From desensitizing hemotherapy of the past to the current immunomodulating therapy with high doses of intravenous immunoglobulin*

Da Hemoterapia dessensibilizante do passado à Terapia imunomoduladora atual por Imunoglobulina Endovenosa em altas doses *

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Eighty years ago, Hildebrando Portugal wrote an article for the Brazilian Annals of Dermatology named "Desensitization in Dermatologic Therapeutics",[1] in which he discussed the aspects of anaphylaxis, intoxication, sensitization and desensitization.

In terms of sensitization, this author presented the ideas of Ravaut,[2,3] and Spillmann who attributed high importance to sensitization in the genesis of some dermatosis.

"According to Ravaut, dermatoses originating from such phenomena are classified into 5 groups as follows:

Group 1. urticaria, Quincke's disease and pruritus.

Group 2. prurigo, strophulus and eczema.

Group 3. artificial dermitis.

Group 4. recurrent dermatosis bullosa, Dühring disease, pregnancy dermatosis.

Group 5. cutaneous infectious diseases, recurrent herpes, furuncles.

At first, let us cover the conditions that favor these illnesses, their relevant causes and the recommended therapy.

Sensitization depends on two factors: the body and the antigen. The body's different reaction results from special conditions and from the repeated action of the antigen; this is called hypersensitivity or sensitization.

Ravaut has provided the following definition: "a sensitized individual is the one whose body has acquired, under repeated influence of an antigen, the property to react constantly to doses that would have been well tolerated otherwise and which in the same conditions do not affect normal individuals". Sensitization "is the clinical and humoral presentations that translated the body's new property".

The artificial dermitis classified by Ravaut as Group 3 of dermatosis originating from sensitization is probably related with the allergic contact dermatitis. In Ravaut's classification it is extremely interesting to note that the author has included in Group 4 the dermatosis bullosa among diseases caused by sensitization. Thus, the author has recognized for these illnesses the immune substrate that was only demonstrated in the 1960's with indirect immunofluorescence assays carried out by Beutner and Jordan[4] who showed the existence of autoantibodies against the surface of keratinocytes in pemphigus. Further on, in the same essay, Portugal elaborates on the desensitization.

"Desensitization – Desensitization therapy consists of reestablishing the disturbed balance, suppressing the abnormal ability of reaction and leading the body to normal sensitivity.

Once the antigen causing the disorder is known, a specific process can be applied to suppress it or, if this is not enough, we can submit the body to the action of small, repeated doses of this substance.

Some successful outcomes have been reported with this method by Widal and Pasteur Vallery-Radot with antipyrine, by Labbé and Haguenau with antipyrine, by Heran Saint Girons with quinine, by Pagniez and Pasteur Vallery-Tadot with egg white and several other cases.

The desensitizing agent can be administered by cutaneous (repeated cutaneous reaction), subcutaneous, intravenous or oral routes.

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The nature of the antigen in most cases is beyond the clinicians' knowledge. In such cases, the alternative is to use different substances to desensitize the body.

We shall now briefly approach the different medications to treat these conditions based on the descriptions by Dracoulidés.

Unspecific agents act by means of slow desensitization or by the effects of the impact they can cause.

To obtain this last effect, foreign substances are injected in the veins such as 10% peptone (Nolf), milk, bacterial vaccines or the individual's own serum (auto-serum therapy).

In slow desensitization, the intravenous route is not used; the intramuscular and oral routes are preferred and the antigen administration must be repeated. The most commonly used substances include peptone, milk, blood, autogenous vaccines and crystalloid substances (sodium hyposulfite, calcium chloride, sodium carbonate).

Peptone is an excellent medication. It can be used as advocated by Pagniez and Pasteur Vallery-Radot, by gastric administration according to the following formulation:

Internal Use	
Peptone	0.50
Calcinated Magnesium	0.25
Powder of	q. s.

In one capsule. Take one capsule one hour before the meals.

Peptone therapy is indicated in cases of urticaria, Quincke's edema, pruritus and eczemas.

Milk is administered by intramuscular route at the dose of 5 ml.

Some satisfactory results with its use were reported by J. M. Peyry in psoriasis, eczema, pyodermitis and prurigo.

Blood is used either with its whole elements (hemotherapy) or only the serum (serum therapy). This serum can be collected from another subject (heterologous serum therapy) or from the individual himself/herself (autologous serum therapy).

Likewise, the blood to be used comes from another individual (heterologous hemotherapy) or from the individual himself/herself (autologous hemotherapy). The latter is the process most commonly employed nowadays.

The technique consists of drawing some amount of blood from the vein in the elbow fold and injecting this blood in the gluteal muscle, starting with 5 ml and progressively increasing the volume over 20 ml.

Ravaut created and obtained the first results with this process. It is recommended by this author to be used in pruriginous conditions, blistering diseases, urticaria and certain types of acne associated with pruritus.

Autovaccines used to treat some dermatosis are prepared with germs from the intestines (Danysz) or urine (Darier). The most promising results were seen in patients with eczema, psoriasis and urticaria."

Among these desensitization techniques cited by Portugal, peptone therapy was largely employed, but the lack of scientific support led to its discontinuation and disappearance from the medical drug arsenal. Although they have been employed until recently by some allergists as unspecific immunotherapy, autovaccines are not currently used.

The last report of autovaccines or bacterial anatoxins use in dermatology was made by some dermatologists who employed autovaccines or staphylococcal anatoxin to treat furunculosis, a therapy that has been completely abandoned owing to lack of scientific evidence in favor of its utilization. Similarly, the vaccines with iodide extracts for treating strophulus have also been discontinued.

Finally, from the desensitization techniques employed by Ravaut, Hildebrando Portugal mentions in his article the utilization of whole blood (hemotherapy) or only serum (serum therapy), which can be from the individual himself/herself (autoserum therapy or auto-hemotherapy) or from another individual (heterohemotherapy or heterologous serum therapy).

Ravaut used to recommend this type of therapy in pruriginous conditions, blistering diseases, urticaria and certain types of acne associated with pruritus.

Evidently, such therapies were abandoned because of lack of scientifically proven results, development of other therapeutic resources and today they would be unacceptable because of the risk of transmitting serious infections such as acquired immunodeficiency syndrome (AIDS) and hepatitis C.

Nowadays, the only link remaining from these approaches with whole blood or blood products is the use of blood and blood products in several medical conditions and the use of immunoglobulins in specific deficiencies of these proteins or as immunomodulator therapy. Thus, transfusion of red cells is used for correcting acute blood losses or severe chronic anemia with cardiac decompensation. Occasionally, granulocytes can be transfused to neutropenic patients with bacterial or fungal infections and poor response to antibiotics. Platelet transfusion is used in patients with bleeding and thrombocytopenia, for example, patients with acute leukemia

and platelet counts below 20,000/mm^3 for prophylaxis of hemorrhage or also in patients with thrombocytopenia who must undergo surgical treatment.

Plasma and its fractions are also employed. The indication for plasma transfusion is hypovolemic shock due to plasma loss such as in burns or in patients with hemorrhagic diathesis of disseminated intravascular coagulation type, overdose of oral anticoagulants and liver diseases.

The current clinical practice also employs plasma fractions such as cryoprecipitate, concentrates of prothrombin complex and albumin.

The cryoprecipitate that contains factor VIII and fibrinogen is widely used for controlling the hemorrhagic episodes of classical hemophilia.

The cryoprecipitate is also used as a source of fibrinogen in patients with disseminated intravascular coagulation and dysfibrinogenemia.

Concentrates of prothrombin complex contain factors II, VII, IX and X and, in addition to the use in patients with specific deficiencies of these factors, they can be used in patients with hemorrhages caused by overdose of oral anticoagulants and in patients with classical hemophilia with anti-factor VIII antibodies.

Albumin can be used in patients with hypovolemic shock due to burns or hemorrhages or in patients with severe hypoproteinemia.

Other blood products used in the clinical practice are serum immunoglobulins and specific immunoglobulins against several infectious microorganisms and in the prevention of hemolytic diseases in the newborn.

Concerning the use of blood products specifically in dermatology, what we currently find is the use of high doses of Intravenous Immunoglobulins (IVIG) whose indications in dermatology have been growing, including some conditions for which in the past autologous or heterologous hemo/serum therapy were indicated such as blistering diseases and urticaria.

We can consider the attempts for desensitization by hemotherapy or serum therapy as the precursor of the current use of high doses of intravenous immunoglobulins (IVIG), which will be the subject of a brief review.

The first type of immunoglobulin used was obtained from a pool of multiple donors containing 95-99% IgG with specificity for a wide spectrum of antigens and cleared from infectious particles and other serum proteins. Some of these purified preparations contained high molecular weight IgG tending to *in vitro* aggregation; when used intravenously, it was able to activate the complement cascade and produce severe anaphylactic responses, and therefore it was possible to use these preparations only by subcutaneous or intramuscular routes, a condition that made administrations extremely painful.

As of 1981, preparations of immunoglobulins that could be safely used by intravenous route and free of high molecular weight complexes became available in the USA, which are used to present.

Those preparations are obtained from the plasma of 10,000-20,000 donors per batch. The safety of such preparations is guaranteed by the careful selection of donors and tests for hepatitis B surface antigen of each plasma donated, hepatitis C antivirus antibodies, anti-HIV1 and HIV2 antibodies, syphilis test and liver function tests. Additionally, viral inactivation of the material is also carried out.[5] In the 1980's, some patients were infected by the hepatitis C virus, i.e., before the introduction of tests capable of excluding this viral disease. HIV[6] infection has never occurred but it is evident that the possibility of transmission of unidentified pathogens always exists.[6]

The World Health Organization (WHO) criteria for therapy with IVIG include the presence of at least 90% intact IgG in the preparations with normal distribution of IgG subclasses, the minimum possible amount of IgA and the absence of protein fragments and aggregates.[7]

MECHANISMS OF IMMUNOMODULATING ACTION OF IVIG

IVIG immunomodulating action is mediated by the Fc portion of IgG that interacts with Fc receptors and complement or through the antigen binding sites or variable regions of the antibody F(ab')2 molecule.[8] The following immunomodulating mechanisms are considered:

1. Functional blockade of Fc receptors in splenic macrophages. The functional blockade of Fc receptors, especially in splenic macrophages, reduces the clearance of cellular elements coated with autoantibodies such as platelets, red blood cells and neutrophils. Apparently, there is protection of these structures coated with autoantibodies. The saturation of Fc splenic receptors has a critical role in the mechanism of action of IVIG in the treatment of thrombocytopenic purpura and other cytopenias.[9]

2. Inhibition of lesions mediated by complement. The Fc region of IgG binds to the C3b and C4b complement components, preventing the precipitation of C3 activated fragments. This must be one of the mechanisms of action in dermatomyositis.[10,11]

3. Modulation of cytokine production and cytokine antagonists. *In vitro* studies point to the modulating action of IVIG in the production of cytokines by T cells, B cells, monocytes and

macrophages, showing a negative regulation of IL-1, IL-2, IL-3, IL-4, IL-5, IL-10, TNF-alpha and GM-CSF, variable effects in gamma interferon and positive regulation on IL-1 receptor antagonist. The proliferative response of lymphocytes to mitogens is decreased by IVIG.[12]

4. Neutralization of circulating antibodies by anti-idiotypic antibodies. High doses of IVIG contain anti-idiotypic antibodies that bind to circulating antibodies and can neutralize them and even modulate the synthesis of antibodies by means of its bounds with auto-reactive B cells. An example of this action is the disappearance of anti-factor VIII antibodies about 36 hours after infusion of IVIG.[13] This same mechanisms must act on other autoantibodies, anti-DNA, antiintrinsic factor, anti-thyroglobulin and anti-neutrophils cytoplasm.[14] These mechanisms depend on the interaction of the variable regions of immunoglobulins and they also occur with other immunologically important molecules such as CD4, human leukocyte antigen and T cell receptor.[15]

5. Neutralization of pathogens possibly involved in the etiology of autoimmune diseases. The same mechanisms of interaction of the variable immunoglobulin regions can happen with infectious agents or super-antigens involved in autoimmune diseases.[9,15]

ADVERSE EFFECTS OF HIGH DOSES OF INTRAVENOUS IMMUNOGLOBULINS (IVIG)

In general, these side effects are mild and occur 30-60 minutes after the beginning of infusion, and they are characterized by flushing, myalgias, headache, shivering, back pain, nausea and vomiting, blood pressure changes and tachycardia. These reactions supposedly happen due to the presence of aggregates of immunoglobulins and antigen-antibody complexes that activate the complement.[8] They can be controlled through the interruption of the infusion or slower administration of the preparation or, still, through the administration of analgesics, antihistaminic drugs or hydrocortisone, which can be done even before the infusion of immunoglobulin.[7]

Anaphylaxis has rarely been seen and it occurs more frequently with infusions of preparations containing IgA in individuals with IgA deficiency, which is relatively frequent (1:700 individuals in the overall population) who produce anti-IgA antibodies. Current preparations are IgA depleted to prevent this possible reaction.[7,16]

Some cases of hemolysis are caused by the presence of antibodies against ABO and RH systems in the preparations. The risk of this rare complication is lower with administration regimens of 5 days of IVIG and with the control of haptoglobin and hemoglobin throughout the treatment. A decrease of haptoglobin associated with reticulosis indicates the occurrence of hemolysis.[16] Transient neutropenias have also been reported as well as reversible renal failure due to damage to the proximal renal tubules caused by excessive solutes administered during the infusion.[18] Cases of aseptic meningitis are rarely described and there are sporadic reports of dermatological side effects, eczema, alopecia and erythema multiforme.[19-21]

Precautions prior to the administration of IVIG[8]

1. Check liver function tests and analyze complete blood count.

2. Test immunoglobulins to exclude deficiencies of IgA. If there is IgA deficiency, check the presence of anti-IgA antibodies.

3. Test the rheumatoid factor. It high titers are present, the patient must be excluded from the therapy due to the possibility of combining the high titers of rheumatoid factor with Fc fraction of immunoglobulins, which can favor the formation of complexes capable of precipitating in the renal tissues and causing severe renal failure. The same can happen in the presence of cryoglobulinemia, which also has to be ruled out before the therapy is initiated.

4. Preferably, use preparations coming from a single batch to expose the patient to a minimum number of donors.

5. Store serum samples for possible future investigations of infectious agents not known yet.

IVIG costs are high. Considering the replacement therapies for individuals with immunoglobulin deficiencies, a 60-kg patient must receive 2g/kg/month. At the cost of US$25.00/gram, the treatment shall have an annual cost of US$36,000.00.

The current indications of IVIG include replacement therapy for individuals with immunoglobulin deficits and immunomodulation therapies, whose indications have increased, including in dermatologic conditions.

1. Indications for IVIG as replacement therapy:[22]

- Primary deficiency of antibodies
- X chromosome-linked agammaglobulinemia
- Immunodeficiency with X chromosome-linked M hypoimmunoglobulinemia
- Variable common immunodeficiency
- Immunodeficiency of IgG subclasses with infection
- Severe combined immunodeficiency prior to bone marrow transplantation
- Failure of B cells grafting after bone marrow transplantation for severe combined immunodeficiency
- Selected cases of antibodies deficiency secondary to intestinal lymphangiectasia

- Chronic lymphocytic leukemia and B cells lymphopenia as hypogammaglobulinemia
- Myeloma with specific antibodies deficiency
- Low weight newborns with risk of septicemia
- Children with HIV infection

The recommended doses in replacement therapies are between 0.2g/kg/month and 0.8g/kg/month depending on the severity and the patient's susceptibility to infections.

2. Indications of IVIG as immunomodulating therapy[23]

- Autoimmune thrombocytopenic purpura
- Kawasaki's disease
- Guillain-Barré syndrome
- Chronic demyelinating inflammatory neuropathy
- Acquired hemophilia
- Dermatomyositis
- Toxic epidermal necrolysis
- Autoimmune blistering diseases

In those cases, the doses used are higher than the doses used for replacement therapy and in general 2 doses of 1g/kg/day or 5 doses of 0.4g/kg/day for 5 days can be administered.

The use of IVIG in dermatological conditions include indications in which the efficacy is completely established and other indications in which the real effectiveness of this therapy has not been totally demonstrated yet. IVIG therapy has been used in the following dermatological conditions:

- Kawasaki's disease
- Dermatomyositis
- Autoimmune blistering diseases
- Pemphigus vulgaris
- Pemphigus foliaceus
- Bullous pemphigoid
- Mucous membranes pemphigoid
- Acquired epidermolysis bullosa
- Toxic epidermal necrolysis

There are reports of IVIG use in other dermatoses, but the data are still insufficient. These conditions include chronic urticaria, pyoderma gangrenosum, atopic dermatitis, Stevens-Johnson syndrome and necrotizing fasciitis.

Dermatomyositis

It is a dermatological condition in which the use of IVIG has been more widely studied[8,24-26] through case reports, uncontrolled trials and even studies with placebo. The existing experience allows the consideration of IVIG use as an effective treatment of dermatomyositis.

The recommended dose is 2g/kg administered in two days, and afterwards it is repeated on a monthly basis. The dose is individualized after the response is obtained. This therapy must be considered for patients in whom the classical therapies have failed or when side effects have made the treatment unbearable. If no response is obtained after 4 treatment courses with IVIG, the treatment must be discontinued. If there is response to IVIG, conventional treatment regimens must have their doses reduced until disease control can be obtained with minimal doses.

Kawasaki's disease

The use of IVIG in Kawasaki's disease was initiated in 1984 by Furusho[27] et al, and the efficacy of this therapy was confirmed by multicenter randomized trials carried out in the USA in 1986.[28]

The currently recommended dose is 2g/kg infused in 8-12 hours associated with 30-40g/kg aspirin. The administration of a single dose has shown faster response and better prevention of coronary artery damage.[29] For maximum efficacy, IVIG must be started in the first 10 days of the disease. Resistance to this therapy is seen in only 10% of the patients and those are the ones with greater risk for coronary heart disease and, in such cases, corticosteroid pulses may be used.

Toxic epidermal necrolysis (TEN)

There are reports of sporadic cases and case series with good response to IVIG in the treatment of toxic epidermal necrolysis, but the evidence of this therapy in TEN has not been fully established yet. [30-33]

The rationale for the use of IVIG in toxic epidermal necrolysis is the existence of anti-Fas antibodies in these preparations, which are able to block the Fas-FasL binding that determines the apoptosis of keratinocytes.

The recommended dose is 1g/kg/day for 3 consecutive days.

Autoimmune blistering diseases

IVIG has been used in the treatment of pemphigus vulgaris,[34-37] pemphigus foliaceus,[34,38,39] bullous pemphigoid,[34,40,41] pemphigoid of mucous membranes[34,42-44] and in acquired epidermolysis bullosa.[34,45-47] There are studies involving case reports and series of patients showing good results with this therapy; however, additional controlled trials are necessary and in 2003 a consensus[34] regarding the use of IVIG in this disease was published with the following indications:

1. Failure of conventional therapy

Failure of conventional therapy is defined when doses of 1mg/kg/day prednisone for 6 weeks,

associated with the administration of immunosuppressant in appropriate doses for 10-12 weeks, are not capable of controlling the disease.

2. Severe side effects from conventional therapy

Those are side effects that bring a risk to the patient's life or cause significant morbidity that compromises the quality of life. Such conditions occur when the necessary doses for controlling the disease are too high.

3. Relative or absolute contraindications to classical therapy

When it is impossible to use drugs that are part of the classical therapy - corticosteroids and immunosuppressant, due to the presence of other comorbidities.

4. Progressive disease

When the disease progresses and threatens the patient's life or causes severe impairment to quality of life, despite high doses of conventional therapy.

5. Rapidly progressive debilitating disease

In this case, the conventional therapy is not able to prevent the very fast disease progression.

6. Epidermolysis bullosa with generalized lesions of rapid progression

Regarding the patient's age and pregnancy status, they are not contraindications to the use of IVIG.

The recommended dose in autoimmune blistering diseases is 2g/kg per course, with the whole dose being divided into 3 doses administered in 3 consecutive days. Infusions must be carried out every 4.0-4.5 hours.

The recommended frequency is 1 cycle every 3-4 weeks, but in patients with pemphigoid of mucous membranes and severe eye lesions, the infusions can be carried out every 2 weeks. Once the disease is under control, infusions are performed within intervals of 6,8,10,12,14 and even 16 weeks, depending on each patient.

There are also reports of the use of IVIG in necrotizing fasciitis but the efficacy of this treatment is still not established for this disease. The doses used were 2g/kg in 6-12 hours, repeating 1-2g/kg for 2-5 days if the disease continued to progress.

IVIG has also been used for treating pyoderma gangrenosum[48] with 2g/kg in 2 days without proven efficacy.

There are reports of use of IVIG at 2g/kg for 2-3 days to treat autoimmune chronic urticaria[50,51] and delayed pressure urticaria.[51] In such cases, the action of IVIG would occur through anti-IgE anti-idiotypic antibodies or IgE anti-receptor antibodies. Larger trials are necessary to verify the real value of this therapy.

IVIG administration has also been reported in the treatment of atopic dermatitis; however, such reports are scarce and the efficacy of IVIG in this condition has not been established yet.

Therefore, the indications for the use of high dose intravenous immunoglobulins in dermatology are being progressively expanded and they are currently accepted as a proven efficient therapy for dermatomyositis and Kawasaki's disease. It is already accepted as an alternative therapy in autoimmune blistering diseases and in toxic epidermal necrolysis. Its use remains to be established in other conditions such as necrotizing fasciitis, pyoderma gangrenosum, chronic urticaria, atopic dermatitis[49] and Stevens-Johnson syndrome,[33] in which this therapy has been exceptionally employed. ❑

REFERENCES

1. Hildebrando Portugal. A desensibilização na therapeutica dermatologica. Annaes Bras de Dermatologia e Syphilographia. 1925;15-22.
2. Ravaut. Essai sur l'auto-hemotherapie dans quelques dermatoses. Annales de Dermatologie et Syphilographie Maio, 1913.
3. Ravaut. Auto-hemotherapie (Therapeutique et Technique). Presse Medicale. 1920;80.
4. Beutner E, Jordan RE. Demonstration of skin antibodies in sera of Pemphigus Vulgaris patients by indirect immunofluorescent staining. Proc Soc Exp Bio Med. 1964;117:505.
5. Rütter GH. Requirements for safety and quality of intra venous immunoglobulin G preparations. J Neurol Nevrosurg Psichiatry. 1994;57:2-5.
6. Yap PL. The vital safety of intravenous immuneglobulin. Clin Exp Immunol 1996;104(supl 1):35-43.
7. Misbah SA, Chapel HM. Adverse effects of intravenous immunoglobulin. Drug Saf. 1993; 9:254-62.
8. Jolles S, Hughes J, Whittaker S. Dermatological uses of high-dose intravenous immunoglobulin. Arch Dermatol. 1998;134:80-6.
9. Mouthon L, Kaveri SV, Spalter SH, Lacroix-Desmazes S, Lefranc C, Desai R, et al. Mechanisms of action of intravenous immune globulin in immune-mediated diseases. Clin Exp Immunol. 1996;104(Suppl 1):3-9. Review.
10. Basta M, Dalakas MC. High-dose intravenous immunoglobulin exerts: its beneficial effect in patients with dermatomyositis by blocking endomysial deposition of activated complement fragments. J Clin Invest. 1994; 54:1729-35.
11. Basta M. Modulation of complement-mediated immunodamage by intravenous immuneglobulin. Clin Exp Immunol. 1996;104:21-6.
12. Anderson J, Skansen-Saphir U, Sparrelid E, Anderson U. Intravenous immuneglobulin affects cytokine production in T lymphocytes and monocytes/macrophages. Clin Exp Immunol. 1996;104:10-21.
13. Sulton Y, Kazatchkine MD, Maisonneuve P, Nydegger UE. Anti-idyotipic supression of autoantibodies to factor VIII (antihemophilic factor) by high-dose intravenous gammaglobulin. Lancet. 1984;2:765-8.
14. Dweyer JM. Manipulating the immune system with immuneglobulin. N Engl J Med. 1992;326:107-16.
15. Hurez V, Kaveri SV, Mouhoub A, Dietrich G, Mani JC, Klatzmann D, et al. Anti-CD4 activity of normal human immunoglobulin G for therapeutic use. (Intravenous immunoglobulin, IVIg). Ther Immunol. 1994;1:269-77.
16. Duhem C, Dicato MA, Ries F. Side effects of intravenous immuneglobulins. Clin Exp Immunol. 1994;97(suppl1): 79-83.
17. Ben-Chekrit E, Putterman C. Transient neutropenia induced by intravenous immuneglobulin. N Engl J Med. 1992; 326:270-1.
18. Tan E, Hajinazarian M, Bay W, Neff J, Mendell JR. Acute renal failure resulting from intravenous immunoglobulin therapy. Arch Neurol. 1993; 50:137-9.
19. Barucha C, McMillan JC. Eczema after intravenous infusion of immunoglobulin. B M J. 1987;295:1141.
20. Chan-Lam D, Fitzsimons EJ, Douglas WS. Alopecia after immunoglobulin infusion. Lancet. 1987;1:1436.
21. Roveghiero F, Castaman G, Vespignani M, Dimi E, Bertazzoni M. Erythema multiforme after intravenous immunoglobulin. Blut. 1988;56:145.
22. Sworos S, Laver SJ, Nopper AJ. Gammaglobulins. 3rd ed. In: Schachner L, Hansen R, editors. Pediatric Dermatology. Hardbound: Elsevier; 2003. p. 124-6.
23. Rutter A, Luger TA. Intravenous immunoglobulin: an emerging treatment for immune-mediated skin diseases. Curr Opin Invest Drugs. 2002; 3:713-9.
24. Cherin P, Piette JC, Wechsler B, Bletry O, Ziza JM, Laraki R, et al. Intravenous gamma globulin as first line therapy in polymyositis and dermatomyositis: an open study in 11 adult patients. J Rheumatol. 1994;21:1092-7.
25. Collet E, Dalac S, Maerensd B, Coutois JM, Izac M, Lambert D. Juvenile dermatomyositis: treatment with intravenous gammaglobulin. Br J Dermat. 1994; 130:231-4.
26. Sansome A, Dubowitz V. Intravenous immunoglobulin in juvenile dermatomyositis: four years review of nine cases. Arch Dis Child. 1995;72:25-8.
27. Furusho K, Kamiya T, Nakano H, Kiyosawa N, Shinomiya K, Hayashidera T, et al. High dose intravenous gamma-globulin for Kawasaki disease. Lancet. 1984;2:1055-8.
28. Newburger JW, Takahashi M, Burns JC, Beiser AS, Chung KJ, Duffy CE, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med. 1986;315:341-7.
29. Newburger JW, Takahashi M, Beiser AS, Burns JC, Bastian J, Chung KJ, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med. 1991;324:1633-9.
30. Prins C, Kerdel FA, Padilla RS, Hunziker T, Chimenti S, Viard I, et al. Treatment of toxic epidermal necrolysis with high-dose intravenous immunoglobulin. Arch Dermatol. 2003;139:26-32.
31. Lisboa MS, Gonçalves E, Conceição F, Leal V, Mesquita Guimarães J. A case of toxic epidermal necrolysis treated with intravenous immunoglobulin. Br J Dermatol. 2000; 142:191-2.
32. Bachut N, Revuz J, Roujean JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and Toxic Epidermal Necrolysis. A prospective noncomparative study showing no benefit on mortality as progression. Arch Dermatol. 2003;139:33-6.
33. Sten RS. Improving the outcome of patients with toxic epidermal necrolysis and Stevens-Johnson syndrome. Arch Dermatol. 2000;136:1410-1.
34. Ahmed AR, Dahl MV. Consensus statement on the u s e

of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. Arch Dermatol. 2003;139:1051-9.
35. Jolles S, Huges J, Rustin M. Therapeutic failure of high-dose intravenous immunoglobulin in pemphigus vulgaris. J Am Acad Dermatol. 1999;40:499-500.
36. Harman KE, Black MM. High-dose intravenous immunoglobulin for the treatment of autoimmune blistering diseases: an evaluation of its use in 14 cases. Br J Dermatol. 1999;140:865-74.
37. Sami N, Oureshi A, Ruono E, Ahmend AR. Corticosteroid-sparing effect of intravenous immunoglobulin therapy in patients with pemphigus vulgaris. Corticosteroid-sparing effect of intravenous immunoglobulin therapy in patients with pemphigus vulgaris. Arch Dermatol. 2002;138:1158-62.
38. Ahmed AR, Sami N. Intravenous immunoglobulin therapy for patients with pemphigus foliaceus unresponsive to conventional therapy. J Am Acad Dermatol. 2002;46:42-9.
39. Sami N, Bhol K, Ahmed AR. Diagnostic features of pemphigus vulgaris in patients with pemphigus foliaceus: detection of both autoantibodies, long term follow-up and treatment response. Clin Exp Immunol. 2001; 125:492-8.
40. Dall M, Bridges AG. Intravenous immunoglobulin: fighting antibodies with antibodies. J Am Acad Dermatol. 2001;45:775-83.
41. Ahmed AR. Intravenous immunoglobulin therapy for patients with bullous pemphigoid unresponsive to conventional immunosupressive treatment. J Am Acad Dermatol. 2001;45:825-35.
42. Foster CS, Ahmed AR. Intravenous immunoglobulin therapy for ocular cicatricial pemphigoid: a preliminary study. Ophtalmology. 1999;106:2136-43.
43. Sami N, Bhol KC, Ahmed AR. Treatment of oral pemphigoid with intravenous immunoglobulin as monotherapy long term follow-up: influence of treatment on autoantibodies titers to human alpha G integrin. Clin Exp Immunol. 2002;129:533-40.
44. Sami N, Bhol KC, Ahmed AR. Intravenous immunoglobulin therapy in patients with multiple mucosal involvement in mucous membrane pemphigoid. Clin Immunol. 2002;102:59-67.
45. Gourgiotou K, Exadaktylou D, Aroni K, Rallis E, Nicolaidou E, Paraskevakou H, et al. Epydermolysis bullosa acquisita: treatment with intravenous immunoglobulin. J Eur Acad Dermatol Venereol. 2002;16:77-80.
46. Engineer L, Ahmed AR. Epydermolysis bullosa acquisita and multiple myeloma. J Am Acad Dermatol. 2001; 47:943-6.
47. Harman KE, Whitman LR, Wakeling SH, Black MM. Severe refunctory epidermolysis bullosa complicated by a aesophageal stricture responding to intravenous immunoglobulin. Br J Dermatol. 1998;139:1126-7.
48. Hagman JH, Carrozzo AM, Campione E, Romanelli P, Chimenti S. The use of high-dose immunoglobulin in the treatment of pyoderma gangrenosus. J Dermatolog Treat. 2001;12:19-22.
49. Paul C, Lahfa M, Bachelez H, Chevret S, Dubertret L. A randomized controlled evaluator-blinded trial of intra venous immunoglobulin in adults with severe atopic dermatitis. Br J Dermatol. 2002;147:518-22.
50. Kroiss M, Vogt T, Landthaler M, et al. The efectivesness of low-dose intravenous immunoglobulin in chronic urticaria. Acta Derm Venereol. 2000; 80:225.
51. Donnel BF, Barr RM, Black AK, Francis DM, Kermani F, Niimi N, et al. Intravenous immunoglobulin in autoimmune chronic urticaria. Br J Dermatol. 1999;138:101-6.
52. Dawn G, Urcelay M, Ah-Weng A, O'Neill SM, Douglas WS. Effect of high-dose intravenous immunoglobulin in delayed pressure urticaria. Br J Dermatol. 2003;149:836-40.

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