** Management of inflammatory neuropathies. *J Neurol Neurosurg Psychiatry* 2003; 74 Suppl 2: ii9-ii14.

• **Hafler DA, Slavik JM, Anderson DE, O'Connor KC, De Jager P, Baecher-Allan C.** Multiple sclerosis. *Immunol Rev* 2005; 204: 208-231.

**Abstract:** Multiple sclerosis (MS) is a complex genetic disease associated with inflammation in the central nervous system (CNS) white matter and is thought to be mediated by autoimmune processes. Clonal expansion of B cells, their antibody products, and T cells, hallmarks of inflammation in the CNS, are found in MS. The association of the disease with major histocompatibility complex genes, the inflammatory white matter infiltrates, similarities with animal models, and the observation that MS can be treated with immunomodulatory and immunosuppressive therapies support the hypothesis that autoimmunity plays a major role in the disease pathology. This review discusses the immunopathology of MS with particular focus given to regulatory T cells and the role of B cells and antibodies, immunomodulatory therapeutics, and finally new directions in MS research, particularly new methods to define the molecular pathology of human disease with high-throughput examination of germline DNA haplotypes, RNA expression, and protein structures that will allow the generation of a new series of hypotheses that can be tested to develop better understandings and therapies for this disease.

• **Hahn AF, Bolton CF, Zochodne D, Feasby TE.** Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy. A double-blind, placebo-controlled, cross-over study. *Brain* 1996; 119 (Pt 4): 1067-1077.

**Abstract:** Thirty patients with definite or probable chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) of chronic progressive (16 patients) or relapsing (14 patients) course were randomly assigned to receive intravenous immunoglobulin (IvIg) 0.4 g per kg body weight or a placebo treatment on 5 consecutive days in a double-blind, cross-over trial. Neurological function was monitored by serial quantitative assessments [neurological disability score (NDS); clinical grade (CG) and grip strength (GS) measurements] and by electrophysiological studies before and after each treatment period. Twenty-five patients completed both treatment periods. A comparison of the observed changes in clinical outcome measures revealed statistically significant differences in favour of IvIg, with (mean +/- SD) improvements in NDS by 24.4 +/- 5.4 points ($P < 0.002$) in CG by 1 +/- 0.3 points ($P < 0.001$) in GS by +6.3 +/- 1.7 kg ($P < 0.005$), whereas scores were unchanged or worse with placebo. A secondary two-groups analysis of the first trial period included all 30 patients; 16 patients had been randomly assigned to IvIg and 14 to placebo treatments. Again significant differences in favour of IvIg were observed in all the clinical end-points: improvement in NDS was 35.6 +/- 25 points ($P < 0.0001$), in CG it was 1.3 +/- 1.9 points ($P < 0.002$) and in GS +9.8 +/- 7.7 kg ($P < 0.001$), whereas all scores worsened with placebo. Of the 30 patients, 19 (63%) improved with IvIg treatments; nine out of 16 patients (56%) with chronic progressive CIDP, and 10 out of 14 patients (71%) with relapsing CIDP (differences were not statistically significant). A placebo response was seen in five patients. Comparison of paired electrophysiological measurements before and 4 weeks after IvIg treatments revealed statistically significant improvements in the summed motor conduction velocities (sigma MCV; $P < -0.0001$) and in the summed compound muscle action potentials (CMAP) evoked with proximal stimulation (sigma proximal CMAP, $P < 0.03$) of median, ulnar, peroneal and tibial nerves. Eight of nine IvIg responders with chronic progressive CIDP improved gradually to normal function with a single 5 day course of IvIg; in five of these, small doses of prednisone were prescribed during follow-up. In 10 IvIg responders with relapsing CIDP, improvements lasted a median 6 weeks (range 3-22 weeks) and was reproducible with open label treatments. All 10 patients have been maintained and stabilized with IvIg pulse therapy of 1 g per kg body weight or less, given as a single infusion prior to the expected relapse. A beneficial response to IvIg was found to be most likely in patients with acute relapse or with disease of one year or less. Patients with predominantly sensory signs did not improve.

• **Hahn JS, Siegler DJ, Enzmann D.** Intravenous gammaglobulin therapy in recurrent acute disseminated encephalomyelitis. *Neurology* 1996; 46: 1173-1174.

• **Hamed LM, Silbiger J, Guy J, et al.** Parainfectious optic neuritis and encephalomyelitis. A report of two cases with thalamic involvement. *J Clin Neuroophthalmol* 1993; 13: 18-23.

Abstract: Two children developed mental status alteration and bilateral profound visual loss secondary to optic neuritis. The clinical picture was consistent with parainfectious encephalomyelitis. Magnetic resonance imaging showed bilateral involvement of the thalamus in both cases. In one case the thalamic involvement was solitary and was suspected initially to represent a primary thalamic neoplasm. This was ruled out by a stereotactic biopsy of the thalamus, which showed perivascular inflammation consistent with parainfectious encephalomyelitis. The clinical and neuroimaging findings improved significantly following corticosteroid administration. Several relapses occurred upon initial attempts at corticosteroid cessation.

• **Hamrock DJ.** Adverse events associated with intravenous immunoglobulin therapy. *Int Immunopharmacol* 2006; 6: 535-542.

**Abstract:** In addition to its U.S. Food and Drug Administration (FDA) approved conditions, immune globulin intravenous (IGIV) is now being used to treat a vast array of autoimmune disorders. Some of the reasons for this overall increase in the use of IGIV include its effectiveness and safety. Despite many years of safe use, side effects and adverse reactions still occur. Common and mild side effects associated with IGIV include: headache, malaise, nausea, low-grade fever, urticaria, arthralgias, and myalgia. These symptoms typically resolve within a few days after their onset. Although rare, the serious and potentially fatal side effects include: anaphylactic reactions, aseptic meningitis, acute renal failure, stroke, myocardial infarction, and other thrombotic complications. Many of these side effects have occurred in patients who have significant, underlying risk factors for the development of the event. Thus, it is vitally important that a thorough and comprehensive medical evaluation be performed on every patient who is being evaluated for potential IGIV therapy. This evaluation can, to some extent, significantly minimize the risk of these side effects. Careful, constant, and close monitoring by trained personnel during the infusion can also result in early detection of such events. Physicians should thoroughly discuss the risks and benefits of IGIV with patients who are being considered for this therapy.

• **Hanson LJ, Cafruny WA.** Current concepts in multiple sclerosis: Part II. S D *J Med* 2002; 55: 477-481.

**Abstract:** Multiple sclerosis (MS) is a complex and challenging autoimmune disease of the central nervous system, affecting approximately 0.1% of the US population. Evidence to date suggests that viral infection triggers autoimmune attack against nerve cells in genetically-susceptible individuals. Neurologic deficits then appear, typically with a variable course and episodes of remission. Partial treatment success has been obtained with immunomodulating agents, such as interferon-beta and intravenous immunoglobulins. Current research is directed at elucidating potential viral causes of MS, as well as the interaction of host genes with the immunopathogenic mechanisms involved in MS. In the future, it may be possible to vaccinate susceptible individuals against MS, as well as refine immunomodulation therapy for the treatment of MS.

• **Hanson LJ, Cafruny WA.** Current concepts in multiple sclerosis: Part I. S D *J Med* 2002; 55: 433-436.

**Abstract:** Multiple sclerosis (MS) is a complex and challenging autoimmune disease of the central nervous system, affecting approximately 0.1% of the US population. Evidence to date suggests that viral infection triggers autoimmune attack against nerve cells in genetically-susceptible individuals. Neurologic deficits then appear, typically with a variable course and episodes of remission. Partial treatment success has been obtained with immunomodulating agents, such as interferon-beta and intravenous immunoglobulins. Current research is directed at elucidating potential viral causes of MS, as well as the interaction of host genes with the immunopathogenic mechanisms involved in MS. In the future, it may be possible to vaccinate susceptible individuals against MS, as well as refine immunomodulation therapy for the treatment of MS.

• **Harel M, Shoenfeld Y.** Intravenous immunoglobulin and Guillain-Barre syndrome. *Clin Rev Allergy Immunol* 2005; 29: 281-287.

**Abstract:** Guillain-Barre syndrome (GBS) is a relatively common, potentially lethal disease of a presumed autoimmune origin, known to cause a progressive flaccid paralysis. The treatment of GBS consists of both supportive and immunomodulatory

treatments, among which intravenous immunoglobulin (IVIg) and plasma exchange (PE) are considered most effective. A number of randomized, controlled studies have shown IVIg to be at least as effective as PE in the treatment of GBS, and in some cases superior. Moreover, IVIg has been found to be safer than PE, having a lower frequency of multiple complications. IVIg has also been found to be both effective and safe in the treatment of pediatric patients with GBS. Thus, its efficacy, safety, and availability make IVIg the treatment of choice in many patients with GBS

• **Harloff A, Rauer S, Hofer M, Klisch J, Els T.** Fulminant acute disseminated encephalomyelitis mimicking acute bacterial menigoencephalitis. *Eur J Neurol* 2005; 12: 67-69.

**Abstract:** Most patients with acute disseminated encephalomyelitis (ADEM) recover quickly under corticosteroid treatment and have a favourable long-term prognosis. We report on a young woman with acute onset of an extensive and solitary white-matter lesion in the left hemisphere. Fever, high pleocytosis and elevated protein in cerebrospinal fluid initially suggested bacterial meningoencephalitis. The patient died from brain herniation despite maximal conservative therapy. Histological changes in necropsy were consistent with the diagnosis ADEM. Treatment options of fulminant ADEM are discussed.

• **Hilario MO, Yamashita H, Lutti D, Len C, Terreri MT, Lederman H.** Juvenile idiopathic inflammatory myopathies: the value of magnetic resonance imaging in the detection of muscle involvement. *Sao Paulo Med J* 2000; 118: 35-40.

**Abstract: CONTEXT:** One of the major current challenges related to juvenile idiopathic inflammatory myopathy is the search for highly sensitive and specific non-invasive methods for diagnosis as well as for follow-up. **OBJECTIVES:** The aim of our study was to describe typical magnetic resonance imaging findings and to investigate the usefulness of this method in detecting active muscle disease in juvenile dermatomyositis and juvenile systemic lupus erythematosus patients. **DESIGN:** Transverse study, blinded assessment. **SETTING:** University referral unit (Pediatric Rheumatology section, Department of Pediatrics, Universidade Federal de Sao Paulo / Escola Paulista de Medicina). **SAMPLE:** Thirteen patients (9 girls) with dermatomyositis, as well as 13 patients (12 girls) with juvenile systemic lupus erythematosus and 10 normal children (5 girls), were enrolled in the study. **MAIN MEASUREMENTS:** Qualitative and quantitative analyses of gluteus maximus, quadriceps, adductors and flexors were performed and evaluated by two radiologists, blinded to all clinical information. Spin-echo in T1, DP, T2 and IR was used in all MRI images. **RESULTS:** The different muscle groups presented non-uniform involvement in the patients. The patients with dermatomyositis presented acute and chronic muscular alterations, while those with lupus presented only chronic myopathy, especially atrophy. In the dermatomyositis group, the major alterations were found in the gluteus and flexor regions (signal intensity and fat replacement). The signal intensity was increased in all acute myopathies. **CONCLUSION:** The qualitative and quantitative resonance analyses are useful in detecting clinically active disease in patients with dermatomyositis.

• **Hiraga A, Mori M, Ogawara K, Hattori T, Kuwabara S.** Differences in patterns of progression in demyelinating and axonal Guillain-Barre syndromes. *Neurology* 2003; 61: 471-474.

**Abstract: BACKGROUND:** Immune treatments are recommended for patients with Guillain-Barre syndrome (GBS) who cannot walk independently, but a considerable number of GBS patients are in the progressive phase at the first examination. **OBJECTIVE:** To investigate whether progression patterns differ in demyelinating and axonal subtypes of GBS. **METHODS:** Clinical, laboratory, and electrophysiologic data on 131 consecutive patients with GBS were reviewed. Patients were classified as having acute inflammatory demyelinating polyneuropathy (AIDP) or acute motor axonal neuropathy (AMAN) based on electrodiagnostic criteria. **RESULTS:** Forty-one patients had AIDP, 62 AMAN, and 28 were unclassified. Age, sex, and Hughes Functional Grading Scale score at the first medical examination did not differ for the AIDP and AMAN patients. Mean periods between neurologic onset and first examination (5.3 vs 4.2 days; $p = 0.01$) and neurologic onset and nadir (18.0 vs 11.5 days; $p = 0.001$) were longer for the AIDP group. In the subgroup of those with mild disability (able to walk independently at the first neurologic examination), 88% of the AMAN patients had reached the nadir, whereas 65% of the AIDP patients had reached it. The remaining 35% progressed to it over the next 1 to 2 weeks and were unable to walk at nadir. **CONCLUSIONS:** The patterns and speeds of progression differ in AMAN and AIDP, AMAN having a rapid progression and an early nadir. AIDP patients frequently have a significantly long progression after the first examination; therefore, they need to be carefully monitored.

• **Hughes R, Swan A.** Treatment of Guillain-Barre syndrome with intravenous methylprednisolone. *Ann Neurol* 1995; 37: 683-684.

• **Hughes R, Bensa S, Willison H, et al.** Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 2001; 50: 195-201.

**Abstract:** This multicenter, randomized, double-blind, crossover trial compared a six week course of oral prednisolone tapering from 60 mg to 10 mg daily with intravenous immunoglobulin (IVIg) 2.0 g/kg given over one to two days for treating chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Twenty-four of the thirty-two randomized patients completed both treatment periods. Both treatments produced significant improvements in the primary outcome measure, change in an 11-point disability scale two weeks after randomization. There was slightly, but not significantly, more improvement after IVIg than with prednisolone, the mean difference between the groups in change in disability grade being 0.16 (95% CI = -0.35 to 0.66). There were also slightly, but not significantly, greater improvements favoring IVIg in the secondary outcome measures: time to walk 10 meters after two weeks and improvement in disability grade after six weeks. Results may have been biased against IVIg by the eight patients who did not complete the second arm of the trial. A serious adverse event (psychosis) attributable to treatment occurred in one patient while on prednisolone and in none with IVIg.

• **Hughes RA, Raphael JC, Swan AV, van Doorn PA.** Intravenous immunoglobulin for Guillain-Barre syndrome. Cochrane Database *Syst Rev* 1906; CD002063.

**Abstract: BACKGROUND:** Guillain-Barre syndrome is a potentially serious, acute, paralysing, probably autoimmune disease caused by inflammation of the peripheral nerves. Recovery has been shown to be speeded by plasma exchange which replaces the patient's own plasma with a plasma substitute. Intravenous immunoglobulin purified from donated blood is beneficial in other autoimmune diseases and is easier to administer. **OBJECTIVES:** To determine the efficacy of intravenous immunoglobulin in comparison with no treatment or other treatments for treating Guillain-Barre syndrome and to determine the most efficacious dose. **SEARCH STRATEGY:** Search of the Cochrane Neuromuscular Disease Group register using Guillain-Barre syndrome and acute polyradiculoneuritis as the search terms, bibliographies of trials and contact with their authors and other experts. **SELECTION CRITERIA:** Randomised and quasi-randomised trials. **DATA COLLECTION AND ANALYSIS:** Two reviewers examined the titles and abstracts of all the papers retrieved by the search, extracted the data onto forms designed for this review, and independently assessed the quality of the trials. **MAIN RESULTS:** The only trial comparing intravenous immunoglobulin with supportive treatment was inadequate to establish its value. Another Cochrane systematic review has shown that plasma exchange (PE) hastens recovery. Plasma exchange has become the gold standard against which other treatments need to be compared. We found three randomised trials that compared intravenous immunoglobulin with PE. We were able to combine the results of the two largest trials in a metaanalysis involving 398 patients. The primary outcome measure in this review was the change in a 7 grade disability scale four weeks after randomisation. The weighted mean difference of this measure was not significant, being only 0.11 (95% CI -0.14 to 0.37) of a disability grade more improvement in the intravenous immunoglobulin group than the PE group. There were also no significant differences in other outcome measures, including time to walk unaided, mortality, and proportion of patients unable to walk without aid after a year but some of these outcome measures were only available for one trial. We also reviewed one trial involving 249 patients which compared PE followed by intravenous immunoglobulin with PE alone and another involving 37 patients which compared immunoabsorption followed by intravenous immunoglobulin with immunoabsorption alone. Neither revealed any significant differences between the regimens with and without intravenous immunoglobulin. We did not discover any dose ranging studies of intravenous immunoglobulin except for one that is ongoing. **REVIEWER'S CONCLUSIONS:** There are no adequate trials to determine whether intravenous immunoglobulin is more beneficial than placebo. Intravenous immunoglobulin and plasma exchange have a similar ability to speed the recovery from Guillain-Barre syndrome. Giving intravenous immunoglobulin after plasma exchange is not significantly better than plasma exchange alone. Randomised trials are needed to decide whether intravenous immunoglobulin helps in mild Guillain-Barre syndrome or in disease which has lasted more than two weeks. Randomised trials also need to establish the optimal dose.

• **Hughes RA, Raphael JC, Swan AV, Doorn PA.** Intravenous immunoglobulin for Guillain-Barre syndrome. *Cochrane Database Syst Rev* 1906; CD002063

**Abstract: BACKGROUND:** Guillain-Barre syndrome is an acute, paralysing, inflammatory peripheral nerve disease. Intravenous immunoglobulin purified from donated blood is beneficial in other autoimmune diseases. **OBJECTIVES:** We aimed to determine the efficacy of intravenous immunoglobulin for treating Guillain-Barre syndrome. **SEARCH STRATEGY:** We searched the Cochrane Neuromuscular Disease Group register (search updated 11 February 2003), MEDLINE and EMBASE (from January 2000 to February 2003) using Guillain-Barre syndrome and acute polyradiculoneuritis as the search terms. We also searched bibliographies of trials and made contact with their authors and other experts. **SELECTION CRITERIA:** We included all randomised and quasi-randomised trials. **DATA COLLECTION AND ANALYSIS:** Two reviewers examined the titles and abstracts of all the papers retrieved by the search, extracted the data and assessed the quality of the trials independently. **MAIN RESULTS:** Two trials comparing intravenous immunoglobulin with supportive treatment were inadequate to establish its value. Another Cochrane systematic review has shown that plasma exchange hastens recovery. We found six randomised trials that compared intravenous immunoglobulin with plasma exchange. In a meta-analysis of five trials involving 536, mostly adult, participants who were unable to walk unaided and had been ill for less than two weeks. The primary outcome measure in this review was the change in a seven grade disability scale four weeks after randomisation. The weighted mean difference of this measure was not statistically significant, being only 0.04 (95% CI -0.26 to 0.19) of a disability grade more improvement in the intravenous immunoglobulin group than the plasma exchange group. There were also no statistically significant differences in time to walk unaided, mortality, and proportion of participants unable to walk without aid after a year.One trial involving 249 participants compared plasma exchange followed by intravenous immunoglobulin with plasma exchange alone, and another involving 37 participants compared immunoabsorption followed by intravenous immunoglobulin with immunoabsorption alone. Neither revealed significant extra benefit from intravenous immunoglobulin.One study of only 39 participants showed a trend towards more improvement with high-dose compared with low-dose intravenous immunoglobulin. **REVIEWER'S CONCLUSIONS:** Although there are no adequate comparisons with placebo, intravenous immunoglobulin hastens recovery from Guillain-Barre syndrome as much as plasma exchange. Giving intravenous immunoglobulin after plasma exchange is not significantly better than plasma exchange alone. Randomised trials are needed to decide the effect of intravenous immunoglobulin in children, in adults with mild disease and in adults who start treatment after more than two weeks.

• **Hughes RA, Newsom-Davis JM, Perkin GD, Pierce JM.** Controlled trial prednisolone in acute polyneuropathy. *Lancet* 1978; 2: 750-753.

**Abstract:** In a multicentre, randomised trial of prednisolone in acute polyneuropathy of undetermined aetiology (Guillain-Barre syndrome), 21 patients were treated with prednisolone (60 mg daily for one week, 40 mg daily for four days, and then 30 mg daily for three days) and 19 did not have steroid treatment. Patients were graded on a six-point scale by one of two neurologists who had no knowledge of the treatment schedule. Reassessment at one, three, and twelve months consistently showed greater improvement in the control than the prednisolone group but the only statistically significant result was in the improvement at three months among patients entered to the trial within a week of onset of illness. The 6 control patients had improved by 2.5 +/- 0.43 grades by three months from entry to the trial whereas the 10 prednisolone patients had only improved by 0.9 +/- 0.46 grades (P less than 0.05). There was 1 death related to the polyneuropathy in each group, and 1 suicide in a control patient during convalescence. 6 prednisolone patients were left with considerable disability compared with 1 control patient. There were 3 relapses in the prednisolone group, but none in the control group. The results indicate that steroid treatment is not beneficial and can be detrimental in acute neuropathy of undetermined aetiology.

• **Hughes RA.** Intravenous IgG in Guillain-Barre syndrome. *BMJ* 1996; 313: 376-377.

• **Hughes RA.** Intravenous IgG in Guillain-Barre syndrome. *BMJ* 1996; 313: 376-377.

• **Hughes RA.** Plasma exchange versus intravenous immunoglobulin for Guillain-Barre syndrome. *Ther Apher* 1997; 1: 129-130.

**Abstract:** Previous randomized controlled trials in the U.S.A. and France have provided strong

evidence that plasma exchange (PE) hastens recovery from Guillain-Barre syndrome (GBS). A Dutch trial compared intravenous immunoglobulin (IVIg) with PE in an open study and showed that recovery was as fast or slightly faster in the group treated with IVIg. This report was followed by accounts of a small series of patients who had seemed to progress or relapse after treatment with IVIg. To resolve this controversy, the Plasma Exchange Sandoglobulin GBS Trial Group (PS GBS Trial Group) selected 383 patients randomly to receive PE, IVIg, or PE followed by IVIg. After 4 weeks, the outcome was similar in each of the 3 groups. These 3 regimens also had similar outcomes during 48 weeks of follow-up.

• **Hughes RA, Hadden RD, Rees JH, Swan AV.** The Italian Guillain-Barre Study Group. The prognosis and main prognostic indicators of Guillain-Barre syndrome: a multicentre prospective study of 297 patients. *Brain* 1998; 121 ( Pt 4): 767-769.

• **Hughes RA, van Der M.** Corticosteroids for treating Guillain-Barre syndrome. *Cochrane Database Syst Rev* 2000; CD001446.

**Abstract: BACKGROUND:** The cause of Guillain-Barre syndrome (GBS) is inflammation of the peripheral nerves which corticosteroids would be expected to benefit. **OBJECTIVES:** To examine the efficacy of corticosteroids in hastening recovery and reducing the long term morbidity from Guillain-Barre syndrome (GBS). **SEARCH STRATEGY:** Search of the Cochrane Neuromuscular Disease Group register for randomised trials and enquiry from authors of trials and other experts in the field. **SELECTION CRITERIA:** Types of studies: quasi-randomised or randomised controlled trials Types of participants: patients with GBS of all ages and all degrees of severity Types of interventions: any form of corticosteroid or adrenocorticotrophic hormone Types of outcome measures: Primary: improvement in disability grade on a commonly used seven point scale four weeks after randomisation Secondary: time from randomisation until recovery of unaided walking, time from randomisation until discontinuation of ventilation (for those ventilated), mortality, proportion of patients dead or disabled (unable to walk without aid) after 12 months, improvement in disability grade after six months, improvement in disability grade after 12 months, proportion of patients who relapse, and proportion of patients with adverse events related to corticosteroid treatment. **DATA COLLECTION AND ANALYSIS:** We identified six randomised trials. One author extracted the data and the other checked them. We obtained some missing data from investigators. **MAIN RESULTS:** The six eligible trials included a total of 195 corticosteroid treated patients and 187 control subjects. One trial of intravenous methylprednisolone accounted for 243 of the total 382 subjects studied (63%). This trial did not show a significant difference in any disability related outcome between the corticosteroid and placebo groups. There was no significant difference between the corticosteroid and control groups for the primary outcome measure, improvement in disability grade four weeks after randomisation. The weighted mean difference of the three trials for which this outcome was available showed no difference. The actual figure was 0.01 (95% CI -0.27 to 0.29) grade in favour of the corticosteroid group. There was also no significant difference between the groups for most of the secondary outcome measures. However in the largest trial hypertension developed less often in the intravenous methylprednisolone group (2/124, 1.6%) than in the control group (12/118, 10.2%), a significant difference in favour of corticosteroid treatment (relative risk 0.20, 95% CI 0.04 to 0.66). **REVIEWER'S CONCLUSIONS:** Corticosteroids should not be used in the treatment of Guillain-Barre syndrome. If a patient with Guillain-Barre syndrome needs corticosteroid treatment for some other reason its use will probably not do harm. The effect of intravenous methylprednisolone combined with intravenous immunoglobulin in Guillain-Barre syndrome is being tested with a randomised trial.

• **Hughes RA.** Systematic reviews of treatment for chronic inflammatory demyelinating neuropathy. *Rev Neurol* (Paris) 2002; 158: S32-S36.

**Abstract:** Chronic inflammatory demyelinating polyradiculoneuropathies include chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN) and paraprotein-associated demyelinating neuropathy. This review summarises the evidence from randomised controlled trials (RCTs) for the treatment of these conditions. It leads to the conclusions that: 1) steroids are beneficial in CIDP but not MMN and their efficacy in paraproteinaemic demyelinating neuropathy (PDN) is uncertain; 2) intravenous immunoglobulin (IVIg) produces short-term benefit in CIDP, MMN and IgM PDN. Its effect in IgG or IgA PDN has not been tested in RCTs; 3) plasma exchange (PE) also produces short-term benefit in CIDP and IgG or IgA PDN but probably not in MMN; 4) there is almost no information from RCTs concerning the

possible benefits of immunosuppressive agents; and 5) volunteers are needed to write Cochrane systematic reviews of IVIg for MMN and of interventions for PDN associated with IgG and IgA.

• **Hughes RA.** Systematic reviews of treatment for inflammatory demyelinating neuropathy. *J Anat* 2002; 200: 331-339.

**Abstract:** This review describes the progress made in preparing Cochrane systematic reviews of randomized controlled trials for Guillain-Barre syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN) and the demyelinating neuropathies associated with paraproteins. The discovery of antibodies against myelin and axolemmal glycolipids and proteins has not yet replaced the clinicopathological classification on which treatment trials have been based. Systematic reviews have endorsed the equivalence of plasma exchange (PE) and intravenous immunoglobulin (IVIg) and the lack of efficacy of steroids in GBS. Systematic reviews have also endorsed the value of steroids, PE and IVIg in CIDP but randomized controlled trials have only shown benefit from IVIg in MMN. There is a paucity of evidence concerning the efficacy of treatments in paraproteinaemic demyelinating neuropathy apartment from small trials showing short-term benefit from PE or IVIg. There is a lack of good quality controlled trials of immunosuppressive agents in any of these conditions. As the number of treatment trials increases, Cochrane systematic reviews will be an increasingly valuable resource for summarizing the evidence from randomised controlled trials on which to base clinical practice. They already demonstrate major deficiencies in the existing evidence base.

• **Iijima M, Yamamoto M, Hirayama M, et al.** Clinical and electrophysiologic correlates of IVIg responsiveness in CIDP. *Neurology* 2005; 64: 1471-1475.

**Abstract:** To identify clinical and electrophysiologic features related to IV immunoglobulin (IVIg) responsiveness in chronic inflammatory demyelinating polyneuropathy (CIDP), the authors conducted a multicenter study on 312 patients with CIDP (199 responders and 113 nonresponders). Muscle atrophy and decreased compound muscle action potential were pronounced in nonresponders of IVIg. Male gender, longer disease duration, and slow progression of symptoms were also associated with IVIg unresponsiveness. Features suggesting axonal dysfunction in peripheral nerves indicated IVIg unresponsiveness in CIDP.

• **Jolles S, Sewell WA, Misbah SA.** Clinical uses of intravenous immunoglobulin. *Clin Exp Immunol* 2005; 142: 1-11.

• **Jorgensen SH, Jensen PE, Laursen H, Sorensen PS.** Intravenous immunoglobulin ameliorates experimental autoimmune encephalomyelitis and reduces neuropathological abnormalities when administered prophylactically. *Neurol Res* 2005; 27: 591-597.

**Abstract: BACKGROUND AND METHODS:** Immunomodulation with intravenous immunoglobulin (IVIG) represents a way of interfering with the disease process in multiple sclerosis (MS). In this study, the effects of IVIG on neurological symptoms and central nervous system (CNS) pathology were evaluated in experimental autoimmune encephalomyelitis (EAE), an MS animal model. EAE was induced in susceptible Dark Agouti rats by active immunization with a spinal cord homogenate, and infusions of 1 g/kg IVIG were given prophylactically or therapeutically. **RESULTS:** The administration of IVIG at the time of immunization significantly suppressed the development of neurological symptoms compared with infusions of placebo (mean EAE score 0.6+/-0.3 versus 2.3+/-0.4). Moreover, the prophylactic IVIG administration resulted in a significant inhibition of the inflammatory response in CNS tissue (inflammation score 1.1+/-0.2 versus 1.8+/-0.2 after placebo). No beneficial effects were obtained by therapeutic IVIG infusions as the EAE disease course and the degree of inflammation and demyelination in the CNS were not different from animals receiving treatment with placebo. **CONCLUSIONS:**The present study indicates that IVIG reduces the symptoms of EAE by suppression of the CNS inflammation that characterizes CNS pathology in these animals. Taking into account data from clinical trials of IVIG in MS, the results further suggest that IVIG acts primarily during the induction phase of the immune response thus preventing the development of relapses in MS.

• **Kalanie H, Gharagozli K, Hemmatie A, Ghorbanie M, Kalanie AR.** Interferon Beta-1a and intravenous immunoglobulin treatment for multiple sclerosis in Iran. *Eur Neurol* 1906; 52: 202-206.

**Abstract:** The aim of the study was to evaluate the efficacy and safety of interferon beta-1a (Avonex)

and intravenous immunoglobulin (IVIG) in clinical practice for the treatment of relapsing-remitting multiple sclerosis. Avonex is the most common disease-modifying therapy used in Iran due to its ease of administration. IVIG is also frequently used due to its alleged effectiveness and fewer side effects. Eighty patients were selected and prospectively monitored according to a predefined protocol. They were then randomized to receive either weekly intramuscular injections of Avonex or 0.4 g/kg monthly IVIG in a single blind fashion and following an attack of exacerbation which was treated with steroids. Basal relapse rate and Expanded Disability Status Scale (EDSS) were similar in both groups of patients ($p > 0.4$). Seventy-two patients remained in the study. The annual relapse rate consistently decreased from 0.95 +/- 0.41 to 0.60 +/- 0.67 (approximately 32%, $p < 0.001$) for 34 patients treated with Avonex and from 1.05 +/- 0.34 to 0.55 +/- 0.46 for 38 patients in the IVIG group (approximately 47%, $p < 0.001$). EDSS decreased by 0.4 units in IVIG-treated patients ($p < 0.001$) and remained stable ($0.2 < p < 0.3$) in the Avonex arm. This study confirms the relative efficacy of both treatments with better safety profile for IVIG in the studied Iranian population. However, the results are very preliminary ones, due to limited numbers of patients and only 12 months of treatment.

• **Kanaheswari Y, Baizura J, Paeds M, Zulfiqar A.** Intravenous immunoglobulin in the treatment of acute disseminated encephalomyelitis. *Med J Malaysia* 2004; 59: 103-107.

**Abstract:** We describe a case of acute disseminated encephalomyelitis in a child. This case is unusual in that the illness was characterised by recurrent episodes rather than a monophasic course and that the choice of treatment was intravenous immunoglobulin over corticosteroids. The rapid and remarkable recovery is highlighted and a review of the treatment for this rare condition is discus.

• **Kashef S, Safari M, Amin R.** Initial intravenous gamma-globulin treatment failure in Iranian children with Kawasaki disease. *Kaohsiung J Med Sci* 2005; 21: 401-404.

**Abstract:** The purpose of this study was to determine the initial rates of intravenous gamma-globulin treatment (IVIG) failure in Kawasaki disease (KD) and their predisposing factors. This study was a retrospective analysis of the initial response to IVIG (2 g/kg), assessed from the medical reports of all patients admitted to Namazee Hospital pediatric ward, from March 1998 to March 2002, and who fulfilled the criteria for KD. Data were available for 64 patients, 58 of whom (90.6%) became afebrile 48 hours after completion of the initial dose of IVIG (Group I) and six (9.4%) who remained febrile (Group II). Two patients had a prompt response to a second dose of IVIG. In Group I, five patients (8.6%) developed coronary artery disease, seen on echocardiography. In Group II, two patients (33.3%) developed coronary artery disease. No significant difference was found in the prevalence of coronary artery disease between the two groups ($p = 0.12$), or in age or gender. The rate of initial treatment failure was 9.4% in this cohort of patients, which is comparable with previous reports. No predictive factors such as coronary artery disease, age or gender were found for initial treatment failure in KD.

• **Kelley RE**. CNS vasculitis. *Front Biosci* 2004; 9: 946-955.

**Abstract:** Vasculitis of the central nervous system can be of several varieties depending upon the vessel(s) involved and type of disorder. One can see primary CNS vasculitis as a distinct entity which is primarily manifested as central nervous system injury in a vascular distribution or the vasculitic process can be secondary to a systemic disorder such as systemic lupus erythematosus (SLE) or polyarteritis nodosa (PAN). The inflammation of the CNS vessels can be immune mediated or infectious in nature and a number of "triggers" have been identified including hypersensitivity states. It is quite probable that there is a genetic predisposition in certain individuals and this can lead to an enhanced risk of a vasculitic process when there is exposure to a particular antigen that "sets off" the immune system. The potential for response of the process to antimicrobials and/or immunosuppressants, and the potential for devastating consequences if the process is left untreated, has heightened the urgency in recognizing CNS vasculitis. Key to the recognition and treatment of CNS vasculitis is the evolution of newer insights into the pathogenesis. For example, it is evident that most vasculitides are cell-mediated. Antigen stimulation of CD4+T cells is believed to play a crucial role in giant cell (temporal) arteritis which is the most common type of CNS vasculitis. Identification of genetic susceptibility has also contributed to our understanding of the cascade of events that leads to vascular injury on an inflammatory basi.

• **Khurana DS, Melvin JJ, Kothare SV, et al.** Acute disseminated encephalomyelitis in

children: discordant neurologic and neuroimaging abnormalities and response to plasmapheresis. *Pediatrics* 2005; 116: 431-436.

**Abstract: OBJECTIVES:** To describe our experience with acute disseminated encephalomyelitis (ADEM), focusing on (1) the relationship between clinical course and MRI findings and (2) the response to plasmapheresis in a subgroup of patients. **METHODS:** A retrospective record review was conducted of 13 children who were admitted as inpatients with the diagnosis of ADEM during the period 1998-2003. **RESULTS:** Diagnosis was established by clinical signs and symptoms, cerebrospinal fluid changes and multifocal involvement of deep gray and white matter based on MRI. Initial therapy was high-dose methylprednisolone and intravenous immunoglobulin in 12 patients. One child improved spontaneously. Six of 12 children did not improve with corticosteroid treatment. All 6 had an acute progressive course neurologically, and 5 of them also showed a delay in the onset of neuroimaging changes, eventually developing lesions in the deep gray matter and brainstem. This latter group received 5 sessions of plasmapheresis and recovered over the course of several months with varying degrees of residual neurologic deficits. **CONCLUSIONS:** Presentation of ADEM with delayed development of MRI lesions in deep gray matter and brainstem may herald a prolonged clinical course and lack of response to glucocorticoid therapy. Plasmapheresis might be an effective therapeutic intervention in these patients. The role of plasmapheresis versus corticosteroids and intravenous immunoglobulin as a primary treatment of ADEM needs to be investigated further.

- **Kleiman M, Brunquell P.** Acute disseminated encephalomyelitis: response to intravenous immunoglobulin. *J Child Neurol* 1995; 10: 481-483.

- **Kloss TM, Haupt WF, Philipp T, Diener HC.** [Therapy of acute Guillain-Barre syndrome. A national multicenter study]. *Nervenarzt* 1994; 65: 881-883.

**Abstract:** Current treatment concepts in Guillain-Barre syndrome (GBS) are discussed, followed by a call for participation in a randomized multicenter trial in GBS. This study compares intravenous immune globulin, plasma exchange, and selective adsorption. The study is currently underway.

- **Korsak J, Zaleska B, Orlowska E, Kotowicz J.** [Use of high dose intravenous immunoglobulin in neurologic disease]. *Pol Merkuriusz Lek* 2005; 19: 98-101.

**Abstract:** Intravenous immunoglobulin has been used generally as a supplement therapy in hypogammaglobulinemia patients. Then it has been shown to be effective in the treatment of patients with thrombocytopenic purpura, and in the last decade, IVIG has been used in the treatment of many autoimmune and systemic inflammatory diseases. In neurologic diseases intravenous immunoglobulin (IVIG) exhibits immunomodulatory properties, depending on the Fc portion of immunoglobulin G. The number of diseases in which IVIG therapy is effective has been demonstrated by controlled clinical trials. The indications for IVIG therapy in neurologic diseases are in four groups: A+ - the basic indication, they have been demonstrated in controlled clinical trials, A - recommended but they have not been proved by clinical trials, B - confirmed by singular trials, C - recommended as a last resort: the indications have not been confirmed any trials. IVIG clinical effect has been shown in trials in patients with GBS, chronic inflammatory demyelinating polyneuropathy, dermatomyositis and multiple sclerosis. An optimal dose and the frequency of IVIG administration depend on the knowledge of the pathophysiology of autoimmune diseases and the mechanism of IVIG action.

- **Koski CL.** Guillain-Barre syndrome and chronic inflammatory demyelinating polyneuropathy: pathogenesis and treatment. *Semin Neurol* 1994; 14: 123-130.

- **Kubori T, Mezaki T, Kaji R, et al.** [The clinical usefulness of high-dose intravenous immunoglobulin therapy for chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy]. No To Shinkei 1999; 51: 127-135.

**Abstract:** To explore the optimum dose of intravenous immunoglobulin (i.v.Ig) for treating patients with chronic inflammatory demyelinating polyrneuropathy and multifocal motor neuropathy, we compared the usefulness of i.v.Ig among 3 treatment doses. Fifty-nine patients were randomly divided into three treatment dosage groups: 20 patients for Group I using 50 mg/kg/day x 5 days, 19 patients Group II using 200 mg/kg/day x 5 days, and 20 patients

Group III using 400 mg/kg/day x 5 days. We assessed clinically and electrophysiologically the effectiveness of the treatment at 5 weeks after the initial infusion. For patients in Group I and II who had not improved (or worsened) with the first treatment, we gave a one-step larger dose in the second treatment (i.e. 200 mg/kg/day x 5 days for those who had been given 50 mg/kg/day x 5 days, 400 mg/kg/day x 5 days for those who had been given 200 mg/kg/day x 5 days) after more than 9 weeks. We found that 15% of the patients in Group I, 21% in Group II and 60% in Group III improved dose-dependently with the first intravenous immunoglobulin treatment. Seven (47%) of 16 patients in Group I and 4 (40%) of 11 patients in Group II improved after the second treatment with larger doses. Adverse reactions including chill sensation, fever, skin eruption and increase in blood GOT and GPT levels were transient and mild. One patient in Group III developed left hemiparesis showing the small infarction in the right thalamus during the course of the treatment, but the symptom was mild. In conclusion, the high-dose intravenous immunoglobulin therapy (400 mg/kg/day x 5 days) is useful for treating patients with CIDP and MMN, although care must be taken of the risk of causing cerebral infarctions.

• **Kurihara T.** Isolated angitis of the central nervous system: early diagnosis and treatment. *Intern Med* 2005; 44: 783-784.

• **Leff RL, Miller FW, Hicks J, Fraser DD, Plotz PH.** The treatment of inclusion body myositis: a retrospective review and a randomized, prospective trial of immunosuppressive therapy. Medicine (Baltimore) 1993; 72: 225-235.

**Abstract:** We have sought to examine the response to immunosuppressive therapeutic intervention in inclusion body myositis (IBM) in a retrospective review of prior responses to therapy and in an open, randomized crossover trial. We collected information on the response to prior therapy on 25 patients, and for prospective therapy on 11 of these patients. All met criteria for a definite idiopathic inflammatory myopathy and had biopsy-proven IBM. Clinical and laboratory results were assessed by interviews of patients and by chart review in the retrospective trial. Manual muscle strength was assessed by a single trained observer; the patients' activities of daily living were assessed by questionnaire; and serum tests of muscle-associated enzymes were measured in the prospective trial. In the retrospective review, prednisone appeared to have been of some, albeit modest, clinical benefit in 10 of 25 (40%) patients. Other therapies, primarily azathioprine and methotrexate, also appeared to have halted the progression of weakness in 8 of 35 trials (23%). In the prospective study, combination therapy of oral azathioprine and methotrexate and a biweekly infusion of high-dose intravenous methotrexate with leucovorin rescue were given for 3 to 6 months in an open, crossover design. Both the oral and the intravenous regimens were clinically effective in some patients. There was clinical improvement in 3 trials, stabilization in 11 trials, and worsening in 5 trials, out of a total of 19 completed (22 intended) trials. The presence of active inflammation at entry into the prospective therapeutic protocol, either directly observed on muscle biopsy or indirectly indicated by serum creatine kinase level, may have been associated with clinical improvement. A complete laboratory response with normalization of creatine kinase and other muscle-associated enzymes did not, however, significantly predict clinical responsiveness in the prospective trial. In this first report, to our knowledge, of a prospective trial of immunosuppressive therapy for this disease, stabilization and even slight improvement of strength and functional abilities appeared to be achieved in some patients. We believe that prednisone and other immunosuppressive therapies were of modest benefit in about half of patients with inclusion body myositis, especially those with some evidence of active inflammation. Stabilization of an otherwise inexorably deteriorating course appears, therefore, to be an attainable goal in some patients with IBM.

• **Leger JM, Chassande B, Musset L, Meininger V, Bouche P, Baumann N.** Intravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. *Brain* 2001; 124: 145-153.

**Abstract:** We conducted a double-blind, placebo-controlled, study of 19 patients fulfilling eligibility criteria for multifocal motor neuropathy with persistent conduction block. They were enrolled and divided into two groups: those who had never been treated previously with intravenous immunoglobulins (IVIg) (Group 1: 10 patients) and those who presented recurrent symptoms after previously successful treatment with IVIg (Group 2: nine patients). They were randomized prospectively to receive either IVIg or placebo at a dose of 500 mg/kg/day for 5 consecutive days, once a month for 3 months. At month 4, patients found to be responders remained on the same treatment for the 3 following months, while non-responders were switched to the alternative study

drug for the 3 following months. Clinical assessment was conducted with the MRC score in 28 muscles and a self-evaluation scale (five daily motor activities scored from 0 to 5). In Group 1, nine patients completed the study, of whom initially four received IVIg and five placebo; four patients responded to IVIg (two at months 4 and 7, and a further two at month 7 after switching treatment at month 4), two patients responded to placebo at months 4 and 7, and three patients did not respond to either treatment. In Group 2, nine patients completed the study. Five patients first received IVIg and all responded at months 4 and 7. Four patients first received placebo and none responded at month 4; all were then switched to IVIg and three responded at month 7. When the 18 patients were considered together, seven out of the nine patients who received IVIg first were responders at month 4, compared with two of the nine patients who received placebo first, a difference that was statistically significant (P = 0.03). On the other hand, there was no significant difference in MRC score but a significant difference in the self-evaluation score, at month 4, between IVIg patients and placebo patients. Electrophysiological studies did not show significant differences at month 4 in motor parameters between IVIg patients and placebo patients. IgM anti-GM1 titres did not change significantly in patients treated with IVIg compared with those who received placebo, between baseline, month 4 and month 7. However, of five patients who had significantly high anti-GM1 titres (>3200) at baseline, four responded to IVIg. This trial confirms that IVIg is a promising therapeutic option for multifocal motor neuropathy.

- **Levy Y, Uziel Y, Zandman GG, et al.** Intravenous immunoglobulins in peripheral neuropathy associated with vasculitis. *Ann Rheum Dis* 2003; 62: 1221-1223.

**Abstract: BACKGROUND:** Peripheral neuropathy is a prominent feature of the systemic and secondary vasculitides. Usually, it is responsive to corticosteroids, but in certain cases it may be resistant to corticosteroid or immunosuppressive treatment, or both. **OBJECTIVE:** To present patients who exhibited various inflammatory diseases accompanied with vasculitic peripheral neuropathies for which intravenous immunoglobulin (IVIg) was used for treatment. **METHODS:** Six patients with Sjogren's syndrome, systemic lupus erythematosus (SLE), vaccination induced vasculitis, Churg-Strauss vasculitis, mixed cryoglobulinaemia associated with hepatitis C infection, or sarcoidosis were included. All developed vasculitic peripheral neuropathy, and were treated with high dose IVIg (2 g/kg body weight). The patients were followed up for 1-5 years after this treatment. **RESULTS:** In four patients (Sjogren's syndrome, Churg-Strauss vasculitis, SLE, and vaccination induced vasculitis) the neuropathy resolved after IVIg treatment. **CONCLUSION:** IVIg may be beneficial in cases of resistant vasculitic peripheral neuropathy. IVIg should probably be considered as a sole or adjuvant treatment for patients with contraindications to conventional treatment, or alternatively, for patients in whom conventional treatment has failed

- **Levy Y, Uziel Y, Zandman G, et al.** Response of vasculitic peripheral neuropathy to intravenous immunoglobulin. *Ann N Y Acad Sci* 2005; 1051: 779-786.

**Abstract:** Peripheral neuropathy is a prominent feature of the systemic and secondary vasculitides. Usually, it responds to corticosteroids therapy, but in certain cases it may resist corticosteroid or immunosuppressive treatment, or both. The objective of this study is to present case reports of patients who exhibited various inflammatory diseases, accompanied with vasculitic peripheral neuropathies, for which intravenous immunoglobulin (IVIg) was used for treatment. The study included 10 patients with the following: Sjogren's syndrome (1), systemic lupus erythematosus (2), vaccination-induced vasculitis (1), Churg-Strauss vasculitis (1), mixed cryoglobulinemia (2), polyarteritis nodosa (1), sarcoidosis (1), and scleroderma (1). All developed vasculitic peripheral neuropathy and were treated with 1-13 cycles of high-dose IVIg (2 g/kg body weight). The patients were followed up for 1-5 years after this treatment. Results showed that in all but two patients (mixed cryoglobulinemia associated with hepatitis C and sarcoidosis), neuropathy improved or completely resolved after IVIg treatment. In conclusion, IVIg may be beneficial in cases of resistant vasculitic peripheral neuropathy. IVIg should probably be considered as a sole or adjuvant treatment in patients for whom conventional treatment is contraindicated, or for patients in whom conventional treatment has failed.

- **Lewanska M, Selmaj K.** [Immunotherapy of intravenous immunoglobulin preparations in neurologic diseases]. *Postepy Hig Med Dosw* 1906; 56 Suppl: 69-83.

**Abstract:** Intravenous immunoglobulin (IVIG) has been used in a wide range of neurological conditions. Clinical effect of IVIG has been shown in controlled trials in patients with Guillain-Barre syndrome,

chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, dermatomyositis and recently in multiple sclerosis. This article aims to provide clinicians with an overview of the potential benefits of intravenous immunoglobulins in neurological practice.

• **Lewanska M, Siger-Zajdel M, Selmaj K.** No difference in efficacy of two different doses of intravenous immunoglobulins in MS: clinical and MRI assessment. *Eur J Neurol* 2002; 9: 565-572.

**Abstract:** We performed a double-blind, placebo-controlled study to evaluate the efficacy of low and high dose of intravenous immunoglobulins (IVIG) in relapsing/remitting (RR) multiple sclerosis (MS). Patients (n = 49) with clinical definite RR MS were randomly allocated to three groups and treated with 0.2 g/kg (n = 17) or 0.4 g/kg (n = 15) once a month of IVIG and placebo (n = 17) for 12 months. Clinical data were assessed monthly and magnetic resonance imaging (MRI) was performed every 3 months during the study period. Annual relapse rate (ARR) and change of the mean Expanded Disability Status Scale (EDSS) and Neurological Rating Scale Score (NRSS) from baseline to study conclusion were used as the clinical end-points. For MRI activity total lesion volume on T2-weighted image (T2WI), new lesions and gadolinium (Gd)-enhanced lesions on T1WI were analysed. ARR in both IVIG groups (0.88 for 0.2 g/kg and 0.86 for 0.4 g/kg) was reduced compared with placebo (1.24) during treatment period. Neurological disability measured with EDSS decreased slightly in both the IVIG groups (0.029 and 0.066, respectively) and increased by 0.29 in placebo (P = 0.0117). The neurologic impairment measured by NRSS showed similar trend. The total lesion volume on T2WI increased by 13.56% in placebo whereas in the 0.4 g/kg IVIG group decreased by -3.95% and in the 0.2 g/kg IVIG group increased by 3.6%. The cumulative numbers of Gd-enhancing lesions and new T2WI lesions in the IVIG groups were reduced in comparison with the placebo group. Our findings suggest that the dose 0.2 g/kg of IVIG is equally effective as 0.4 g/kg in reducing MS activity.

• **Lorusso L, Hart IK, Giometto B, et al.** Immunological features of neurological paraneoplastic syndromes. *Int J Immunopathol Pharmacol* 2004; 17: 135-144.

**Abstract:** Neurological paraneoplastic syndromes are a rare group of disorders that occur in 1-2% of people with malignancy. They are usually caused by an immune response, triggered by and directed against a tumour, that cross-reacts with protein expressed by the peripheral or central nervous system. Any part of the nervous system can be affected and patients often develop severe and permanent disability. Diagnosis can be difficult as in two-thirds of patients the neurological problems appear up to 5 years before the tumour manifests. However, certain of these syndromes are often associated with specific serum autoantibodies that can be useful both in diagnosis of the neurological syndrome and in focusing the search for a particular tumour. Thus, these antibodies can allow earlier identification and treatment of cancer and, potentially, a reduction in morbidity and mortality. It was only in the 1980s that the first anti-neuronal autoantibodies were characterized and their associations with clinical syndromes and tumours defined. Further antibodies have been isolated over the past 20 years and novel pathogenic mechanisms for several syndromes have been recognized. For example, voltage-gate ion channels seem to be a common target for autoantibodies involved in peripheral nerve diseases such as the Lambert-Eaton myasthenic syndrome and neuromyotonia (Isaacs' syndrome). However, the place of most paraneoplastic antibodies in the pathogenesis of central syndromes is yet to be fully elucidated.

• **Lunn MP, Nobile-Orazio E.** Immunotherapy for IgM anti-Myelin-Associated Glycoprotein paraprotein-associated peripheral neuropathies. *Cochrane Database Syst Rev* 1906; CD002827

**Abstract: BACKGROUND:** Serum monoclonal anti-Myelin Associated Glycoprotein antibodies may be pathogenic in some patients with IgM paraprotein and demyelinating neuropathy. Immunotherapies aimed at reducing the level of these antibodies might be expected to be of benefit in the treatment of the neuropathy. Many potential therapies have been described in small trials, uncontrolled studies and case reports. **OBJECTIVES:** To examine the efficacy of any form of immunotherapy in reducing disability and impairment resulting from IgM anti-Myelin Associated Glycoprotein paraprotein-associated demyelinating peripheral neuropathy. **SEARCH STRATEGY:** We searched the Cochrane Neuromuscular Disease Group register (August 2002) and MEDLINE (January 1966 - August 2002) and EMBASE (January 1980 - August 2002) for controlled trials, checked the bibliographies to identify other controlled trials and contacted authors and other experts in the field. **SELECTION CRITERIA:** Types of studies: randomised or quasi-

randomised controlled trials. Types of participants: patients of any age with anti-Myelin Associated Glycoprotein antibody associated demyelinating peripheral neuropathy with monoclonal gammopathy of undetermined significance of any severity. Types of interventions: any type of immunotherapy. Types of outcome measures: Primary: improvement in the Neuropathy Disability Score or Modified Rankin Scale six months after randomisation Secondary: Neuropathy Disability Score and/or the Modified Rankin Score 12 months after randomisation. Ten metre walk time, subjective clinical scores and electrophysiological parameters at six and 12 months after randomisation. IgM paraprotein levels and anti-Myelin Associated Glycoprotein antibody titres six months after randomisation. Adverse effects of treatments. **DATACOLLECTIONANDANALYSIS:** We identified six randomised controlled trials of which five were included after discussion between the authors. One author extracted the data and the other checked them. No missing data could be obtained from authors. **MAIN RESULTS:** The five eligible trials used four of the many available immunotherapy treatments. Only two had comparable interventions and outcomes but these were only short-term studies. There were no significant benefits of the treatments used in the predefined outcomes. However intravenous immunoglobulin showed benefits in terms of improved Modified Rankin Scale at two weeks and 10 metre walk time at four weeks. Serious adverse effects of intravenous immunoglobulin are known to occur from observational studies but none were encountered in these trials. **REVIEWER'S CONCLUSIONS:** There is inadequate reliable evidence from trials of immunotherapies in anti-Myelin Associated Glycoprotein paraproteinaemic neuropathy to recommend any particular immunotherapy treatment. Intravenous immunoglobulin is relatively safe and may produce some short-term benefit. Large well designed randomised trials are required to assess the efficacy of promising new therapies.

- **MacDuff A, Grant IS.** Critical care management of neuromuscular disease, including long-term ventilation. *Curr Opin Crit Care* 2003; 9: 106-112.

**Abstract: PURPOSE OF REVIEW:** This review highlights recent advances in the critical care management of neuromuscular disease, particularly in the long-term management of chronic respiratory failure occurring as a consequence of neuromuscular disease. **RECENTFINDINGS:** Although randomized clinical trial evidence of benefit is sparse, a large volume of nonrandomized clinical trial evidence has accumulated demonstrating that noninvasive positive pressure ventilation prolongs and improves quality of life in conditions such as Duchenne muscular dystrophy and motor neuron disease. **SUMMARY:** Immunomodulatory treatments favorably modify the course of neuromuscular diseases such as Guillain-Barre syndrome, whereas long-term noninvasive positive pressure ventilation has transformed the outlook in previously untreatable conditions such as motor neuron disease and muscular dystrophies. The availability of long-term noninvasive positive pressure ventilation raises major medical, social, economic, and ethical issues that are increasingly being investigated and discussed.

- **Maddison P, Newsom-Davis J.** Treatment for Lambert-Eaton myasthenic syndrome. *Cochrane Database Syst Rev* 1906; CD003279

**Abstract: BACKGROUND:** Lambert-Eaton myasthenic syndrome is an autoimmune presynaptic disorder of neuromuscular transmission. Treatments attempt to overcome the harmful autoimmune process, or to improve residual neuromuscular transmission, in order to reverse muscle weakness. **OBJECTIVES:** The objective was to examine the efficacy of treatment in Lambert-Eaton myasthenic syndrome. **SEARCH STRATEGY:** We searched the Cochrane Neuromuscular Disease Group trials register (December 2004), MEDLINE (January 1966 to December 2004) and EMBASE (January 1980 to December 2004), and checked bibliographies and contacted authors to identify additional published or unpublished data. **SELECTIONCRITERIA:** All randomised or quasi-randomised trials of adults and children with a diagnosis of Lambert-Eaton myasthenic syndrome, with or without small-cell lung cancer, receiving any form of pharmacological or physical treatment. The primary outcome measure was change in muscle strength scale score (Quantitative Myasthenia Gravis score), or limb muscle strength measured by myometry. The secondary outcome measure was improvement in the mean amplitude of the resting compound muscle action potentials. The mean amplitude used was the mean of all muscles tested. **DATA COLLECTION AND ANALYSIS:** We identified three randomised controlled trials. **MAIN RESULTS:** Two controlled trials of the effects of 3,4-diaminopyridine compared with placebo in a total of 38 patients with Lambert-Eaton myasthenic syndrome were eligible, one of which was of crossover design. A third crossover trial compared intravenous immunoglobulin treatment to placebo in nine patients.Two trials of 3,4-diaminopyridine

reported a significant improvement in muscle strength score, or myometric limb measurement following treatment, and a significant improvement in resting compound muscle action potential amplitude following 3,4-diaminopyridine, compared with placebo.A meta-analysis of the primary endpoint results was not possible because of marked differences in primary outcome measures. However, a meta-analysis of the secondary endpoint was possible. The overall weighted mean difference was 1.80 mV (95% confidence interval 0.82 to 2.78), favouring treatment.A crossover trial reported a significant improvement in myometric limb strength and a non-significant improvement in change in the mean resting compound muscle action potential amplitude when patients received intravenous immunoglobulin compared to placebo infusions. Clinical improvement lasted for up to eight weeks. **AUTHORS'CONCLUSIONS:** Limited evidence from randomised controlled trials showed that either 3,4-diaminopyridine or intravenous immunoglobulin improved muscle strength scores and compound muscle action potential amplitudes in patients with Lambert-Eaton myasthenic syndrome. There are insufficient data at present to quantify this treatment effect. Other possible treatments have not been tested in randomised controlled trials.

• **Marchioni E, Marinou-Aktipi K, Uggetti C, et al.** Effectiveness of intravenous immunoglobulin treatment in adult patients with steroid-resistant monophasic or recurrent acute disseminated encephalomyelitis. *J Neurol* 2002; 249: 100-104.

**Abstract:** Randomized Controlled Trials have not let established the best pharmacological management of Acute Disseminated Encephalomyelitis (ADEM). High dose steroids are usually employed with good results, but in a few cases the clinical outcome is poor. In other patients, particularly those affected by the site restricted ADEM variants (myelitis), the disease shows a recurrent course resembling that of Multiple Sclerosis. We present here five patients, 3 of them affected by classic disseminated encephalomyelitis and 2 by a post infectious myelitis, which showed a good response to intravenous immunoglobulin (IVIg) after steroid treatment failure. In our report high dose steroids administration was substantially uneffective in all but one case, who showed a good response only during the first episode. On the contrary IVIg injection (0,4 gr/kg/day) produced a marked functional improvement in all patients starting within the first five days of drug administration and reaching a maximum within three weeks. One patient experienced a good effect nothwithstanding a steady dysability. In all cases, clinical evidence was supported by MRI controls showing improving posttreatment changes

• **Mariette X, Chastang C, Clavelou P, Louboutin JP, Leger JM, Brouet JC.** A randomised clinical trial comparing interferon-alpha and intravenous immunoglobulin in polyneuropathy associated with monoclonal IgM. The IgM-associated Polyneuropathy Study Group. *J Neurol Neurosurg Psychiatry* 1997; 63: 28-34.

**Abstract: OBJECTIVES:** The polyneuropathy associated with a monoclonal IgM directed to the myelin associated glycoprotein (MAG) is a specific entity with a putative causal link between the IgM and the neuropathy. The small benefit offered by alkylating agents or plasma exchanges in these patients justifies the search for alternative treatments. **METHODS:** A 12 month multicentre, prospective, randomised, open clinical trial was carried out comparing intravenous immunoglobulin (IVIg; 2g/kg and then 1 g/kg every three weeks) and recombinant interferon-alpha (IFN-alpha; 3 MU/m2 subcutaneously three times weekly). The main end point was a clinical neuropathy disability score (CNDS) after six months of treatment. Twenty patients were enrolled; 10 were assigned to IVIg and 10 to IFN-alpha. **RESULTS:** At six months, one out of 10 patients treated with IVIg had a CNDS improvement of more than 20% whereas eight out of 10 patients treated with IFN-alpha had such an improvement (P=0.005). The mean CNDS worsened by 2.3 (SD 7.6) (8%) in the IVIg group whereas it improved by 7.5 (SD 11.1) (31%) in the IFN-alpha group (P=0.02). This improvement persisted after 12 months and was mainly related to an improvement of the sensory component (P=0.02) whereas the motor component was unchanged (P=0.39). Electrophysiological data did not show improvement of motor nerve conduction velocities whereas sensory nerve conduction velocities improved in the upper limbs. A decrease in the level of the monoclonal IgM was seen in two patients treated with IFN-alpha. At the end of the treatment, antibody activity to MAG was still detected in the serum of all patients. **CONCLUSION:** IVIg, as used in this study, did not improve patients with polyneuropathy and monoclonal IgM. By contrast, although its mechanism of action remains to be fully elucidated, IFN-alpha was effective in eight out of 10 patients at six months.

• **Martins HM, Teixeira ALJ, Lana-Peixoto MA.** Acute hemorrhagic leukoencephalitis mimicking herpes simplex encephalitis:

case report. *Arq Neuropsiquiatr* 2004; 62: 139-143.

**Abstract:** Acute hemorrhagic leukoencephalitis (AHLE) is a more severe form of acute disseminated encephalomyelitis (ADEM) characterized by a fulminant clinical course and the presence of hemorrhagic necrosis of the white matter. We report the case of a 57-year-old woman who developed delirium following a respiratory infection. Magnetic resonance imaging of the brain disclosed signal abnormalities in the frontal and temporal lobes, usually found in herpes simplex encephalitis (HSE). Gram stain, India ink and acid-fast bacilli staining were all negative in CSF as was a polymerase chain reaction (PCR) for herpes simplex virus. A diagnosis of AHLE was made and the patient was treated with i.v. methylprednisolone 1g/day for 5 days. Despite treatment, the patient developed several neurological sequelae compatible with the severity of her illness

- **Mathy I, Gille M, Van Raemdonck F, Delbecq J, Depre A.** Neurological complications of intravenous immunoglobulin (IVIg) therapy: an illustrative case of acute encephalopathy following IVIg therapy and a review of the literature. *Acta Neurol Belg* 1998; 98: 347-351.

**Abstract:** We report the case of a 73-year-old man who developed an acute encephalopathy during IVIg therapy for AIDP. The signs and symptoms of the encephalopathy completely resolved after discontinuation of the treatment. We also reviewed the literature over the major neurological complications of IVIg therapy, including aseptic meningitis, cerebral infarction, and acute encephalopathy. About 30 cases of aseptic meningitis are reported. They are probably related to an immunoallergic reaction, caused by the entry of the exogenous IgG into the CSF compartment. CSF examinations usually show a neutrophilic or a mixed pleocytosis. Three cases of cerebral infarction and 2 patients with acute encephalopathy, following IVIg therapy, were also reported in the literature. Cerebral vasospasm, cerebral vasculitis, and/or serum hyperviscosity may be implicated in the pathogenesis of these neurological complications. There is a clinical similarity between these IVIg-related encephalopathy and the "reversible posterior leukoencephalopathy syndrome", described by Hinchey et al., 1996.

- **Mazer BD, Al-Tamemi S, Yu JW, Hamid Q.** Immune supplementation and immune modulation with intravenous immunoglobulin. *J Allergy Clin Immunol* 2005; 116: 941-944.

- **McCrone P, Chisholm D, Knapp M, et al.** Cost-utility analysis of intravenous immunoglobulin and prednisolone for chronic inflammatory demyelinating polyradiculoneuropathy. *Eur J Neurol* 2003; 10: 687-694.

**Abstract:** The aim of this study was to provide an incremental cost-effectiveness analysis comparing intravenous immunoglobulin (IVIg) and prednisolone treatment for chronic inflammatory demyelinating polyradiculoneuropathy. Patients were recruited to a double-blind randomized crossover trial from nine European centres and received either prednisolone or IVIg during the first 6-week treatment period on which the economic evaluation was based. A societal perspective was adopted in measuring service use and costs, although the costs of lost employment were not included. The main outcome measure in the economic evaluation was the number of quality adjusted life years (QALYs) gained, with change in a 11-point disability scale used to measure clinical outcomes. Service use and quality of life data were available for 25 patients. Baseline costs were controlled for using a bootstrapped multiple regression model. The cost difference between the two treatments was estimated to be euro 3754 over the 6-week period. Health-related quality of life, as measured by the EuroQol EQ-5D instrument, increased more in the IVIg group but the difference was not statistically significant. Using a net-benefit approach it was shown that the probability of IVIg being cost-effective in comparison with prednisolone was 0.5 or above (i.e. was more likely to be cost-effective than cost-ineffective) only if one QALY was valued at over euro 250 000. The cost-effectiveness of IVIg is greatly affected by the price of IVIg and the amount administered. The impact of later side-effects of prednisolone on long-term costs and quality of life are likely to reduce the cost per QALY of IVIg treatment.

- **Mendell JR, Barohn RJ, Freimer ML, et al.** Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology* 2001; 56: 445-449.

**Abstract: OBJECTIVE:** To determine the efficacy of IV immunoglobulin (IVIg) given patients with untreated chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). **METHODS:** A

randomized, double-blind, multicenter, investigator-initiated study compared IVIg (Aventis Behring LLC, King of Prussia, PA) with placebo (5% albumin). On days 1, 2, and 21, IVIg (1 g/kg) or placebo was given. The primary outcome measure was the change in muscle strength from baseline to day 42, using the average muscle score (AMS). Secondary outcome measures included change from baseline AMS at days 10 and 21, the Hughes' functional disability scale, forced vital capacity (FVC), and nerve conduction studies (NCS) of four motor nerves (median, ulnar, peroneal, and tibial). **RESULTS:** The patients (n = 33) were randomized. Of these, 30 (14 women, 16 men, aged 54 +/- 20 years, range 13 to 82) received IVIg and 23 were given placebo (12 women, 11 men, aged 50 +/- 18 years, range 23 to 73). Baseline AMS values of the groups were similar (IVIg 7.06 +/- 1.31 versus placebo 7.28 +/- 1.18, p = 0.53). There were two dropouts in placebo group and one in the IVIg group. Mean AMS improved at day 42 comparing IVIg with placebo (0.63 versus -0.1, p = 0.006). Improved strength was seen by day 10. The placebo group lost strength over this same interval. In the IVIg, 11 subjects improved by the functional disability scale; none worsened. This differed (p = 0.019) from those in the placebo-treated group (two improved, two got worse, remainder unchanged). Forced vital capacity did not improve with IVIg treatment. IVIg improved ulnar motor distal latency (p = 0.005), tibial distal compound muscle amplitude (p = 0.003), and peroneal nerve conduction velocity (p = 0.03). **CONCLUSIONS:** IVIg improves strength in patients with untreated CIDP by day 10 with continued benefit through day 42; more than one third improve by at least a functional grade on a disability scale. This study provides data supporting IVIg as the initial treatment for CIDP.

- **Menge T, Hemmer B, Nessler S, et al.** Acute disseminated encephalomyelitis: an update. *Arch Neurol* 2005; 62: 1673-1680.

**Abstract:** Acute disseminated encephalomyelitis (ADEM) is a monophasic autoimmune demyelinating disease of the central nervous system that typically follows a febrile infection or a vaccination. Children are predominantly affected. A plethora of viral and bacterial pathogens and a number of vaccinations have been associated with ADEM. Experimental animal studies indicate that both primary and secondary autoimmune responses contribute to central nervous system inflammation and subsequent demyelination. The clinical diagnosis of ADEM is strongly suggested by a close temporal relationship between an infectious incident or an immunization and the onset of leukoencephalopathic neurological symptoms. Paraclinical tests may support the diagnosis. Particularly helpful are acute signs of newly developed extensive, multifocal, subcortical white matter abnormalities on magnetic resonance images of the brain. The cerebrospinal fluid may disclose a mild lymphocytic pleocytosis and elevated albumin levels. Oligoclonal bands are not always present in ADEM and, if so, may be transient. The major differential diagnosis of ADEM is multiple sclerosis. Treatment options for ADEM consist of anti-inflammatory and immunosuppressive agents. In general, the disease is self-limiting and the prognostic outcome favorable. In the absence of widely accepted clinical or paraclinical diagnostic guidelines, a number of recently conducted observational case series have substantially broadened our understanding about the clinical phenotype, diagnosis, and prognosis of ADEM.

- **Mihai C, Jubelt B.** Post-infectious encephalomyelitis. *Curr Neurol Neurosci Rep* 2005; 5: 440-445.

**Abstract:** The term post-infectious encephalomyelitis (PIEM) is frequently used interchangeably with acute disseminated encephalomyelitis (ADEM), although technically PIEM occurs after a known infection whereas with ADEM there is no antecedent infection. PIEM represents one of the primary demyelinating disorders of the central nervous system, along with multiple sclerosis and Devic's disease. There is no specific diagnostic test for any of these conditions and at onset it may be difficult to differentiate between ADEM and the first attack of multiple sclerosis. However, there are clinical and magnetic resonance imaging features that allow differentiation between PIEM/ADEM and a relapsing disease such as multiple sclerosis. Some patients improve spontaneously; most improve with methylprednisolone. If that fails, plasma exchange or intravenous immunoglobulin may be effective.

- **Milstone AM, Meyers K, Elia J.** Treatment of acute neuropsychiatric lupus with intravenous immunoglobulin (IVIG): a case report and review of the literature. *Clin Rheumatol* 2005; 24: 394-397.

**Abstract:** Neuropsychiatric lupus can be difficult to diagnose, and little prospective data exists to help direct management. In this case report we describe the acute onset of symptoms of depression, mania, and psychosis and their complete resolution 48 h following a 5-day treatment course of intravenous immunoglobulin (IVIG) in a 20-year-old woman

with systemic lupus erythematosus (SLE). We review the literature on IVIG for the management of neuropsychiatric lupus. We propose that when more toxic therapies are refused or symptoms do not remit with other treatments, IVIG should be considered in patients with neuropsychiatric lupus.

• **Monaco S, Turri E, Zanusso G, Maistrello B.** Treatment of inflammatory and paraproteinemic neuropathies. *Curr Drug Targets Immune Endocr Metabol Disord* 2004; 4: 141-148.

**Abstract:** Acquired demyelinating and inflammatory neuropathies encompass a number of acute and chronic autoimmune conditions characterized by variable degrees of clinical involvement. These disorders, including Guillain-Barre syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), and paraprotein-associated neuropathy, have an overall annual incidence of 2-4/100,000 worldwide and are potentially treatable. Over the last few years, several investigations have helped clarify the pathogenesis of immune neuropathies and the definition of molecular targets involved in these diseases, thus providing firmer grounds for treatment with classical immunosuppressive drugs and new biological agents. In GBS and related variants, which are characterized by cellular inflammation and alterations of the blood-nerve barrier, randomized clinical trials show that plasma exchange (PE) and intravenous immunoglobulin (IVIg) are equally effective as disease-modifying treatments, although IVIg has been adopted as the favourite treatment in most centres. In CIDP, controlled clinical trials have established the efficacy of oral prednisone, PE and IVIg, with intermittent IVIg treatment or corticosteroids being usually preferred. Adding azathioprine can help keep lower the required dose of prednisone, while other immunosuppressive agents, such as cyclophosphamide and cyclosporin A may have side effects, limiting their use to selected cases. Currently, the efficacy of interferon beta and alfa is under evaluation. Controlled trials support the view that IVIg is the treatment of choice in MMN. Patients resistant to IVIg administration may benefit of treatments which deplete B cells, such as cyclophosphamide and rituximab. Demyelinating neuropathies associated with circulating paraproteins are clinically heterogeneous, depending on the reactivity and type of the monoclonal (M) protein. In many cases, neuropathies associated with IgM M proteins are not treated because of their slow progression. In patients with a disabling or rapid progression, small trials have shown short-term benefits from IVIg or PE. Recently, fludarabine and rituximab have been reported as beneficial in selected cases.

• **Mori K, Hattori N, Sobue G.** [Clinical guideline review: Guillain-barre syndrome and chronic inflammatory demyelinating polyneuropathy]. *Nippon Naika Gakkai Zasshi* 2002; 91: 2443-2457.

• **Myers LW.** Immunologic therapy for secondary and primary progressive multiple sclerosis. *Curr Neurol Neurosci Rep* 2001; 1: 286-293.

**Abstract:** Multiple sclerosis (MS) is generally considered an immune-mediated demyelinating disease, and treatments designed to modify the course of MS are immunosuppressive or immunomodulatory. Although most people with MS have a relapsing-remitting course initially, the majority will eventually experience a more gradual decline in neurologic function, termed secondary progressive MS. Some patients have gradual worsening from the beginning, termed primary progressive MS. Recent pathologic studies have revealed that axonal injury and neuronal degeneration are much more prominent in MS than previously recognized, and may be the explanation for the gradual decline in neurologic function that characterizes progressive MS. The results of several clinical trials in MS indicate that suppression of the immune-mediated inflammation may decrease the relapse rate in MS, but not stop the progressive loss of neurologic function. There are many promising approaches to this clinical dilemma, but none has been proven to be effective in stopping or retarding progressive MS. More well-designed, controlled, blinded, randomized clinical trials are needed to test these putative therapies. In the mean time, we should avoid subjecting patients to potentially dangerous and unproven regimens.

• **Nagpal S, Benstead T, Shumak K, Rock G, Brown M, Anderson DR.** Treatment of Guillain-Barre syndrome: a cost-effectiveness analysis. *J Clin Apher* 1999; 14: 107-113.

**Abstract:** Acute Guillain-Barre syndrome is the most common cause of neuromuscular paralysis. Plasma exchange and intravenous immune globulin (IV IgG) are both effective treatments for this condition and the purpose of this report was to compare the cost-

effectiveness of these two modalities. A MEDLINE search was performed to identify randomized studies that compared the use of IV IgG and plasma exchange for treatment of acute Guillain-Barre syndrome to determine if one modality was more effective and/or safer for the management of this condition. A decision analysis was structured around the alternatives facing neurologists who must choose a treatment regimen for patients diagnosed with acute Guillain-Barre syndrome who require active therapy. Cost information was obtained directly from product manufacturers and hospital sources. Two head-to-head trials comparing the effectiveness of plasma exchange and IV IgG for treatment of acute Guillain-Barre syndrome determined that there was insufficient evidence to suggest one therapy was more effective than the other; therefore, a cost minimization analysis was performed. The costs per patient of plasma exchange and IV IgG for the treatment of acute Guillain-Barre syndrome were $6,204 and $10,165, respectively. A sensitivity analysis determined the model was sensitive to the cost of IV IgG. The cost savings per patient treatment for the use of plasma exchange varied from $304 to $6,625 depending on the IV IgG product selected. Plasma exchange and IV IgG are both effective treatments for Guillain-Barre syndrome. However, our analysis determined plasma exchange on average was almost $4,000 less costly per patient than IV IgG. Further research is required to determine the impact of patient and physician preferences on the treatment of this disorder.

• **Nemni R, Gerosa E, Piccolo G, Merlini G.** Neuropathies associated with monoclonal gammapathies. *Haematologica* 1994; 79: 557-566.

**Abstract:** There is increasing evidence that monoclonal proteins are implicated in the development of peripheral neuropathy. Approximately ten percent of patients with peripheral neuropathy of unknown cause have a monoclonal protein and this rate is significantly higher than prevalence rates of monoclonal protein in comparable segments of the general population. Extensive clinical, electrophysiological and immunopathological evidences indicate that peripheral neuropathy associated with monoclonal protein are heterogeneous, including: 1. the demyelinating, predominantly sensory neuropathies associated with anti-MAG antibodies; 2. the axonal, sensory neuropathies associated with anti-sulfatide and anti-chondroitin sulfate antibodies; 3. the motor neuropathies associated with anti-GM1 antibodies. Patients with chronic polyneuropathies should be evaluated for underlying plasma cell dyscrasia.

• **Nishikawa M, Ichiyama T, Hayashi T, Ouchi K, Furukawa S.** Intravenous immunoglobulin therapy in acute disseminated encephalomyelitis. *Pediatr Neurol* 1999; 21: 583-586.

**Abstract:** Three children ranging in age from 2 to 5 years with acute disseminated encephalomyelitis (ADEM) were successfully treated with high-dose intravenous immunoglobulin (IVIG). Their symptoms were somnolence, fever, headache, vomiting, and resting tremor. In all of these patients, it was difficult to distinguish the condition from viral encephalitis before analyzing the myelin basic protein. ADEM was diagnosed because of increased levels of myelin basic protein in their cerebrospinal fluid and abnormal high-signal intensity on T2-weighted magnetic resonance imaging. All patients were given IVIG at a dose of 400 mg/kg/day for 5 consecutive days. The patients rapidly regained consciousness in 14 hours, 2 days, and 4 days and demonstrated a complete clinical improvement within 18 days, 10 days, and 7 days of the initiation of the treatment, respectively. IVIG may prove useful as an alternative treatment to corticosteroids for ADEM.

• **Noseworthy JH, O'Brien PC, Weinshenker BG, et al.** IV immunoglobulin does not reverse established weakness in MS. *Neurology* 2000; 55: 1135-1143.

**Abstract: BACKGROUND:** Immunoglobulin (Ig) administration induces remyelination in the Theiler's virus model of MS. **METHODS:** A randomized, double-blinded, placebo-controlled trial of IV immunoglobulin (IVIg) was performed in patients with MS who had persistent muscle weakness that had been stable for between 4 and 18 months to determine whether this would improve muscle strength (primary outcome: isometric muscle strength). Patients received either IVIg (0.4 g/kg) or placebo daily for 5 days, then single infusions every 2 weeks for 3 months (total, 11 infusions). Muscle groups identified by clinical measures to have unchanging significant weakness were the major targets for therapeutic response (targeted neurologic deficit [TND]). **RESULTS:** IVIg was well tolerated. An interim analysis after 67 patients were enrolled indicated no difference in the degree of change in strength between treatment groups in either the TND or non-TND muscle groups at 6 months, and the trial was terminated. There was no apparent benefit in relapse behavior or impairment measures during the 6-month observation period. Nor was there apparent benefit in either patients who remained clinically stable or in those with evidence of disease

activity. Patients with active MS during the trial worsened in both TND and non-TND muscle groups. This worsening was seen regardless of whether the clinical manifestations of disease activity involved the TND muscle groups. **CONCLUSIONS:** IVIg does not reverse established weakness in MS. Measurements of isometric muscle strength were reliable (reproducible) indices of strength and may be sensitive, objective methods to document functional changes in impairment in future MS trials.

• **Noseworthy JH, O'Brien PC, Petterson TM, et al.** A randomized trial of intravenous immunoglobulin in inflammatory demyelinating optic neuritis. *Neurology* 2001; 56: 1514-1522.

**Abstract: OBJECTIVE:** To determine whether IV immunoglobulin (IVIg) reverses chronic visual impairment in MS patients with optic neuritis (ON). **METHODS:** In this double-blind, placebo-controlled Phase II trial, 55 patients with persistent acuity loss after ON were randomized to receive either IVIg 0.4 g/kg daily for 5 days followed by three single infusions monthly for 3 months, or placebo. **RESULTS:** The trial was terminated by the National Eye Institute because of negative results when 55 of the planned 60 patients had been enrolled. Fifty-two patients completed the scheduled infusions, and 53 patients completed 12 months of follow-up. Analysis of this data indicated that a difference between treatment groups was not observed for the primary outcome measure, improvement in logMAR visual scores at 6 months ($p = 0.766$). Exploratory secondary analyses suggested that IVIg treatment was associated with improvement in visual function (including logMAR visual scores at 6 months and visual fields at 6 and 12 months) in patients with clinically stable MS during the trial. **CONCLUSIONS:** IVIg administration does not reverse persistent visual loss from ON to a degree that merits general use.

• **O'Connor PW, Goodman A, Willmer-Hulme AJ, et al.** Randomized multicenter trial of natalizumab in acute MS relapses: clinical and MRI effects. *Neurology* 2004; 62: 2038-2043.

**Abstract: BACKGROUND:** Relapses in multiple sclerosis (MS) can cause significant neurologic disability. Natalizumab (Antegren) is a humanized anti-alpha4-integrin antibody that inhibits the trafficking of leukocytes across endothelium by blocking binding of alpha4beta1-integrin to vascular cell adhesion molecule-1. **OBJECTIVE:** To assess the effects of a single dose of IV natalizumab administered soon after the onset of MS relapses. **METHODS:** In this randomized, double-blind, multicenter trial, the effects of a single dose of IV natalizumab administered soon after the onset of MS relapses were assessed. MS patients (n = 180) in acute relapse were randomly assigned to receive a single dose of natalizumab 1 or 3 mg/kg or placebo and were followed for 14 weeks. **RESULTS:** There was no difference in Expanded Disability Status Scale (EDSS) score change over time between treatment and placebo groups. In all three groups, approximately half of patients showed EDSS improvement after 2 weeks, rising to 67% by 8 weeks. EDSS improved by a mean value of 0.8 point at week 1, 1.2 points at week 4, and 1.6 points at week 8 in the natalizumab group compared with EDSS improvement of 1.0 point at week 1, 1.6 points at week 4, and 1.6 points at week 8 in the placebo group. A significant decrease in Gd-enhancing lesion volume was seen in both active treatment groups at weeks 1 and 3 compared with placebo. **CONCLUSIONS:** A single dose of IV natalizumab did not hasten clinical recovery after relapse, although a significant decrease in Gd-enhancing lesion volume was observed at 1 and 3 weeks after treatment. These MRI findings are consistent with prior studies of natalizumab and support its further investigation as an agent for the treatment of MS.

• **Orrell RW.** Grand rounds--Hammersmith Hospitals. Distinguishing acute disseminated encephalomyelitis from multiple sclerosis. *BMJ* 1996; 313: 802-804.

• **Ota K.** [Intravenous immunoglobulin in multiple sclerosis]. *Nippon Rinsho* 2003; 61: 1374-1380.

**Abstract:** Intravenous immunoglobulin(IVIg) is a immunomodulating therapy to administer a relatively high dose of human immunoglobulins to a number of autoimmune diseases. Clinical trials of IVIg for neurological disorders including autoimmune peripheral neuropathy were carried out since the later of 1980's, and the efficacy of IVIg for such diseases was proved. In recent years the effectiveness of IVIg for multiple sclerosis(MS) has been reported in several randomized controlled trials(RCTs). MS patients in the trials were given immunoglobulin or placebo every month or two months for more than half a year. IVIg in particular is beneficial in prevention a recurrence of relapsing remitting MS and in improvement of MRI findings in a part of RCTs. However, IVIg does not recognize the distinct effectiveness in progression

of secondary progressive MS yet. Some problems, for example, optimal dose or dosage frequency are unsolved. Generally a adverse effect of IVIg in MS patient is slightness and the continuation treatment of IVIg is tolerate for most patients. Now, in Europe where a clinical trial goes ahead, IVIg might be considered the therapy for MS when a already established treatment for MS such as interferon--beta is not effective or not be able to use. On the other hand, unfortunately the effectiveness of IVIg for MS could not be recognized by RCT executed in Japan.

• **Pittock SJ, Keir G, Alexander M, Brennan P, Hardiman O.** Rapid clinical and CSF response to intravenous gamma globulin in acute disseminated encephalomyelitis. *Eur J Neurol* 2001; 8: 725-ittock, S.

• **Pradhan S, Gupta RP, Shashank S, Pandey N.** Intravenous immunoglobulin therapy in acute disseminated encephalomyelitis. *J Neurol Sci* 1999; 165: 56-61.

**Abstract:** We describe 4 patients with acute disseminated encephalomyelitis (ADEM) who were treated with intravenous immunoglobulins (IVIg) after getting no immediate response from a 3-5 day course of high dose intravenous methylprednisolone. All had clinical features to suggest poor prognosis and MRI findings to indicate extensive white matter changes in the brain. Two patients who had spinal cord involvement as well, required ventilatory support during acute phase of the illness. All the 4 patients recovered dramatically. Recovery pattern suggested that IVIg might be useful in fulminant ADEM. Further trials are needed to look for the efficacy of IVIg alone and in combination with methylprednisolone in the treatment of ADEM.

• **Pritchard J, Gray IA, Idrissova ZR, et al.** A randomized controlled trial of recombinant interferon-beta 1a in Guillain-Barre syndrome. *Neurology* 2003; 61: 1282-1284.

**Abstract:** The authors recruited 19 nonambulant patients with Guillain-Barre syndrome into a pilot, double-blind, randomized, placebo-controlled safety trial of interferon beta 1a (IFN[beta]-1a) (Rebif). Participants received IFN[beta]-1a or placebo subcutaneously three times weekly, 22 microg for the first week and then 44 microg for up to 24 weeks, in addition to IV immunoglobulin (IVIg). IFN[beta] did not have any unexpected interaction with IVIg and there was no significant difference in rate of improvement.

• **Raju R, Dalakas MC.** Gene expression profile in the muscles of patients with inflammatory myopathies: effect of therapy with IVIg and biological validation of clinically relevant genes. *Brain* 2005; 128: 1887-1896.

**Abstract:** To explore the biological significance of gene expression in the pathogenesis of inflammatory myopathies, we performed microarray experiments followed by real-time PCR and immunohistochemistry on muscle biopsies obtained before and after therapy from patients with dermatomyositis (DM) who improved and patients with inclusion body myositis (sIBM) who did not improve after controlled trials with three monthly intravenous immunoglobulin (IVIg) infusions. The pretreatment biopsies showed high expression of immunoglobulin, adhesion molecules, chemokines and cytokine genes in both sIBM and DM (sIBM > DM). In the repeated biopsies of DM patients who clinically improved, 2206 genes were downregulated more than 1.5-fold; in contrast, 1700 of the same genes remained unchanged in sIBM patients who did not improve. Genes markedly downregulated in DM, but not sIBM, were interleukin 22, Kallmann syndrome 1 (KAL-1), an adhesion molecule shown for the first time in muscle, ICAM-1, complement C1q, and several structural protein genes. Because mRNA for KAL-1 was selectively upregulated in vitro by transforming growth factor (TGF) beta1, a fibrogenic cytokine immunolocalized in the endomysial connective tissue of pretreatment DM muscles, the downregulation of both TGF-beta and KAL-1 after IVIg only in DM suggests that these molecules have a functional role in connective tissue proliferation and fibrosis. The improved muscles of DM, but not sIBM, showed upregulation of chemokines CXCL9 (Mig) and CXCL11, and several immunoglobulin-related genes, suggesting an effect on muscle remodelling and regeneration. The results suggest that IVIg modulates several immunoregulatory or structural muscle genes, but only a subset of them associated with inflammatory mediators, fibrosis and muscle remodelling are connected with the clinical response. Gene arrays, when combined with clinical assessments, may provide important information in the pathogenesis of inflammatory myopathies.

• **RamachandranNair R, Parameswaran M, Girija AS.** Acute disseminated encephalomyelitis treated with plasmapheresis. *Singapore Med J* 2005; 46: 561-563.

**Abstract:** Accepted modes of therapy in acute disseminated encephalomyelitis include intravenous methyl prednisolone, intravenous immunoglobulin or a combination of both. Effectiveness of plasmapheresis has been demonstrated by previous case reports. We report two patients with steroid non-responsive acute disseminated encephalomyelitis in which plasmapheresis resulted in complete clinical and radiological recovery, though the therapy was initiated in the fifth week of illness. A total of 45-50 ml/kg body weight of plasma was removed in six equal exchanges over a period of two weeks. This report highlights that plasmapheresis could be of use even in the early second month of illness.

• **Raphael JC, Chevret S, Harboun M, Jars-Guincestre MC.** Intravenous immune globulins in patients with Guillain-Barre syndrome and contraindications to plasma exchange: 3 days versus 6 days. *J Neurol Neurosurg Psychiatry* 2001; 71: 235-238.

**Abstract:** Plasma exchange is contraindicated in 10 to 20% of patients with Guillain-Barre syndrome (GBS). The optimal schedule for intravenous immune globulin (IVIg) therapy has not yet been established in these patients. The objective was to compare the efficacy and safety of two IVIg treatment durations in patients with GBS with contraindications for plasma exchange. In this randomised, double blind, multicentre phase II trial conducted in seven French centres, patients with GBS with severe haemostasis, unstable haemodynamics, or uncontrolled sepsis were randomly assigned to 0.4 g/kg/day IVIg for 3 or 6 days. The primary outcome measure was the time needed to regain the ability to walk with assistance. Thirty nine patients were included from March 1994 to May 1997, 21 in the 3 day group and 18 in the 6 day group. Time to walking with assistance was non-significantly shorter in the 6 day group (84 (23-121) v 131 days (51-210), p=0.08); the difference was significant in ventilated patients (86 days (13-151) in the 6 day group v 152 days (54-332) in the 3 day group; p=0.04). The prevalence and severity of IVIg related adverse effects were comparable between the two groups. In conclusion, in patients with GBS and contraindications for plasma exchange, especially those who need ventilatory assistance, IVIg (0.4 g/kg/day) may be more beneficial when given for 6 days rather than 3 days.

• **Rehman HU.** Primary angiitis of the central nervous system. *J R Soc Med* 2000; 93: 586-588.

• **Roca B, Ferrer D, Calvo B.** Temporal arteritis and Guillain-Barre syndrome. *South Med J* 2002; 95: 1081-1082.

**Abstract:** The association of temporal arteritis and Guillain-Barre syndrome has rarely been reported. We describe a patient who sequentially suffered from both disorders. An 81-year-old woman presented with headache and loss of appetite. Analysis showed anemia and an erythrocyte sedimentation rate of 94 mm/hr. Temporal artery biopsy disclosed giant cell arteritis. Upon treatment with prednisone, all symptoms improved. A few weeks later, the patient began having low back pain, paresthesias, ascending weakness, and unexplained intermittent hypotension. Examination showed absent tendon reflexes in the knees. Cerebrospinal fluid contained one mononuclear cell/dL, and a protein level of 81 mg/dL. An electrophysiologic study revealed reduced nerve conduction velocities. Intravenous immunoglobulin therapy was instituted, and all symptoms slowly disappeared. This is the third reported case of Guillain-Barre syndrome in association with temporal arteritis. The other two patients recovered. Although the association of Guillain-Barre syndrome and temporal arteritis in these three patients could be coincidental, a common immunologic mechanism is also a possibility.

• **Ronager J, Ravnborg M, Hermansen I, Vorstrup S.** Immunoglobulin treatment versus plasma exchange in patients with chronic moderate to severe myasthenia gravis. *Artif Organs* 2001; 25: 967-973.

**Abstract:** The purpose of this study was to compare the efficacy of high-dose intravenous immunoglobulin (IVIG) treatment with plasma exchange in patients suffering from moderate to severe myasthenia gravis (MG) in a stable phase. There are no controlled studies comparing IVIG with plasma exchange in patients who despite immunosuppressive treatment have persistent incapacitating MG symptoms. This was a controlled crossover study. Twelve patients with generalized moderate to severe MG on immunosuppressive treatment for at least 12 months were included. The patients were evaluated clinically using a quantified MG clinical score (QMGS) before and at follow-up visits after each treatment. One week after the treatments, the patients who received plasma exchange treatment showed a significant improvement in QMGS compared to baseline but although some improvement was seen after IVIG this did not reach statistical significance. Four weeks after both plasma exchange and IVIG treatments, there was a significant improvement in QMGS compared to baseline. One

week and 4 weeks after treatment, no significant difference between the 2 treatments was found. Both treatments have a clinically significant effect 4 weeks out in patients with chronic MG, but the improvement has a more rapid onset after plasma exchange than after IVIG.

• **Ropper AH.** Current treatments for CIDP. *Neurology* 2003; 60: S16-S22.

**Abstract:** This article reviews the efficacy and tolerability of currently available therapies, including intravenous immunoglobulin (IVIg), corticosteroids, and plasma exchange (PE), for treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Data show that current therapies are effective in approximately two-thirds of patients. However, they fail to provide a durable clinical response. Furthermore, current treatments have several limitations that make them problematic for long-term therapy. IVIg dosing is required approximately every 2 to 8 weeks in most patients to maintain improvement. It is expensive, time-consuming to administer, and availability can be a problem. Furthermore, IVIg is a blood product that is associated with rare thromboembolic events. Corticosteroids have poor safety and tolerability profiles, and PE is invasive, time-consuming, expensive, and can be performed only at specialized centers. An alternative to single-agent therapy with current treatments is the use of combination therapy. Combination therapy may increase the duration of response, provide increased efficacy or independent efficacy in unresponsive patients, and reduce the need for standard therapies. Research is needed to find agents suitable for single and combination therapy in CIDP.

• **Rudick RA, Schiffer RB, Schwetz KM, Herndon RM.** Multiple sclerosis. The problem of incorrect diagnosis. *Arch Neurol* 1986; 43: 578-583.

**Abstract:** Various neurologic disorders may be diagnosed incorrectly as multiple sclerosis (MS) since there is no test that is entirely specific for the disease. We report ten patients who met clinical criteria for probable or definite MS and who were given incorrect diagnoses. All of the patients were subsequently shown to have alternative diagnoses, three of which were directly treatable. From these illustrative cases, five characteristics were identified that alerted us to the possibility of an alternative diagnosis. We have called these characteristics "red flags," and suggest that they may be useful as features casting doubt on the diagnosis of MS if used judiciously in conjunction with clinical diagnostic criteria.

• **Sahlas DJ, Miller SP, Guerin M, Veilleux M, Francis G.** Treatment of acute disseminated encephalomyelitis with intravenous immunoglobulin. *Neurology* 2000; 54: 1370-1372.

**Abstract:** Acute disseminated encephalomyelitis (ADEM) is a presumed immune-mediated, demyelinating disease of the CNS for which the standard treatment is high-dose steroids. We describe two patients with ADEM in whom treatment with IV methylprednisolone coincided with deterioration in their clinical status. They were subsequently treated with IV immunoglobulin and exhibited dramatic clinical improvement, with return to their previous level of functioning.

• **Sandberg-Wollheim M.** Interferon-beta1a treatment for multiple sclerosis. *Expert Rev Neurother* 2005; 5: 25-34.

**Abstract:** Although multiple sclerosis is probably the most common cause of neurologic disability in young adults, the cause is unknown, the prognosis uncertain and available treatments unsatisfactory. Multiple sclerosis is an inflammatory autoimmune disorder of the CNS and the result of both environmental factors and susceptibility genes. The prognosis is difficult or impossible to predict at the time of diagnosis. Treatments that modulate the course of the disease have only recently become available but the long-term aim to prevent disability and promote repair remains distant. Interferon-beta is the most widely used therapy. The efficacy of interferon-beta in the short term is well documented in many large treatment trials, but the treatment effects are only modest and many issues relating to efficacy in the long term are unresolved. These include uncertain benefit on conversion to secondary-progressive multiple sclerosis, the relevance of neutralizing antibodies and the controversial effect on multiple sclerosis-related brain atrophy.

• **Sanna G, Bertolaccini ML, Mathieu A.** Central nervous system lupus: a clinical approach to therapy. *Lupus* 1906; 12: 935-942.

**Abstract:** Management of central nervous system (CNS) involvement still remains one of the most challenging problems in systemic lupus erythematosus (SLE). The best available evidence for the treatment of CNS lupus is largely based on retrospective series, case reports and expert opinion. Current therapy is empirical and tailored to the individual patient. Symptomatic, immunosuppressive and anticoagulant therapies are

the main strategies for the management of CNS lupus. The choice depends on the most probable underlying pathogenic mechanism and the severity of the presenting neuropsychiatric symptoms. Thrombotic and nonthrombotic CNS disease needs to be differentiated and requires different management strategies. However, this is often challenging since many, if not most CNS manifestations, may be due to a combination of different pathogenic mechanisms and multiple CNS events may occur in the individual patient. Patients with mild manifestations may need symptomatic treatment only, whereas more severe acute nonthrombotic CNS manifestations may require pulse intravenous cyclophosphamide. Plasmapheresis may also be added in patients with more severe illness refractory to conventional treatment. Recently, the use of intrathecal methotrexate and dexamethasone has been reported in a small series of patients, with a good outcome in patients with severe CNS manifestations. Anticoagulation is warranted in patients with thrombotic disease, particularly in those with the antiphospholipid syndrome (APS). This article reviews the clinical approach to therapy in patients with CNS lupus.

- **Schaublin GA, Michet CJJ, Dyck PJ, Burns TM.** An update on the classification and treatment of vasculitic neuropathy. *Lancet Neurol* 2005; 4: 853-865.

**Abstract:** Vasculitic neuropathy usually presents with painful mononeuropathies or an asymmetric polyneuropathy of acute or subacute onset. The disorder should be classified as being systemic or non-systemic. Systemic vasculitis should be further classified into one of the primary and secondary forms. Although specific treatment regimens vary among neurologists, basic principles can be applied. Corticosteroids and cytotoxic drugs have been the mainstay of treatment for most forms of vasculitic neuropathy. Here we discuss dosing, potential side-effects, and management recommendations of conventional treatments. New treatments showing promise include intravenous immunoglobulin and biological agents and trials of the newest treatments are being reviewed. Future trials should compare commonly used treatment regimens and better establish the efficacy of newer, potentially safer, treatments.

- **Sekul EA, Chow C, Dalakas MC.** Magnetic resonance imaging of the forearm as a diagnostic aid in patients with sporadic inclusion body myositis. *Neurology* 1997; 48: 863-866.

**Abstract:** Because weakness of finger flexors and atrophy of the forearms are frequent findings in inclusion body myositis (IBM) patients, we examined the forearm muscles by MRI to determine if involvement of the distal musculature has a characteristic diagnostic pattern. We performed MRI of the forearms in 21 randomly selected patients with histologically confirmed IBM and in 9 patients with other, age-matched, neuromuscular diseases who served as controls. In addition, we analyzed axial images of 10 individual forearm muscles blindly without knowledge of the clinical status or diagnosis of the patients. T1-weighted MR images showed marbled brightness of the flexor digitorum profundus (FDP) in 20 of 21 IBM patients, of the flexor carpi ulnaris in 7, the flexor digitorum superficialis (FDS) in 6, the flexor carpi radialis in 4, the supinator in 3, and the brachioradialis in 1. The extensors were normal. The abnormalities of the FDP correlated with the severity but not the duration of the disease and in some patients preceded overt clinical signs of FDP weakness. In contrast, the FDS was spared even late in the disease. We conclude that selective involvement of the FDP may occur early in the course of IBM and can be easily demonstrated by MRI in up to 95% of patients. Because selective FDP involvement appears to be a very frequent and characteristic finding in patients with IBM, MRI of the forearm is a useful noninvasive test in supporting the diagnosis of sporadic IBM.

- **Shahar E, Andraus J, Savitzki D, Pilar G, Zelnik N.** Outcome of severe encephalomyelitis in children: effect of high-dose methylprednisolone and immunoglobulins. *J Child Neurol* 2002; 17: 810-814.

**Abstract:** Acute encephalomyelitis in children refers to an insult of cortical white matter leading to acute disseminated encephalomyelitis, insult of the spinal cord leading to multifocal myelopathy, or a combined form of encephalomyelitis. We report here the clinical presentations and outcome of 16 children with severe acute encephalomyelitis analyzing the effect of high-dose methylprednisolone or intravenous immunoglobulins, administered separately or in combination. Five children developed acute disseminated encephalomyelitis alone, eight developed severe multifocal myelopathy accompanied in two of them by radiculoneuropathy, and three developed the most severe form of combined encephalomyeloradiculoneuropathy. The indications for treatment with either high-dose methylprednisolone, intravenous immunoglobulin, or a combination of the two were severe acute disseminated encephalomyelitis, visual loss, or severe flaccid weakness accompanied by bladder and bowel incontinence.

Overall, 10 children had remarkably responded to high-dose methylprednisolone alone and recovered within 10 days. One patient with severe myelopath, developing paraplegia, who failed oral corticosteroids completely recovered following intravenous immunoglobulin. Of the isolated acute disseminated encephalomyelitis group, all patients were initially treated with high-dose intravenous methylprednisolone and recovered within 10 days, including visual remission in the child with severe optic neuritis. All six children with solitary severe multifocal myelopathy were treated with high-dose methylprednisolone alone and recovered within the first week. Two patients had severe myeloradiculoneuropathy and were therefore treated with combined high-dose methylprednisolone and intravenous immunoglobulin: one remains paraplegic, whereas the second was ventilated for 3 weeks and recovered after 2 months. The three children with the most severe form of encephalomyeloradiculoneuropathy were treated with combined high-dose methylprednisolone and intravenous immununoglobulin; two remain severely handicapped, of whom one is paraplegic, and the third unexpectedly recovered within 3 months. Therefore, our experience indicates that either high-dose methylprednisolone or intravenous immunoglobulin, given separately or combined, may be efficacious in severe debilitating pediatric-onset acute encephalomyelitis. In children with the most severe form of encephalomyeloradiculoneuropathy, we suggest initially administering high-dose methylprednisolone and intravenous immunoglobulin combined, given the poorer outcome of our patients with combined severe central and peripheral demyelination.

• **Silvia MT, Licht DJ.** Pediatric central nervous system infections and inflammatory white matter disease. *Pediatr Clin North Am* 2005; 52: 1107-26, ix.

**Abstract:** This article reviews the immunology of the central nervous system and the clinical presentation, diagnosis, and treatment of children with viral or parainfectious encephalitis. The emphasis is on the early recognition of treatable causes of viral encephalitis (herpes simplex virus), and the diagnosis and treatment of acute disseminated encephalomyelitis are described in detail. Laboratory and imaging findings in the two conditions also are described.

• **Sorensen PS, Wanscher B, Jensen CV, et al.** Intravenous immunoglobulin G reduces MRI activity in relapsing multiple sclerosis. *Neurology* 1998; 50: 1273-1281.

**Abstract:** We wanted to assess whether intravenous immunoglobulin G (IVIG) decreases disease activity on MRI in relapsing MS. Previous trials of IVIG in relapsing-remitting MS demonstrated a reduction of acute relapses, but these studies did not include MRI. We treated 26 patients in a randomized, double-blind, crossover study of IVIG 1 g/kg daily or placebo on 2 consecutive days every month during two 6-month treatment periods. The primary end point was the number of gadolinium-enhancing lesions on monthly serial MRI. Secondary efficacy variables were the occurrence of exacerbations, clinical neurologic ratings, total MS lesion load on T2-weighted MRI, and multimodal evoked potentials. Eighteen patients completed the entire trial; eight patients did not. Twenty-one patients completed the first treatment period and at least two MRI examinations in the second treatment period and were included in the intention-to-treat analysis. On serial MRI, we observed fewer enhancing lesions per patient per scan during IVIG treatment (median, 0.4; range, 0 to 9.3) than during placebo treatment (median, 1.3; range, 0.2 to 25.7; $p = 0.03$). During IVIG treatment, 15 patients were exacerbation free compared with only 7 on placebo ($p = 0.02$). The total number of exacerbations in the IVIG period was 11 and in the placebo period, 19 (not significant). None of the remaining secondary efficacy measures were significantly different between the two treatment periods. The number of adverse events, in particular eczema, was significantly higher during IVIG therapy than during placebo treatment. These results suggest that IVIG treatment is beneficial to patients with relapsing MS.

• **Spalice A, Properzi E, Lo FV, Acampora B, Iannetti P.** Intravenous immunoglobulin and interferon: successful treatment of optic neuritis in pediatric multiple sclerosis. *J Child Neurol* 2004; 19: 623-626.

**Abstract:** Optic neuritis is a common clinical condition that causes loss of vision. It can be clinically isolated or can occur as one of the manifestations of multiple sclerosis. Multiple sclerosis is a severe disabling demyelinating disease of the central nervous system, which is rare among children. The treatment of optic neuritis has been investigated in several trials, the results of which have shown that corticosteroids speed up the recovery of vision without affecting the final visual outcome. Treatment of neurologic disorders with intravenous immunoglobulin is an increasing feature of our practice for an expanding range of indications, including multiple sclerosis. Owing to its anti-inflammatory properties, intravenous immunoglobulin can be beneficial in the treatment of

acute relapses and in the prevention of new relapses of multiple sclerosis. To our knowledge, there is only one experience of treatment of optic neuritis with intravenous immunoglobulin in multiple sclerosis, even if therapeutic trials are used in the therapy of multiple sclerosis. We report on a girl with optic neuritis and multiple sclerosis in whom treatment with intravenous immunoglobulin at first alone and subsequently associated with interferon achieved great improvement in visual acuity.

• **Stuve O, Zamvil SS.** Pathogenesis, diagnosis, and treatment of acute disseminated encephalomyelitis. *Curr Opin Neurol* 1999; 12: 395-401.

**Abstract:** Acute disseminated encephalomyelitis is considered a monophasic, inflammatory demyelinating disorder of the central nervous system. A temporal relationship usually exists between the onset of neurologic symptoms and an infection or a vaccination. A viral exanthem facilitates the diagnosis. Some heterogeneity exists with regard to etiology and clinical course of this disease. Immunosuppression is considered the treatment of choice.

• **Takigawa N, Kawata N, Shibayama T, et al.** Successful treatment of a patient with severe Churg-Strauss syndrome by a combination of pulse corticosteroids, pulse cyclophosphamide, and high-dose intravenous immunoglobulin. *J Asthma* 2005; 42: 639-641.

**Abstract:** A 24-year-old woman with a 4-year history of bronchial asthma suffered from bloody sputum, numbness of the extremities, elevated eosinophil count, and hypoxemia. A diagnosis of alveolar hemorrhage was made by bronchoalveolar lavage. Echocardiogram revealed severe hypokinesis of the left ventricular wall. Her respiratory condition deteriorated despite administration of pulse corticosteroids. A second pulse corticosteroids and pulse cyclophosphamide followed by high-dose intravenous immunoglobulin brought about a dramatic improvement of alveolar hemorrhage, cardiac impairment, and peripheral neuropathy. Levels of antimyeloperoxidase-antineutrophil cytoplasmic antibodies, soluble thrombomodulin, soluble interleukin-2 receptor, eosinophil cationic protein were elevated and returned to the normal range in remission. The combination of pulse corticosteroids, pulse cyclophosphamide, and high-dose intravenous immunoglobulin seemed effective for the acute phase of severe Churg-Strauss syndrome.

• **Thomas GS, Hussain IH.** Acute disseminated encephalomyelitis: a report of six cases. *ed J Malaysia* 2004; 59: 342-351.

**Abstract:** Six children with Acute Disseminated Encephalomyelitis (ADEM) were seen at the Penang Hospital over a two year period (July 1999-June 2001). Diagnosis was based upon typical clinical features and characteristic findings on neuroimaging. Cerebrospinal fluid examination and other investigations were done, where appropriate, to rule out other causes of central nervous system disease. Three children had a prodromal illness. The most common presenting symptoms were fever, seizures, ataxia, focal neurological deficits and labile mood. Two children presented with status epilepticus. All children had an abnormal neurological examination. Brain magnetic resonance imaging revealed hyperintense signals on T2-weighted and FLAIR sequences in the subcortical and deep white matter regions of the frontal, parietal, and temporal lobes, as well as in the thalami, cerebellum and brainstem. One child had multiphasic disseminated encephalomyelitis (three episodes). The child with multiphasic disease had only one treated episode, and has suffered mild disability. Three children were treated with either methylprednisolone or immunoglobulins, and remain well. One child received both treatments but expired as a result of severe gastrointestinal bleeding from the use of methylprednisolone. The child who was not treated has severe disability.

• **Thompson N, Choudhary P, Hughes RA, Quinlivan RM.** A novel trial design to study the effect of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol* 1996; 243: 280-285.

**Abstract:** Using a novel trial design, we prospectively examined the effect of intravenous immunoglobulin in seven patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in a double-blind, placebo-controlled cross-over study.We suggest that the commonly used manual muscle testing and Rankin scale are not sufficiently sensitive to measure changes in CIDP and should not be used as isolated outcome measures. We propose a timed 10-m walk, the Nine-Hole Peg Test, the Hammersmith Motor Ability Score, and myometry as alternative measures which are valid, reliable and sensitive. Our trial design permitted the measurement of a treatment response in three responders despite different patterns of disability typical of the broad clinical picture seen in CIDP.

• **Trojano M, Defazio G, Ricchiuti F, De Salvia R, Livrea P.** Serum IgG to brain microvascular endothelial cells in multiple sclerosis. *J Neurol Sci* 1996; 143: 107-113.

**Abstract**: Serum IgG to brain microvascular endothelial cells (BMECs) were assessed in the sera from 50 patients with definite multiple sclerosis, 24 patients with other inflammatory and non-inflammatory neurological diseases and 30 healthy individuals. Standard indirect immunofluorescence on BMEC culture was used as the bioassay system. Positive immunostaining was found in the sera (1:5 to 1:50 dilution) from 0/15 inactive relapsing remitting (RR), 12/16 active RR (p = 0.0001), 1/8 relapsing progressive (RP) and 0/11 primary progressive (PP) patients. No specific binding was detected when sera from neurologic and healthy controls were used. The specificity of the immune reaction for brain endothelium was established by the absence of staining on human umbilical vein endothelial cell and brain pericyte cultures. Gadolinium (Gd)-enhanced magnetic resonance imaging of the brain and spinal cord was performed in 36 MS patients within a 10-day interval from serum collection. Anti-brain endothelium antibodies were found in 9/12 patients with, and in 1/24 patients without Gd-enhanced lesions (p = 0.00002). Regardless of a pathogenetic role in the blood-brain barrier breakdown, serum IgG to BMECs may be a marker of disease activity in RR and RP MS and a factor differentiating RR/RP and PP MS.

• **Tselis AC, Lisak RP.** Multiple sclerosis: therapeutic update. *Arch Neurol* 1999; 56: 277-280.

**Abstract:** Therapy for multiple sclerosis (MS) is undergoing rapid changes. We discuss recent developments in the therapy of MS, failures as well as successes, and consider some newer approaches. Multiple sclerosis, a multifocal, initially remitting-relapsing, and in some cases primarily progressive, inflammatory central nervous system immune-mediated demyelinating disease, with some axonal involvement, is currently the most common disabling neurologic disease of young people in North America and Europe. Although much is known about the pathogenesis, there is no cure and the disease must be managed long-term. Recently, there have been a number of advances in the treatment of MS.

• **Unay B, Sarici SU, Bulakbasi N, Akin R, Gokcay E.** Intravenous immunoglobulin therapy in acute disseminated encephalomyelitis associated with hepatitis A infection. *Pediatr Int* 2004; 46: 171-173.

• **van den Berg LH, Kerkhoff H, Oey PL, et al.** Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study. *J Neurol Neurosurg Psychiatry* 1995; 59: 248-252.

**Abstract:** The effect of high dose intravenous immunoglobulin (IVIg) treatment was studied in six patients with multifocal motor neuropathy (MMN). All patients responded to treatment (0.4 g/kg for five consecutive days) in an open trial. The effect of IVIg treatment was confirmed for each patient in a single patient, double blind, placebo controlled trial. Four patients received two IVIg treatments and two placebo treatments, and two patients received one IVIg and one placebo treatment in a randomised order. Five out of six patients responded to IVIg but not to placebo. One patient responded to IVIg in the same manner as to placebo treatment. Thus IVIg treatment can lead to improvement of muscle strength in patients with MMN.

• **van den Berg LH, Franssen H, Wokke JH.** The long-term effect of intravenous immunoglobulin treatment in multifocal motor neuropathy. *Brain* 1998; 121 ( Pt 3): 421-428.

**Abstract:** We studied the long-term effect of intravenous immunoglobulin (IV Ig) treatment in seven patients with multifocal motor neuropathy. In six patients, treatment with a full IV Ig course (0.4 g/kg for 5 consecutive days) improved muscle strength but for not longer than 12 weeks. These patients received IV Ig maintenance treatment consisting of one infusion every week for 2-4 years. One patient in whom the effect of the initial full IV Ig treatment lasted for more than 1 year received incidental IV Ig treatment when muscle strength deteriorated. In all patients IV Ig treatment had a beneficial effect on most muscle groups during the follow-up period. However, in three of the seven patients muscle strength deteriorated during IV Ig maintenance treatment in four of the 28 muscle groups that had initially shown an improvement of muscle strength after the start of IV Ig treatment, and in two muscle groups with normal strength at the start of IV Ig treatment. The electrophysiological follow-up studies indicated that there was an improvement of conduction block, but also that there were new sites of

conduction block and ongoing axonal degeneration during IV Ig maintenance treatment.

- **van der Meche FG, Schmitz PI.** A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barre syndrome. Dutch Guillain-Barre Study Group. *N Engl J Med* 1992; 326: 1123-1129.

**Abstract: BACKGROUND.** The subacute demyelinating polyneuropathy known as Guillain-Barre syndrome improves more rapidly with plasma exchange than with supportive care alone. We conducted a multicenter trial to determine whether intravenous immune globulin is as effective as the more complicated treatment with plasma exchange. **METHODS.** To enter the study, patients had to have had Guillain-Barre syndrome for less than two weeks and had to be unable to walk independently. They were randomly assigned to receive either five plasma exchanges (each of 200 to 250 ml per kilogram of body weight) or five doses of a preparation of intravenous immune globulin (0.4 g per kilogram per day). The predefined outcome measure was improvement at four weeks by at least one grade on a seven-point scale of motor function. **RESULTS.** After 150 patients had been treated, strength had improved by one grade or more in 34 percent of those treated with plasma exchange, as compared with 53 percent of those treated with immune globulin (difference, 19 percent; 95 percent confidence interval, 3 percent to 34 percent; P = 0.024). The median time to improvement by one grade was 41 days with plasma exchange and 27 days with immune globulin therapy (P = 0.05). The immune globulin group had significantly fewer complications and less need for artificial ventilation. **CONCLUSIONS.** In the acute Guillain-Barre syndrome, treatment with intravenous immune globulin is at least as effective as plasma exchange and may be superior.

- **van der Meche FG, van Doorn PA, Schmitz PI.** Intravenous immunoglobulin versus plasma exchange in Guillain-Barre syndrome. *Neurology* 1993; 43: 2730-2731.

- **van der Meche FG.** Intravenous immune globulin in the Guillain-Barre syndrome. *Clin Exp Immunol* 1994; 97 Suppl 1: 43-47.

**Abstract:** Guillain-Barre syndrome is an acute immune-mediated polyneuropathy with a severe clinical course. Plasma exchange (PE) was the first proven effective treatment ameliorating morbidity and outcome. However, it is not readily available and contraindications and complications frequently occur. High-dose intravenous immune globulin (IVIG) was demonstrated recently to be at least as effective and possibly more effective. The evidence is summarized in this article. Although specific treatment is now available, a proportion of patients do deteriorate with either IVIG (25%) or PE (34%) over the first 2 weeks after onset of treatment. A new dilemma has therefore arisen: is it worthwhile to switch therapy in patients who show further deterioration during therapy? As will be discussed, only a pragmatic approach is possible for the moment. In general it will be most effective to give just one full dose of IVIG or, alternatively, a full course of PE. More effective treatments are still being developed. The results of a pilot study of IVIG combined with high-dose methyl-prednisolone are promising and warrant a large scale clinical trial for further confirmation.

- **van der Meche FG, van Doorn PA, Jacobs BC.** Inflammatory neuropathies--pathogenesis and the role of intravenous immune globulin. *J Clin Immunol* 1995; 15: 63S-69S.

**Abstract:** The inflammatory neuropathies may be subdivided into an acute form, Guillain-Barre syndrome, and a chronic form referred to as chronic inflammatory demyelinating polyneuropathy. More recently a chronic, asymmetrical pure motor neuropathy with multifocal conduction blocks has been described. All three neuropathies are considered to be immune-mediated. Their response to therapy is discussed, with special emphasis on high-dose intravenous immune globulin. For Guillain-Barre syndrome the efficacy of intravenous immune globulin has been proven in a randomized clinical trial. In chronic inflammatory demyelinating polyneuropathy a response rate of over 60% in newly diagnosed patients is suggested. Clinical prognostic criteria, however, seem to be very important to predict the effect of intravenous immune globulin. In multifocal motor neuropathy intravenous immune globulin is at present the only alternative to cyclophosphamide.

- **van der Meche FG, van Doorn PA.** The current place of high-dose immunoglobulins in the treatment of neuromuscular disorders. *Muscle Nerve* 1997; 20: 136-147.

**Abstract:** High-dose immunoglobulins for intravenous administration (IVIg) have originally been developed for substitution therapy in hypogammaglobulinemia.

Over the last decade they are increasingly used in the treatment of immune-mediated diseases. In this review the results in immune-mediated neuromuscular diseases are summarized. Positive effects are demonstrated in open studies in dermato- and polymyositis, myasthenia gravis, and inflammatory neuropathies. Properly conducted randomized clinical trials demonstrating the effect of IVIg are available in dermatomyositis, Guillain-Barre syndrome, and chronic inflammatory demyelinating polyneuropathy, and smaller ones in multifocal motor neuropathy. In myasthenia gravis a trial is at present underway and only interim results are available. The results of a trial in the Lambert-Eaton myasthenic syndrome are in the process of publication. The therapeutic approach in individual patients is discussed, but often appears to be difficult. Considering chronic treatment with IVIg, proper long-term studies including cost-benefit studies are needed. Future developments aim for combination therapies, since IVIg and immune suppressants like prednisone are suggested to have a synergistic effect.

- **van Doorn PA, Brand A, Strengers PF, Meulstee J, Vermeulen M.** High-dose intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy: a double-blind, placebo-controlled, crossover study. *Neurology* 1990; 40: 209-212.

**Abstract:** We discontinued high-dose intravenous immunoglobulin treatment (IVIg) in 7 patients with chronic inflammatory demyelinating polyneuropathy (CIDP) who seemed to have responded to IVIg. After discontinuation of treatment, all 7 patients deteriorated. We then randomized the patients to IVIg or placebo (albumin) treatment in a double-blind crossover study. The clinical condition of all patients improved after IVIg and did not improve after placebo treatment. The mean time lapse from the end of the trial treatment to the occurrence of deterioration was 6.4 weeks after treatment with IVIg and 1.3 weeks after treatment with placebo. This selected group of patients with CIDP had a beneficial response to IVIg.

- **van Doorn PA.** Treatment of Guillain-Barre syndrome and CIDP. *J Peripher Nerv Syst* 2005; 10: 113-127.

Abstract: Guillain-Barre syndrome (GBS) and chronic inflammatory demyelinating poly-(radiculo)neuropathy (CIDP) are immune-mediated disorders with a variable duration of progression and a range in severity of weakness. Infections can trigger GBS and exacerbate CIDP. Anti-ganglioside antibodies are important, but there is debate on the role of genetic factors in the pathogenesis of these disorders. Randomized controlled trials (RCT) have shown that intravenous immunoglobulin (IVIg) and plasma exchange (PE) are effective in both GBS and CIDP. Most CIDP patients also improve after steroid therapy. Despite current treatment options, many patients have residual deficits or need to be treated for a long period of time. Therefore, new treatment trials are highly indicated. This review focuses on the current and possible new treatment options that could be guided by recent results from laboratory experiments.

- **van Koningsveld R, Schmitz PI, Meche FG, Visser LH, Meulstee J, van Doorn PA.** Effect of methylprednisolone when added to standard treatment with intravenous immunoglobulin for Guillain-Barre syndrome: randomised trial. *Lancet* 2004; 363: 192-196.

**Abstract: BACKGROUND:** Despite available treatment with intravenous immunoglobulin (IVIg), morbidity and mortality are considerable in patients with Guillain-Barre syndrome (GBS). Our aim was to assess whether methylprednisolone, when taken with IVIg, improves outcome when compared with IVIg alone. **METHODS:** We did a double-blind, placebo-controlled, multicentre, randomised study, to which we enrolled patients who were unable to walk independently and who had been treated within 14 days after onset of weakness with IVIg (0.4 g/kg bodyweight per day) for 5 days. We assigned 233 individuals to receive either intravenous methylprednisolone (500 mg per day; n=116) or placebo (n=117) for 5 days within 48 h of administration of first dose of IVIg. Because age is an important prognostic factor, we split treatment groups into two age-groups-ie, younger than age 50 years, or 50 years and older. Our primary outcome was an improvement from baseline in GBS disability score of one or more grades 4 weeks after randomisation. Analysis was by intention to treat. **FINDINGS:** We analysed 225 patients. GBS disability scores increased by one grade or more in 68% (76 of 112) of patients in the methylprednisolone group and in 56% (63 of 113) of controls (odds ratio [OR] 1.68, 95% CI 0.97-2.88; p=0.06). After adjustment for age and degree of disability at entry, treatment OR was 1.89 (95% CI 1.07-3.35; p=0.03). Side-effects did not differ greatly between groups. **INTERPRETATION:** We noted no significant difference between treatment with methylprednisolone and IVIg and IVIg alone. Because of the relevance of prognostic factors and the limited side-effects of methylprednisolone,

the potential importance of combination treatment with the drug and IVIg, however, warrants further investigation.

- **van S, I, van den Berg LH, de Haan R, Vermeulen M.** Intravenous immunoglobulin for multifocal motor neuropathy. *Cochrane Database Syst Rev* 1906; CD004429.

**Abstract: BACKGROUND:** Multifocal motor neuropathy is a rare, probably immune mediated disorder characterised by slowly progressive, asymmetric, distal weakness of one or more limbs with no objective loss of sensation. It may cause prolonged periods of disability. The treatment options for multifocal motor neuropathy are sparse. Patients with multifocal motor neuropathy do not usually respond to steroids or plasma exchange, and may even worsen with these treatments. Many uncontrolled studies have suggested a beneficial effect of intravenous immunoglobulin. **OBJECTIVES:** To review systematically the evidence from randomised controlled trials concerning the efficacy and safety of intravenous immunoglobulin in multifocal motor neuropathy. **SEARCH STRATEGY:** We used the search strategy of the Cochrane Neuromuscular Disease Review Group to search the Disease Group register (searched September 2003), MEDLINE (January 1990 to September 2003), EMBASE (January 1990 to September 2003) and ISI (January 1990 to September 2003) databases for randomised controlled trials. **SELECTION CRITERIA:** Randomised controlled studies examining the effects of any dose of intravenous immunoglobulin versus placebo in patients with definite or probable multifocal motor neuropathy.Outcome measures had to include one of the following: disability, strength, or conduction block. Studies which reported the frequency of adverse effects were used to assess safety. **DATA COLLECTION AND ANALYSIS:** Two authors reviewed literature searches to identify potentially relevant trials, scored their quality and extracted data independently. For dichotomous data, we calculated relative risks, and for continuous data, effect sizes and weighted pooled effect sizes. Statistical uncertainty was expressed with 95% confidence intervals. **MAIN RESULTS:** Four randomised controlled trials including a total of 34 patients were suitable for this systematic review. Strength improved in 78% of patients treated with intravenous immunoglobulin and only 4% of placebo-treated patients. Disability improved in 39% of patients after intravenous immunoglobulin treatment and in 11% after placebo (statistically not significantly different). Mild, transient side effects were reported in 71% of intravenous immunoglobulin treated patients. Serious side effects were not encountered. **AUTHORS' CONCLUSIONS**: Limited evidence from randomised controlled trials shows that intravenous immunoglobulin has a beneficial effect on strength. There was a non-significant trend towards improvement in disability. More research is needed to discover whether intravenous immunoglobulin improves disability and is cost-effective.

- **van S, I, Winer JB, de Haan R, Vermeulen M.** Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 1906; CD001797.

**Abstract: BACKGROUND:** Chronic inflammatory demyelinating polyradiculoneuropathy is an immune mediated disorder characterised by progressive or relapsing symmetrical motor or sensory symptoms and signs in more than one limb, developing over at least two months. It may cause prolonged periods of disability and even death. Several uncontrolled studies have suggested a beneficial effect of intravenous immunoglobulin. **OBJECTIVES:** To review systematically the evidence from randomised controlled trials concerning the efficacy and safety of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. **SEARCH STRATEGY:** We used the Search Strategy of the Cochrane Neuromuscular Disease Review Group to search the Disease Group register and other databases for randomised controlled trials from 1985 onwards. **SELECTION CRITERIA:** Randomised controlled studies examining the effects of any dose of intravenous immunoglobulin versus placebo, plasma exchange or corticosteroids in patients with definite or probable chronic inflammatory demyelinating polyradiculoneuropathy. Outcome measures had to include one of the following: a disability score, the Medical Research Council sum score, electrophysiological data or walking distance. Studies which reported the frequency of adverse effects were used to assess the safety of treatment. **DATA COLLECTION AND ANALYSIS:** Two reviewers independently reviewed literature searches to identify potentially relevant trials, scored their quality and extracted data independently. For dichotomous data, we calculated relative risks, and for continuous data, effect sizes (for definition see statistical analysis section) and weighted pooled effect sizes. Statistical uncertainty was expressed in 95% confidence intervals. Sensitivity analysis excluding studies with quality scores below A 0.50 and below B 0.75 was planned but not performed as all studies had quality scores above 0.75. **MAIN RESULTS:** Six randomised controlled

trials were considered eligible including 170 patients. Four studies on 113 patients compared intravenous immunoglobulin against placebo. One trial with 17 patients compared intravenous immunoglobulin with plasma exchange in a cross-over design and one trial compared intravenous immunoglobulin with prednisolone in 32 patients. A significantly higher proportion of patients improved in disability within one month after the onset of intravenous immunoglobulin treatment as compared with placebo (relative risk 3.17, 95% confidence interval 1.74 to 5.75). Whether all these improvements are equally clinically relevant cannot be deduced from this analysis because each trial used a different disability scale with a unique definition of a significant improvement. To overcome this problem an attempt was made to transform the various disability scales to the modified Rankin score. In three trials including 87 patients this transformation could be carried out. A significantly higher proportion of patients improved one point after intravenous immunoglobulin treatment compared to placebo (relative risk 2.47, 95% confidence interval 1.02 to 6.01). The effect size for change of mean disability score at six weeks comparing intravenous immunoglobulin with plasma exchange revealed no difference between the two therapies (effect size -0.07, 95% confidence interval -0.76 to 0.63.) The proportion of patients with a significant improvement did not differ significantly between prednisolone and intravenous immunoglobulin (relative risk of 0.91 (95% CI 0.50 to 1.68). Also, no difference in mean improvement on the disability scale was found at two weeks (effect size -0.12, 95% confidence interval -0.68 to 0.45) or six weeks (effect size -0.07, 95% confidence interval -0.63 to 0.50) between prednisolone and intravenous immunoglobulin. There were no statistically significant differences in frequencies of side effects between the three types of treatment. **REVIEWER'SCONCLUSIONS:** The evidence from randomised controlled trials shows that intravenous immunoglobulin improves disability for at least two to six weeks compared with placebo, with a number needed to treat of three. During this period it has similar efficacy to plasma exchange and oral prednisolone. Since intravenous immunoglobulin, plasma exchange and prednisolone seem to be equally effective, it is currently uncertain which of these treatments should be the first choice. Cost, side effects, duration of treatment, dependency on regular hospital visits and ease of administration all have to be considered before such a decision can be made.

• **van S, I, Winer JB, de Haan R, Vermeulen M.** Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review. *Lancet Neurol* 2002; 1: 491-498.

**Abstract:** This review discusses the efficacy and safety in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) of intravenous immunoglobulin and compares this treatment with plasma exchange and prednisolone. We searched publications from 1985 onwards for randomised controlled studies examining the effects of intravenous immunoglobulin in patients with this immune-mediated neuromuscular disorder. Six trials, with 170 patients in total, were judged eligible. A significantly higher proportion of patients improved in disability within a month after the start of treatment with intravenous immunoglobulin than with placebo (relative risk 3.17 [95% CI 1.74 to 5.75]). During this period, intravenous immunoglobulin has similar efficacy to plasma exchange and oral prednisolone; therefore which of these treatments should be the first choice is currently uncertain. An algorithm on treatment approaches for CIDP is proposed.

• **Vermeulen M, van Doorn PA, Brand A, Strengers PF, Jennekens FG, Busch HF.** Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy: a double blind, placebo controlled study. *J Neurol Neurosurg Psychiatry* 1993; 56: 36-39.

**Abstract:** Patients with a clinical diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) were randomised in a double-blind, placebo-controlled multicentre trial to investigate whether high-dose intravenous immunoglobulin treatment (IVIg) for 5 consecutive days has a beneficial effect. Fifteen patients were randomised to IVIg and 13 to placebo. In the IVIg treatment group 4 patients improved and 3 patients in the placebo group. The degree of improvement of the patients in the IVIg treatment group was no different from the patients in the placebo group. Electrophysiological studies did not show significant differences between the groups. Since a previously performed cross-over trial showed that a selected group of CIDP patients responded better to IVIg than to placebo, it is concluded that we need better criteria to select CIDP patients for treatment with IVIg.

• **Visser LH, van der Meche FG, Meulstee J, van Doorn PA.** Risk factors

for treatment related clinical fluctuations in Guillain-Barre syndrome. Dutch Guillain-Barre study group. *J Neurol Neurosurg Psychiatry* 1998; 64: 242-244.

**Abstract:** The risk factors for treatment related clinical fluctuations, relapses occurring after initial therapeutic induced stabilisation or improvement, were evaluated in a group of 172 patients with Guillain-Barre syndrome. Clinical, laboratory, and electrodiagnostic features of all 16 patients with Guillain-Barre syndrome with treatment related fluctuations, of whom 13 were retreated, were compared with those who did not have fluctuations. No significant differences were found between patients with Guillain-Barre syndrome treated with plasma exchange and patients treated with intravenous immune globulins either alone or in combination with high dose methylprednisolone. None of the patients with Guillain-Barre syndrome with preceding gastrointestinal illness, initial predominant distal weakness, acute motor neuropathy, or anti-GM1 antibodies showed treatment related fluctuations. On the other hand patients with fluctuations showed a trend to have the fluctuations after a protracted disease course. It is therefore suggested that treatment related clinical fluctuations are due to a more prolonged immune attack. There is no indication that the fluctuations are related to treatment modality. The results of this study may help the neurologist to identify patients with Guillain-Barre syndrome who are at risk for treatment related fluctuations.

- **Walter MC, Lochmuller H, Toepfer M, et al.** High-dose immunoglobulin therapy in sporadic inclusion body myositis: a double-blind, placebo-controlled study. *J Neurol* 2000; 247: 22-28.

**Abstract:** Sporadic inclusion body myositis (s-IBM) is an acquired inflammatory muscle disease of unknown cause. In general, s-IBM presents with slowly progressive, asymmetric weakness, and atrophy of skeletal muscle. There is a mild transitory or nil responsiveness to standard immunosuppressive treatment. A controlled cross-over study of 22 s-IBM patients over 3 months showed a partial improvement in those treated with high-dose intravenous immunoglobulin therapy (IVIG) versus placebo. The present study included 22 patients aged 32-75 years and with a mean duration of disease of 5.2+/-3.6 years. They were randomized by a double-blind, placebo-controlled, cross-over design to monthly infusions of 2 g/kg bodyweight IVIG or to placebo for 6 months each, followed by the alternative treatment. After 6 and 12 months the response to treatment was evaluated, using a modified Medical Research Council scale, Neuromuscular Symptom Score (NSS), the patient's own assessment of improvement, arm outstretched time, and electromyography. No serious side effects were seen, in particular no viral infection and no major cardiac or neurological complications. Overall there was no progression of the disease in 90% of patients, unlike that which might have been expected in untreated patients. A mild and significant improvement (11%) in clinical symptoms was found using NSS, but not with other test procedures. There was a trend to mild improvement in treated patients when using other tests. Individual responses to treatment was heterogeneous. The validity of this study may be reduced by mismatch of groups with regard to age at onset and variability in disease expression. The findings of this study largely confirm those of a previous IVIG trial. Treatment with IVIG may be mildly effective in s-IBM by preventing disease progression or inducing mild improvement. Long-term studies are needed to evaluate further the benefit of IVIG therapy in s-IBM.

- **Warrington AE, Bieber AJ, Ciric B, et al.** Immunoglobulin-mediated CNS repair. *J Allergy Clin Immunol* 2001; 108: S121-S125

**Abstract:** Our view of the immune system continues to evolve from a system dedicated primarily to defense against pathogens to a system that monitors the integrity of the organism and aids in repair following damage. Repair following injury to the central nervous system (CNS) is facilitated by both cellular and humoral components of the immune system. Transfer of macrophages or T cells activated against CNS antigens promote axon regrowth and protect axons from further damage. Animals immunized with spinal cord antigens and subsequently challenged with demyelination or transection of the spinal cord demonstrate better repair than animals without prior immunization. In both experimental systems, antibodies are the biologically active immune component. Human mAbs reactive to oligodendrocytes that arise in the absence of neurologic injury promote remyelination. These data support the hypothesis that B-cell clones producing mAbs reactive to CNS epitopes are a normal part of the human antibody repertoire. They challenge the assertion that an immune response to CNS antigens is pathogenic. Treatment with CNS-reactive human mAbs following CNS disease may facilitate CNS regeneration.

• **Wesselius T, Heersema DJ, Mostert JP, et al.** A randomized crossover study of bee sting therapy for multiple sclerosis. *Neurology* 2005; 65: 1764-1768.

**Abstract: BACKGROUND:** Bee sting therapy is increasingly used to treat patients with multiple sclerosis (MS) in the belief that it can stabilize or ameliorate the disease. However, there are no clinical studies to justify its use. **METHODS:** In a randomized, crossover study, we assigned 26 patients with relapsing-remitting or relapsing secondary progressive MS to 24 weeks of medically supervised bee sting therapy or 24 weeks of no treatment. Live bees (up to a maximum of 20) were used to administer bee venom three times per week. The primary outcome was the cumulative number of new gadolinium-enhancing lesions on T1-weighted MRI of the brain. Secondary outcomes were lesion load on T2*-weighted MRI, relapse rate, disability (Expanded Disability Status Scale, Multiple Sclerosis Functional Composite, Guy's Neurologic Disability Scale), fatigue (Abbreviated Fatigue Questionnaire, Fatigue Impact Scale), and health-related quality of life (Medical Outcomes Study 36-Item Short Form General Health Survey). **RESULTS:** During bee sting therapy, there was no significant reduction in the cumulative number of new gadolinium-enhancing lesions. The T2*-weighted lesion load further progressed, and there was no significant reduction in relapse rate. There was no improvement of disability, fatigue, and quality of life. Bee sting therapy was well tolerated, and there were no serious adverse events. **CONCLUSIONS:** In this trial, treatment with bee venom in patients with relapsing multiple sclerosis did not reduce disease activity, disability, or fatigue and did not improve quality of life.

• **West SG.** Central nervous system vasculitis. *Curr Rheumatol Rep* 2003; 5: 116-127.

**Abstract:** Vasculitis of the central nervous system (CNS) is classified as primary angiitis or as vasculitis secondary to a variety of diseases. A wide spectrum of clinical features may occur. A definite diagnosis is hampered by the difficulty in obtaining tissue for histology. Consequently, a diagnosis is frequently made on the basis of clinical presentation, brain magnetic resonance imaging, and cerebral angiography without pathologic confirmation. Recent experience shows that there are multiple other conditions that can mimic CNS vasculitis, many of which have different therapies. Most patients with CNS vasculitis should be treated aggressively with a combination of immunosuppressive medications. The prognosis is greatly improved with early recognition and therapy.

• **Wicklund MP, Kissel JT.** Paraproteinemic Neuropathy. Curr Treat Options Neurol EDAT- 2001/02/17 11:00 MHDA- 2001/02/17 11:00 PST - ppublish 2001; 3: 147-156.

**Abstract:** Few prospective, randomized, placebo-controlled trials have been performed to guide clinicians in the management of neuropathies seen in the setting of monoclonal gammopathies (paraproteins). Recommendations must be made on the basis of clinical experience and information gleaned from various uncontrolled and open-label trials. In every instance, decisions concerning therapy must be based on the clinical setting in which the paraprotein occurs. Treatment of paraproteinemic neuropathies associated with multiple myeloma, amyloidosis, and Waldenstrom's macroglobulinemia should be directed at the treatment of the underlying disease. These neuropathies often remain recalcitrant to therapy. If the paraprotein results from cryoglobulinemia due to hepatitis C virus infection, interferon-alpha (with or without ribavirin) provides optimal subjective and objective relief from symptoms. For neuropathy associated with osteosclerotic myeloma (POEMS syndrome) and solitary bone lesions, radiation therapy is the most effective and least toxic initial therapy. In those patients with monoclonal gammopathies of undetermined significance (MGUS), consideration of the clinical syndrome may be very helpful in selecting appropriate treatment. Patients who fulfill diagnostic criteria for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are best treated in a manner similar to that used for idiopathic CIDP (ie, with intravenous immunoglobulin, plasma exchange, and corticosteroids). Class I evidence documents plasma exchange to be effective in peripheral neuropathies associated with MGUS of the IgG and IgA, but not IgM, types. The most difficult cases to treat are those with peripheral neuropathies associated with IgM monoclonal gammopathies, with or without reactivity to myelin-associated glycoprotein (MAG). A number of published case series propose therapeutic regimens for these conditions, yet optimal treatment remains to be established. In many cases, mildly symptomatic patients should not be subjected to the morbidity associated with current treatment regimens. In those patients requiring treatment, this author initially tries plasma exchange, followed by a course of chlorambucil if the symptoms and signs are predominantly sensory. For cases with rapid progression or significant disability, a regimen of monthly pulses with prednisone and cyclophosphamide is recommended. If improvement does not ensue, a trial of a newer agent, such as rituximab, is recommended. Supportive treatment with physical therapy, orthotics, and ambulatory aids enhances patient independence at a relatively low cost.

• **Wiles CM, Brown P, Chapel H, et al.** Intravenous immunoglobulin in neurological disease: a specialist review. *J Neurol Neurosurg Psychiatry* 2002; 72: 440-448.

**Abstract:** Treatment of neurological disorders with intravenous immunoglobulin (IVIg) is an increasing feature of our practice for an expanding range of indications. For some there is evidence of benefit from randomised controlled trials, whereas for others evidence is anecdotal. The relative rarity of some of the disorders means that good randomised control trials will be difficult to deliver. Meanwhile, the treatment is costly and pressure to "do something" in often distressing disorders considerable. This review follows a 1 day meeting of the authors in November 2000 and examines current evidence for the use of IVIg in neurological conditions and comments on mechanisms of action, delivery, safety and tolerability, and health economic issues. Evidence of efficacy has been classified into levels for healthcare interventions (tables 1 and 2).

• **Wiles CM, Brown P, Chapel H, et al.** Intravenous immunoglobulin in neurological disease: a specialist review. *J Neurol Neurosurg Psychiatry* 2002; 72: 440-448.

**Abstract:** Treatment of neurological disorders with intravenous immunoglobulin (IVIg) is an increasing feature of our practice for an expanding range of indications. For some there is evidence of benefit from randomised controlled trials, whereas for others evidence is anecdotal. The relative rarity of some of the disorders means that good randomised control trials will be difficult to deliver. Meanwhile, the treatment is costly and pressure to "do something" in often distressing disorders considerable. This review follows a 1 day meeting of the authors in November 2000 and examines current evidence for the use of IVIg in neurological conditions and comments on mechanisms of action, delivery, safety and tolerability, and health economic issues. Evidence of efficacy has been classified into levels for healthcare interventions (tables 1 and 2).

• **Wingerchuk DM.** Acute disseminated encephalomyelitis: distinction from multiple sclerosis and treatment issues. *Adv Neurol* 1906; 98: 303-318.

• **Wolfe GI, Barohn RJ, Foster BM, et al.** Randomized, controlled trial of intravenous immunoglobulin in myasthenia gravis. *Muscle Nerve* 2002; 26: 549-552.

**Abstract:** We initiated a randomized, double-blinded, placebo-controlled trial of intravenous immunoglobulin (IVIG) treatment in myasthenia gravis (MG). Patients received IVIG 2 gm/kg at induction and 1 gm/kg after 3 weeks vs. 5% albumin placebo. The primary efficacy measurement was the change in the quantitative MG Score (QMG) at day 42. Fifteen patients were enrolled (6 to IVIG; 9 to placebo) before the study was terminated because of insufficient IVIG inventories. At day 42, there was no significant difference in primary or secondary outcome measurements between the two groups. In a subsequent 6-week open-label study of IVIG, positive trends were observed.

• **Yousry TA, Major EO, Ryschkewitsch C, et al.** Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med* 2006; 354: 924-933.

**Abstract: BACKGROUND:** Progressive multifocal leukoencephalopathy (PML) was reported to have developed in three patients treated with natalizumab. We conducted an evaluation to determine whether PML had developed in any other treated patients. **METHODS:** We invited patients who had participated in clinical trials in which they received recent or long-term treatment with natalizumab for multiple sclerosis, Crohn's disease, or rheumatoid arthritis to participate. The clinical history, physical examination, brain magnetic resonance imaging (MRI), and testing of cerebrospinal fluid for JC virus DNA were used by an expert panel to evaluate patients for PML. We estimated the risk of PML in patients who completed at least a clinical examination for PML or had an MRI. **RESULTS:** Of 3417 patients who had recently received natalizumab while participating in clinical trials, 3116 (91 percent) who were exposed to a mean of 17.9 monthly doses underwent evaluation for PML. Of these, 44 patients were referred to the expert panel because of clinical findings of possible PML, abnormalities on MRI, or a high plasma viral load of JC virus. No patient had detectable JC virus DNA in the cerebrospinal fluid. PML was ruled out in 43 of the 44 patients, but it could not be ruled out in one patient who had multiple sclerosis and progression of neurologic disease because data on cerebrospinal fluid testing and follow-up MRI were not available. Only the three previously reported cases of PML were confirmed (1.0 per 1000 treated patients; 95 percent confidence interval, 0.2 to 2.8 per 1000). **CONCLUSIONS:** A detailed review of possible cases

of PML in patients exposed to natalizumab found no new cases and suggested a risk of PML of roughly 1 in 1000 patients treated with natalizumab for a mean of 17.9 months. The risk associated with longer treatment is not known.

• **Zamvil SS, Steinman L.** Diverse targets for intervention during inflammatory and neurodegenerative phases of multiple sclerosis. *Neuron* 2003; 38: 685-688.

**Abstract:** Multiple sclerosis (MS) is an autoimmune central nervous system (CNS) demyelinating disease that causes relapsing and chronic neurologic impairment. Recent observations have altered certain traditional concepts regarding MS pathogenesis. A greater diversity of cell types and molecules involved in MS is now evident. While remyelination can occur during the early inflammatory phase when damage may be reversible, it is impaired in the later stages, which involve axonal death. These observations have important therapeutic implications.

• **Zinman LH, Sutton D, Ng E, Nwe P, Ngo M, Bril V.** A pilot study to compare the use of the Excorim staphylococcal protein immunoadsorption system and IVIG in chronic inflammatory demyelinating polyneuropathy. *Transfus Apher Sci* 2005; 33: 317-324.

**Abstract:** Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune mediated neuropathy responding to immunomodulation with IVIG or plasma exchange (PE). We tested the efficacy and safety of selective immunoglobulin removal by Excorim immunoadsorption (IA) in a pilot trial in CIDP patients randomized to monthly IA or IVIG treatments for 6 months. Response rates at 2 and 6 months were greater with IA due to longer disease duration and greater disability at baseline in the patients receiving IVIG. IA appears to be a safe and efficacious therapy for patients with CIDP, but an appropriately powered clinical trial with stratification for disease duration is required.