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TERAPÊUTICAS ADJUVANTES NA INFECÇÃO QUAIS E QUANDO?



Filipa Prata

19º Congresso
Nacional
de Pediatria

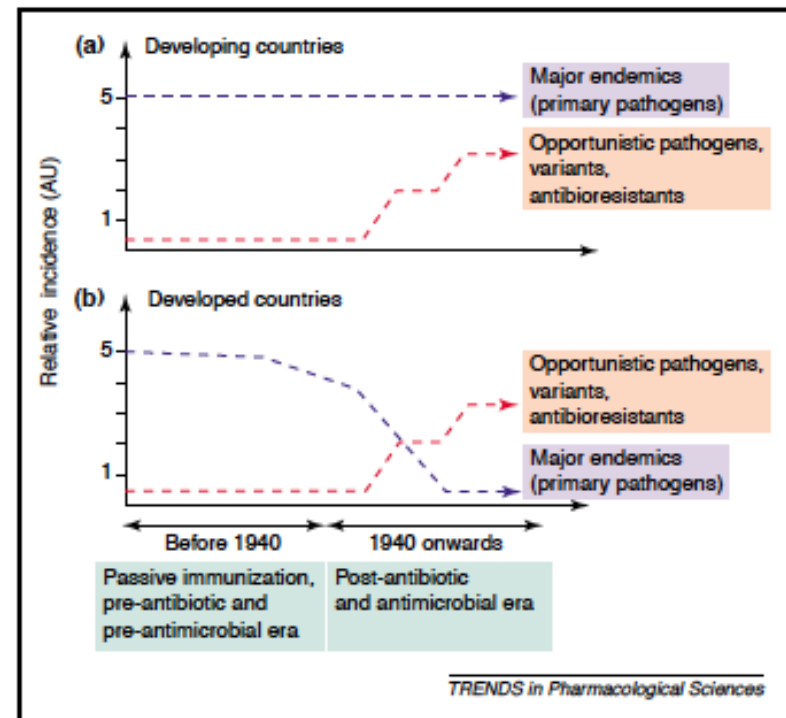


26-26 out 2018
Centro de Congressos do Estoril

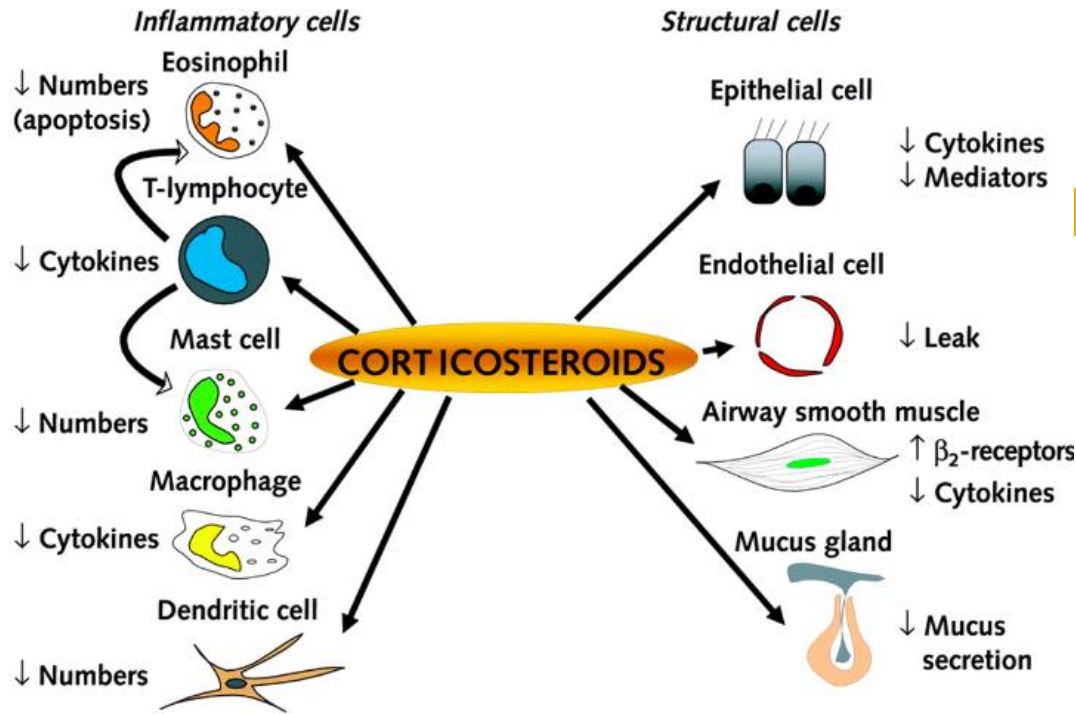
TERAPÊUTICAS ADJUVANTES NA INFECÇÃO

The dramatic increase in both the number of novel infectious agents and resistance to antimicrobial drugs has incited the need for adjunct therapies in the war against infectious diseases. Exciting recent studies

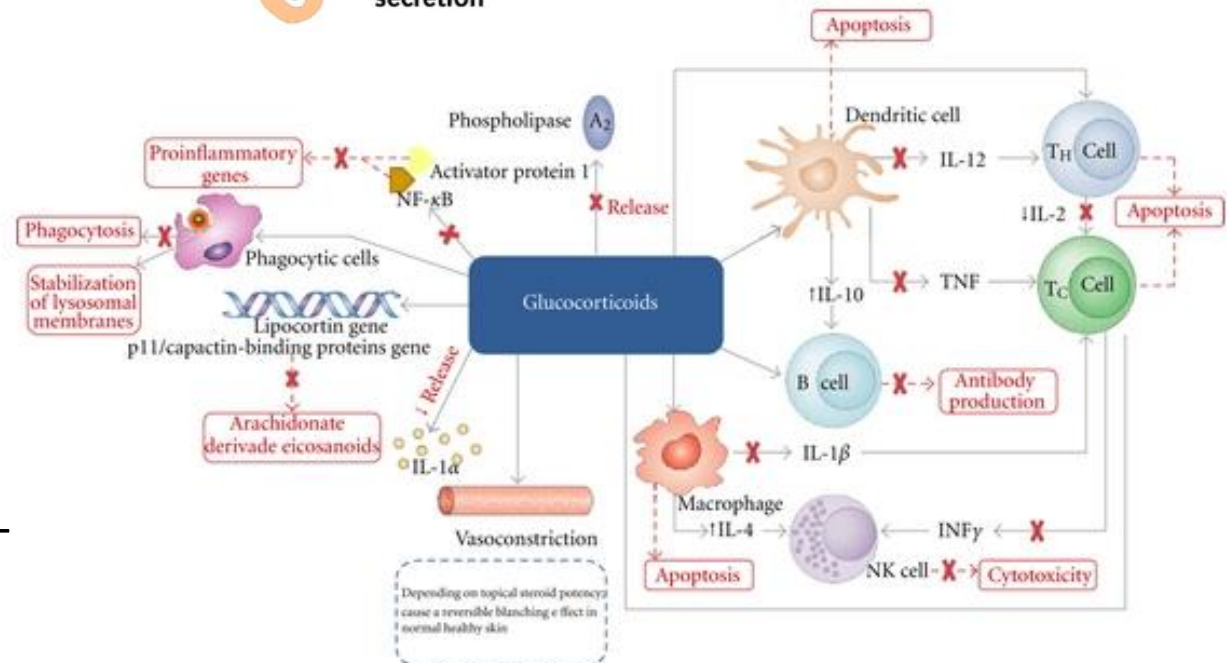
- Corticóides
- Gamaglobulina
- Rituximab



Corticóides



Propriedades
imunossupressoras e anti-
inflamatórias



CORTICÓIDES NAS INFEÇÕES

- **Consensual:**

- ✧ Meningite por Hib
- ✧ Tuberculose
- ✧ Choque séptico refractário
- ✧ Pneumonia *P. jirovecii*

- **Outros:** Artrite séptica

Febre tifóide grave

Celulite orbitária complicada ???

- São necessários mais **ensaios clínicos aleatorizados** pediátricos para confirmar a sua eficácia (definir tipo, dose, início e duração)

CORTICÓIDES NA MENINGITE BACTERIANA AGUDA

Rápida proliferação bacteriana LCR (ausência de anticorpos e complemento)
+ resposta imune hospedeiro



Inflamação importante do espaço subaracnoideu com graves consequências em termos de morbilidade e mortalidade

Antibióticos esterilizam LCR

Corticóides adjuvantes – alteram o processo agudo inflamatório

- Propriedades anti-inflamatórias e imunossupressoras
- Limitam produção dos mediadores inflamação (IL-1, IL-6, TNF)
- Limitam a produção de exsudado, reduzindo o edema e a PIC
- Melhoram a circulação do LCR e estabilizam a BHE

CORTICÓIDES NA MENINGITE BACTERIANA AGUDA

Utilização aprovada e recomendada

Meningite por *Haemophilus influenzae* tipo b (Hib)

Maioria estudos efectuados na era pré vacina Hib - principal causa de meningite

Redução do défice auditivo

Sem redução da mortalidade ou outros défices neurológicos

Em países desenvolvidos

2015 meta-análise, 18 ensaios (2511 crianças): redução da perda auditiva grave (Hib), em países desenvolvidos, sem redução da mortalidade ou outros défices neurológicos

[Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev 2015; :CD004405.](#)

Estudo retrospectivo 27 hospitais EUA (2780 crianças, 2001-2006): sem redução da mortalidade

[Mongelluzzo J, Mohamad Z, Ten Have TR, Shah SS. Corticosteroids and mortality in children with bacterial meningitis. JAMA 2008; 299:2048.](#)

CORTICÓIDES NA MENINGITE BACTERIANA AGUDA

DEXAMETASONA

- Melhor penetração na BHE, baixa atividade mineralocorticoide
- Administrar antes ou em simultâneo com a 1ª toma de AB
- 0,15 mg/kg/dose ev, 6/6 horas durante 2 a 4 dias
- Esquema 2 dias eficácia $\approx$ 4 dias, menor risco de toxicidade
- Efeitos adversos: Hemorragia GI (1 a 2%), recorrência da febre (após 24 de apirexia) após descontinuação, atrasar esterilização do LCR (+meningite pneumocócica), mascarar a clínica dando uma falsa sensação de melhoria

CORTICÓIDES NA MENINGITE BACTERIANA AGUDA

Controverso

- **Meningite por *Streptococcus pneumoniae***

Poucos casos para ensaios alargados com significado estatístico

Dexametasona – redução permeabilidade da BHE – risco de menor passagem de vancomicina para o LCR (atraso na esterilização?)

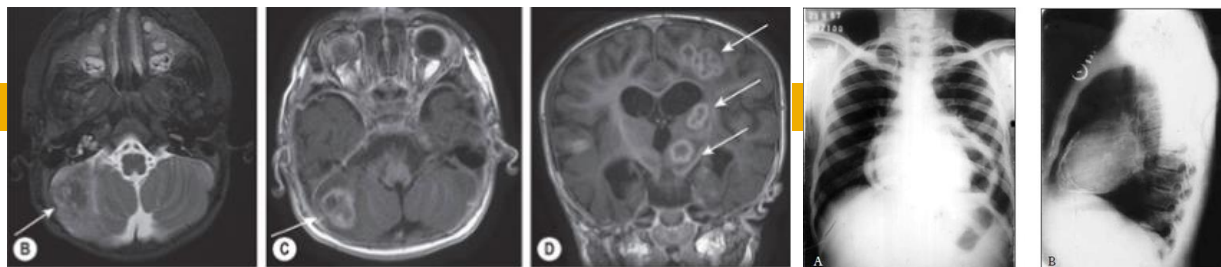
A penetração da Rifampicina e do ceftriaxone não é afectada

Não recomendada

- **Meningite por *Neisseria meningitidis*, ou por gram-**

CORTICÓIDES NA INFEÇÃO POR *M. tuberculosis*

Utilização consensual



- **Meningite:** ↓ inflamação causada Mt e pela ação dos antibióticos
↓ Mortalidade, sequelas, tuberculomas e hepatite iatrogénica
sem efeito resolução hidrocefalia, hemiparesia, coma, tempo hospitalização
Riscos: imunossupressão, ↓ inflamação meníngea, interação R
- **Pericardite:** ↓ Inflamação pericárdio, derrame, fibrose, P. adesiva e constrictiva
↓ mortalidade, ↓ nº de pericardiocenteses e/ou pericardiectomia
- Tuberculose miliar
- Granuloma endobrônquico

Sem resultados conclusivos

- Derrame pleural
- Doentes VIH

CORTICÓIDES NA SÉPSIS E CHOQUE SÉPTICO

- Utilização controversa desde os anos 50
- Poucos ensaios clínicos aleatorizados
- Na maioria dos estudos não houve diferença entre os 2 grupos
 - Mortalidade
 - Dias de administração de inotrópicos, duração ventilação mecânica
 - Tempo de resolução da falência orgânica
 - Duração do internamento em Cuidados Intensivos
- **Hidrocortisona** – maior experiência em ensaios
 - substitui directamente o cortisol
 - actv. mineralocorticóide e vasopressora
 - Tx *life-saving* – insuf. SR na sépsis grave
 - perfusão 50 mg/m²/24h

CORTICÓIDES NA SÉPSIS E CHOQUE SÉPTICO

Consensual a administração de corticóides:

- **Choque séptico refratário** – Falência orgânica por hipotensão refractária à terapêutica com aminas vasopressoras mantida após adequada administração de fluidos e/ou hipoglicemia
➡ **falência da SR** (avaliar nível cortisol sérico antes da adm?)
- **Choque séptico em doentes com risco de Insuficiência da SR**
 - Terapêutica crónica com corticóides
 - Alterações do eixo hipotálamo-hipófise-SR
 - Hiperplasia congénita da SR

ARTRITE SÉPTICA

TABLE 4 Clinical and Laboratory Parameters of Improvement in Children With Septic Arthritis Treated With Antibiotics Alone or With Dexamethasone

Parameter	Antibiotics, Mean (95% CI)	Antibiotics and Dexamethasone, Mean (95% CI)	<i>P</i> ^a
First day fever <38°C	3.9 (2.9–4.9)	2.3 (2.1–2.5)	.002
First day CRP <1 mg/dL	8.4 (6.9–9.9)	5.3 (4.0–6.6)	.002
Hospital stay, d	10.7 (9.4–12.1)	8.0 (6.8–9.2)	.004
Duration intravenous treatment, d	11.4 (9.7–13.1)	7.1 (5.9–8.3)	<.001
Time to full recovery, d	10.0 (8.5–11.6)	6.3 (4.9–7.7)	<.001

Dexametasona 0,2 mg/kg,3xd, 4 dias, EV

- Reduz níveis de cel. T e macrófagos intrasinovial, produção de citocinas e metaloproteinases, produção de elastase e collagenase e inibe fosfolipase A2
- Melhoria clínica (febre, dor, limitação movimento) e laboratorial mais rápida
- Redução tempo de hospitalização
- **Redução da disfunção articular no final da terapêutica, 6 e 12 meses depois e das sequelas**

Recorrência sintomas durante hospitalização após 4 dias de corticoide

Duração total de antibioticoterapia semelhante ambos grupos (3 a 4 semanas)

FEBRE TIFÓIDE

Reduction of mortality in chloramphenicol-treated severe typhoid fever by high-dose dexametasone. Hoffman SL, et al. N Engl J Med. 1984; 310(2):82.

Febre tifoide grave: febre, diarreia, alterações SNC (obnubilação, delírio, estupor, coma) e choque, diagnóstico confirmado, todos medicados com cloranfenicol

Mortalidade 10% grupo Dexametasona vs 55,6% grupo placebo

High-dose intravenous dexamethasone in the management of diarrheal patients with enteric fever and encephalopathy. Southeast Asian J Trop Med Public Health 2009

3/3 doentes não medicados com Dexametasona faleceram mortalidade 100% 20/20 doentes medicados com Dexametasona sobreviveram

Mecanismo de acção dexametasona na encefalopatia não está completamente esclarecido – utilização não consensual mas recomendada pela OMS e vários grupos de peritos na Febre Tifóide complicada (encefalopatia e choque)

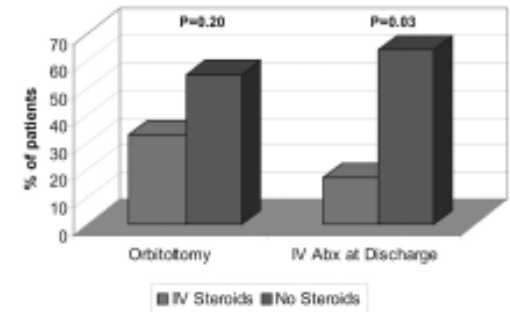
CELULITE DA ÓRBITA E ABCESSO SUBPERIÓSTEO

Effect of Corticosteroids in the Acute Management of Pediatric Orbital Cellulitis With Subperiosteal Abscess

Michael T. Yen, M.D.*, and Kimberly G. Yen, M.D.*†

Ophthalmic Plastic and Reconstructive Surgery
Vol. 21, No. 5, pp 363–367

- Sem diferenças nos dias de internamento
- Diminuição sem significado estatístico na necessidade de drenagem cirúrgica ou tempo de antibiótico ev



Management of orbital cellulitis and subperiosteal orbital abscess in pediatric patients: A ten-year review

V. Sciarretta et al / International Journal of Pediatric Otorhinolaryngology 96 (2017) 72–76

Conclusions: The use of intravenous corticosteroids does not appear to adversely affect clinical outcomes and may be beneficial in the treatment of pediatric orbital cellulitis with subperiosteal abscess. Review of our data suggests that a prospective, randomized trial is warranted to further clarify the role of corticosteroids in the acute management of pediatric orbital cellulitis with subperiosteal abscess.

Pneumonia adquirida na Comunidade (PAC)

Authors' conclusions:

Corticosteroid therapy reduced mortality and morbidity in adults with severe CAP; the number needed to treat for an additional beneficial outcome was 18 patients (95% CI 12 to 49) to prevent one death.

Corticosteroid therapy reduced morbidity, but not mortality, for adults and children with non-severe CAP. Corticosteroid therapy was associated with more adverse events, especially hyperglycaemia, but the harms did not seem to outweigh the benefits.

People with CAP treated with corticosteroids had lower clinical failure rates (death, worsening of imaging studies, or no clinical improvement), shorter time to cure, a shorter hospital stay, and fewer complications. We found good-quality evidence that corticosteroids reduced clinical failure rates in children with pneumonia, but the data were based on a small number of children with different types of pneumonia.

Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M.

Corticosteroids for pneumonia.

Cochrane Database of Systematic Reviews 2017, Issue 12. Art. No.: CD007720.

DOI: 10.1002/14651858.CD007720.pub3.



Cochrane
Library

Cochrane Database of Systematic Reviews

Hepatosplenic cat scratch disease treated with corticosteroids

K Bryant and G S Marshall

Arch Dis Child 2003 88: 345-346
doi: 10.1136/adc.88.4.345

A 3 year old girl with hepatosplenic cat scratch disease developed prolonged fever unresponsive to treatment with multiple antibiotics, including gentamicin, azithromycin, rifampin, and ciprofloxacin. Fever resolved with corticosteroid treatment.

suggests that prednisone may be useful as adjunctive therapy for hepatosplenic CSD in children with symptoms unresponsive to antibiotics.

ADJUNCTIVE CORTICOSTEROIDS FOR LYME NEUROBORRELIOSIS WITH PERIPHERAL FACIAL PALSY TREATED WITH ORAL DOXYCYCLINE

Daniel Bremell and Lars Hagberg
Department of Infectious Diseases, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Sweden

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27th **ECCMID** Vienna, Austria
22 – 25 April 2017

Conclusions

Patients with peripheral facial palsy caused by Lyme neuroborreliosis that were treated with corticosteroids in addition to standard antibiotic treatment with oral doxycycline showed a high degree of complete recovery, although not significantly higher than controls only treated with antibiotics. The addition of corticosteroids did not lead to impaired clearance of the infection as measured by decline in CSF mononuclear cell count. Further studies are needed to establish the role of adjunctive corticosteroids in the treatment of LNB.

CORTICOTERAPIA NAS INFEÇÕES VIRAIS

■ Infecção por EBV

Aciclovir + prednisolona (n=94)

↓ eliminação viral

= duração sintomas (odinofagia, adenopatias, astenia)

= regresso a escola/trabalho

J Infect Dis 1996; 174:324-

■ Infecção por EBV Grave

- risco de obstrução da via aérea
- púrpura trombocitopénica, anemia hemolítica
- miocardite, falência hepática, esplenomegalia grave ??

Prednisolona 1mg/kg/dia (max. 20mg), 7 dias, desmame posterior

Infecção complicada por **HLH** (EBV, CMV, Herpes vírus...)

Dexametasona, esquema HLH-2004, 10-1,25mg/m²/dia, 8 sem*

CORTICOTERAPIA NAS INFEÇÕES VIRAIS

Laringite e laringotraqueíte viral

Evidência variável: usar no risco de obstrução da via aérea

Redução da hospitalização, novas consultas de urgência, necessidade entubação

Dexametasona oral (ou IM) (0,15-0,6mg/kg), budesonide neb. (2mg)

Infecção por Herpes Zoster – início precoce associado a aciclovir

- redução da dor aguda, sem efeito na nevralgia pós herpética
- redução do uso de analgésicos
- melhoria do sono
- cicatrização mais rápida das lesões
- retorno mais rápido às atividades diárias

CORTICOTERAPIA NA PNEUMONIA *P. jirovecii*

- **Pneumonia** hipoxemiante **por *Pneumocystis jirovecii*** moderada a grave em doentes VIH+ → Corticóides 10 a 21 dias
 - Acelera resolução da febre, taquipneia e dispneia. Diminuição do risco de ins. respiratória e de morte
 - Efeito 2^{rio} – aumento de lesões herpéticas localizadas, Candidíase oral?
 - VIH negativos? ATS recomenda utilização = VIH+

Treatment Guidelines for Neurocysticercosis

Modified from Garcia HH, Del Brutto OH. Neurocysticercosis: updated concepts about an old disease. Lancet Neurol 2005;4:653–661.

Tratamento na NCC

sintomática não é sempre
linear e depende:

Localização, número e tipo
de quistos (fase)

Prednisona 1 mg/kg/d

Dexametasona 0,1mg/kg/d



↑ Resolução lesão
↓ Risco convulsão

Target	Treatment
PARENCHYMAL NEUROCYSTICERCOSIS	
Vesicular Cysts	
Single	Albendazole 15 mg/kg/day (maximum dose: 800 mg) in 2 divided doses for 10–14 days with simultaneous use of <u>corticosteroid</u> <i>or</i> Praziquantel 75 mg/kg in 3 divided doses is an alternative to albendazole
Moderate infections	Albendazole 15 mg/kg/day in 2 divided doses for 10–14 days ^a with simultaneous use of <u>corticosteroid</u>
Heavy infections (≥100 cysts)	Albendazole 15 mg/kg/day in 2 divided doses for 10–14 days ^a with simultaneous high doses of <u>corticosteroid</u>
Degenerating (Colloidal) Cysts	
Single lesions	Albendazole 15 mg/kg/day in 2 divided doses for 10–14 days ^a with simultaneous use of <u>corticosteroid</u> or no antiparasitic treatment
Moderate infections	Albendazole 15 mg/kg/day in 2 divided doses for 10–14 days ^a with simultaneous use of <u>corticosteroid</u>
Heavy infections (encephalitis)	High doses of corticosteroid; antiparasitic treatment not indicated

Table 5. Effects of Corticosteroids in Infections: 5 Groups

Group	Diseases
1: Treatment effective, improves survival	Bacterial meningitis Tuberculous meningitis Tuberculous pericarditis Severe typhoid fever Tetanus PCP, moderate or severe Bacterial arthritis
2: Treatment effective, provides long-term benefits	
3: Treatment effective, improves symptoms	Herpes zoster Infectious mononucleosis Acute laryngotracheobronchitis (croup) Pneumococcal pneumonia (not treated in ICU) Pharyngitis Peritonsillar abscess Cellulitis Chronic middle ear effusion Cerebral cysticercosis (single lesion) Pulmonary tuberculosis Lymph node-bronchial tuberculosis Pleural tuberculosis
4: Treatment ineffective or uncertain	Acute bronchiolitis (RSV) Viral hemorrhagic fever Pertussis Severe community-acquired pneumonia (treated in ICU)
5: Treatment harmful	Viral hepatitis Cerebral malaria

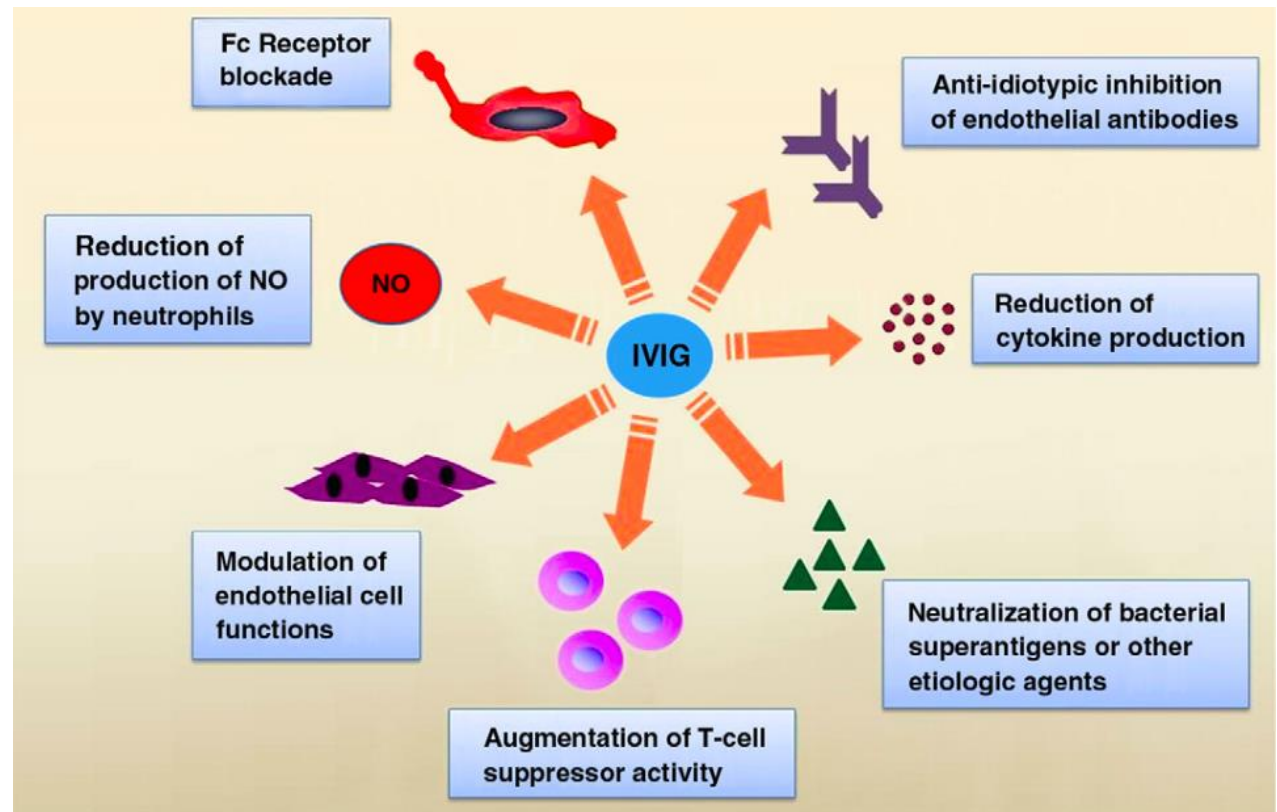
Abbreviations: ICU, intensive care unit; PCP, pneumocystis pneumonia; RSV, respiratory syncytial virus.

GAMAGLOBULINA

against infectious diseases. Exciting recent studies have demonstrated the use of antibodies in the form of intravenous immunoglobulin (IVIg) against infections. By virtue of the diverse repertoire of immunoglobulins that possess a wide spectrum of antibacterial and antiviral specificities, IVIg provides antimicrobial efficacy independently of pathogen resistance and represents a promising alternative strategy for the treatment of diseases for which a specific therapy is not yet available.

ACÇÃO DA GAMAGLOBULINA

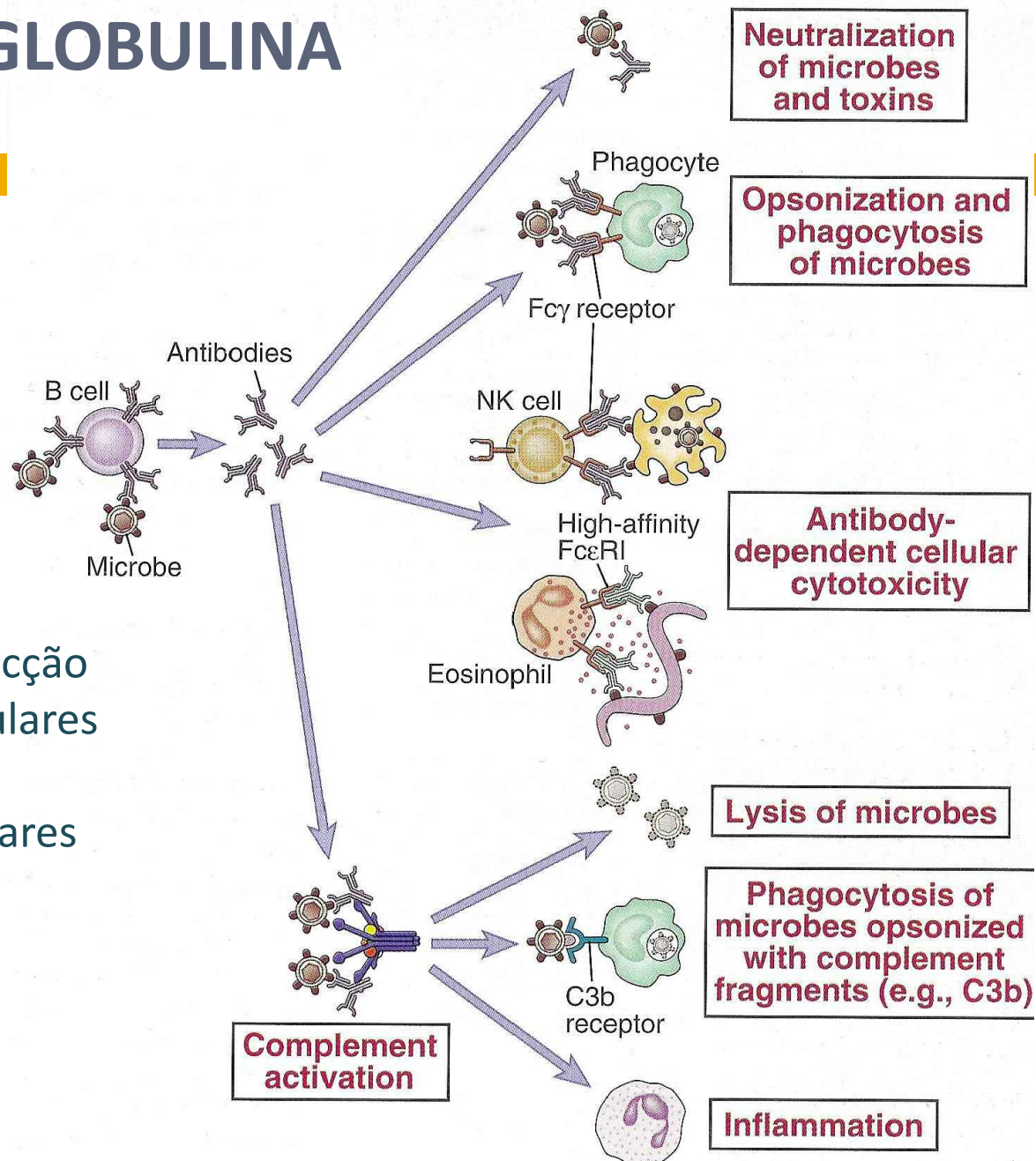
Acção anti-inflamatória e imunomoduladora



ACÇÃO DA GAMAGLOBULINA

Anticorpos específicos

- **previnem** ou reduzem a infecção por agentes extra e intracelulares
- eliminam agentes extracelulares



Currently available IgG commercial preparations

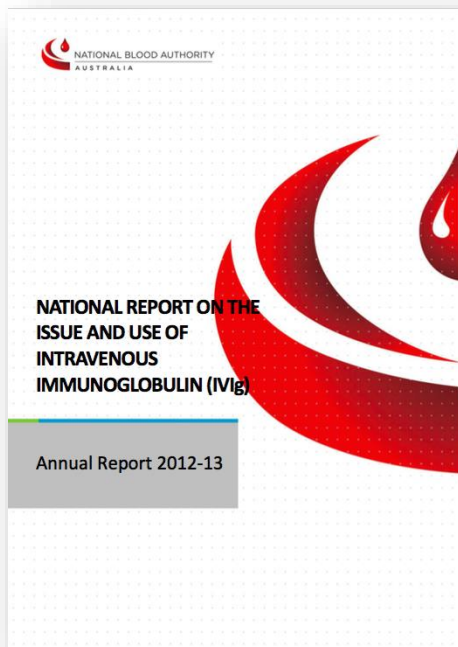
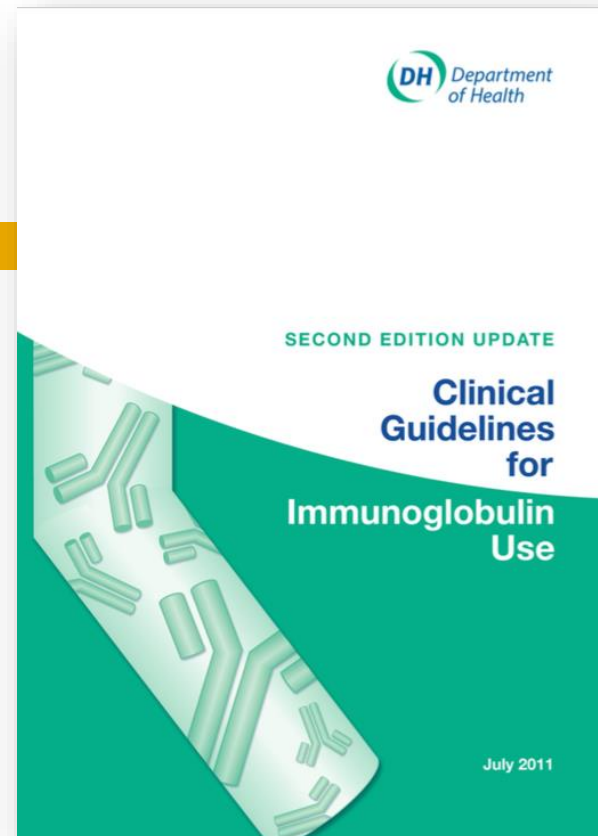
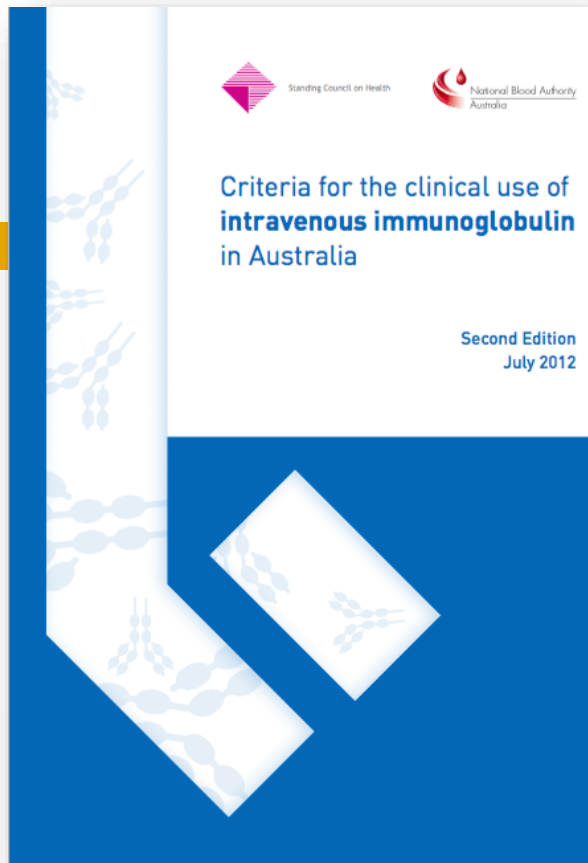
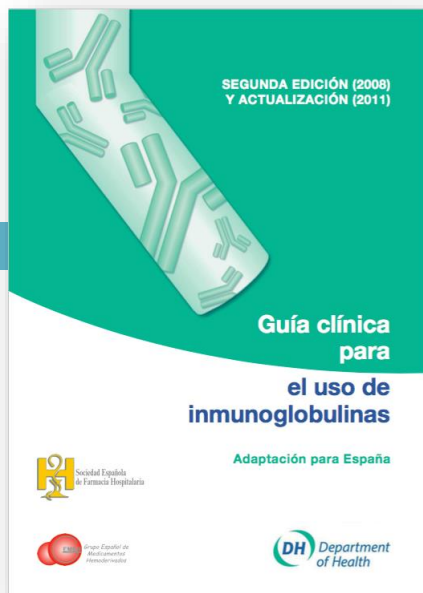
Composed of >95 % IgG monomers plus 1-2 % dimers;
small amounts of IgM, IgA,
other plasma proteins that vary across products

One gram of IGIV contains 4×10^{18} molecules of antibody
with specificities against a broad range of
bacterial and viral pathogens.

These preparations are stabilized with sugars
or amino acids; this varies across products

Methods for viral removal / inactivation from IgG

- Fractioning -polyethylene glycol
- Low pH
- Enzymes
- Ultrafiltration
- Ion exchange chromatography
- Solvent/detergent
- Pasteurisation
- Nanofiltration
- Capriate



Patologias para as quais o uso de IGIV:

- É recomendado (evidência aceitável)
- Aceite em circunstâncias específicas (evidência limitada)
- Não está recomendado

INDICAÇÕES PARA GAMAGLOBULINA

Red High priority

Conditions	Short term	Long term
Alloimmune Thrombocytopenia (Foeto - Maternal/Neonatal)		
Chronic inflammatory demyelinating polyradiculoneuropathy		
Gullian-Barre Syndrome		
Haemolytic disease for the newborn		
HSCT in primary immunodeficiencies		
Immune thrombocytopenic purpura (acute and persistent, excluding chronic*)		
Kawasaki disease		
Paraprotein - associated demyelinating neuropathy (IgM, IgG or IgA)		
Primary immunodeficiencies		
Specific antibody deficiency		
Thymoma with immunodeficiency		
Toxic epidermal necrolysis, stevens Johnson syndrome		

*Updated February 2016

Blue Medium priority

Conditions	Short term	Long term
Acquired red cell aplasia		
Autoimmune congenital heart block		
Autoimmune haemolytic anaemia		
Autoimmune uveitis		
Coagulation factor inhibitors (allon antibodies and autoantibodies)		
Haemophagocytic syndrome		
Immunobullous disease		
Inflammatory myopathies		
Multifocal motor neuropathy		
Myasthenia gravis (including Lambert - Eaton myasthenic syndrome)		
Necrotising (PVL - associated) staphylococcal sepsis		
Post - transfusion purpura		
Rasmussen syndrome		
Secondary antibody deficiency (any cause)		
Severe or recurrent clostridium difficile colitis		
Staphylococcal/Streptococcal toxic shock syndrome		
Stiff person syndrome		
Transplantation (solid organ)		

Grey Low Priority

Conditions	
Immune-mediated disorders with limited evidence of immunoglobulin efficiency	Presumed immune-mediated disorders with little or no evidence of efficiency
Acute disseminated encephalomyelitis (If high dose steroids have failed)	Acquired red cell aplasia not due to parvovirus B19
Autoimmune encephalitis (including NMDA and VGKC antibodies, among others)	Acute idiopathic dysautonomia
Catastrophic antiphospholipid syndrome	
Cerebral infection with antiphospholipid antibodies	Aplastic anaemia/pancytopenia
Chronic ITP	Atopic dermatitis/eczema
CNS Vasculitis	Autoimmune neutropenia
Complex regional pain syndrome	Chronic facial pain
Neuromyotonia	Diabetic proximal neuropathy
Intractable childhood epilepsy	Haemolytic uraemic syndrome
Opsoclonus Myoclonus	PANDAS
Post exposure prophylaxis for viral or pathogenic infection if intramuscular infections is contraindicated, or treatment when hyper-immune	Paraneoplastic disorders that are known not to be B- or T-cell mediated
Immunoglobulins are unavailable	POEMS
Pyoderma gangrenosum	SLE without secondary immunocytopenias (including juvenile)
Systemic juvenile idiopathic arthritis	
Systemic vasculitides and ANCA disorders	
Urticaria (Severe, intractable)	

Black

Conditions
Immunodeficiency secondary to paediatric HIV infection
Autologous BMT
Adrenoleukodystrophy
Alzheimer's disease
Amyotrophic lateral sclerosis
Critical illness neuropathy
Multiple sclerosis
Rheumatoid arthritis
Neonatal sepsis (prevention or treatment)
Sepsis in the intensive care unit not related to specific toxins or C. difficile
Asthma
Graves ophthalmopathy IVF failure
Recurrent spontaneous pregnancy loss

INDICAÇÕES PARA UTILIZAÇÃO GAMAGLOBULINA, RESULTADOS E DOSES

Acquired red cell aplasia	2 g/kg in two to five divided doses; repeated on relapse and for a second relapse.	Parvovírus (PCR+) Falência de corticóide e outros imunossupressores
Necrotising (PVL-associated) staphylococcal sepsis	2g/kg as a single dose	Sind. Choque Tóxico grave Sem resposta rápida a ABs e Tx de suporte  Redução parâmetros falência órgão,  tempo internamento e mortalidade
Severe or recurrent <i>Clostridium difficile</i> colitis	0.4 g/kg, one dose, and consider repeating	Dç grave com colite fulminante Refractária a Vancomicina oral +/- metronidazol ev +/- rifampicina oral Dç recorrente (associada a malnutrição)  diminuição tempo internamento, eliminação <i>C. difficile</i>

INDICAÇÕES PARA UTILIZAÇÃO GAMAGLOBULINA, RESULTADOS E DOSES

Staphylococcal or streptococcal toxic shock syndrome	2 g/kg as a single dose	Sind. Choque Tóxico grave (isolamento agente) Sem resposta rápida a ABs e Tx de suporte ↓ Redução parâmetros falência órgão, ↓ tempo internamento e mortalidade
Transplantation (solid organ)	AIT Up to 2 g/kg to be repeated as per DSA, in renal desensitisation at 0.1 g/kg for 8–12 doses AMR Up to 2 g/kg to be repeated for 2–3 doses Viral pneumonitis 0.5 g/kg for 5 days	Pneumonite viral CMV + Ganciclovir, VZV + aciclovir, HSV, RSV, vírus influenza NÃO incluído Em doentes após transplante coração e/ou pulmão ↓ Resolução infiltrados pulmonares Diminuição tempo hospitalização Aumento da sobrevivência

SEM INDICAÇÃO ACTUAL PARA GAMAGLOBULINA

UK Guidelines for IVIG use, 2011 update

- Sépsis neonatal (prevenção ou tratamento)
- Sépsis em UCIP não associada a toxinas (Choque Tóxico) nem a *C. difficile*

...

UK Guidelines for IVIG use, 2011 update

PARA ALÉM DAS GUIDELINES – EFICÁCIA DA GGEV NA INFEÇÃO POR ENTEROVÍRUS

Green M et al, Long S, Pediatric Infect Dis, 2018

- Infecção neonatal grave ?
- Miopericardite ?
- Infecção crónica no imunodeficiente
 - Meningoencefalite (Echo)
 - Miosite

400 mg/kg, 4 dias ou **2g/kg dose única EV** +/- Ig intraventricular

Eficácia relaciona-se com título elevado Ac neutralizantes específicos

- Determinar os serotipos predominantes no início do Verão
- Seleccionar lotes de IGIV que cubram o > nº destes serotipos

Update on the use of immunoglobulin in human disease: A review of evidence



PEREZ ET AL

J ALLERGY CLIN IMMUNOL
MARCH 2017

TABLE VI. Uses of immunoglobulin in infectious and infection-related diseases

Benefit	Indication	Evidence category	Strength of recommendation
Definitely beneficial	KD*	Ia	A
	Reduction of secondary infections in pediatric HIV infections*	Ib	A
	CMV pneumonitis in solid organ transplants	Ib	A
Probably beneficial	Neonatal sepsis	Ia	A
	Rotaviral enterocolitis	Ib	A
	Bacterial infections in lymphoproliferative diseases	Ib	B
	Toxic shock syndrome	III	C
	Enteroviral meningoencephalitis	III	C
May provide benefit	Cystic fibrosis with hypogammaglobulinemia	III	C
	Postoperative sepsis	III	C
	RSV lower respiratory tract infection (proven for palivizumab)	III	C
	Pseudomembranous colitis	III	C
	Campylobacter enteritis	III	C
	Chronic parvovirus B19	III	D
Unlikely to be beneficial	Chronic fatigue syndrome	Ib	A
	Cystic fibrosis without hypogammaglobulinemia	Ib	A
	Acute rheumatic fever	IIa	B
	Viral load in HIV infection	IIb	B

*FDA-approved indication.

Intravenous immunoglobulin for infectious diseases: back to the pre-antibiotic and passive prophylaxis era?

Jagadeesh Bayry, Sébastien Lacroix-Desmazes, Michel D. Kazatchkine and Srinivasa V. Kaveri

Table 1. Human infectious diseases for which beneficial effects of intravenous immunoglobulin has been reported^a

Infectious conditions	Prophylaxis (P) or therapeutic (T)	Refs
Streptococcal toxic shock syndrome	P, T	[6,7]
Recurrent bacterial infections ^b in patients with hypogammaglobulinemia	P	[4,5]
Polyneuropathy associated with <i>Campylobacter jejuni</i>	T	[33]
<i>Clostridium difficile</i>	T	[34]
<i>Chlamydia pneumoniae</i>	T	[35]
<i>Salmonella typhimurium</i>	T	[36]
West Nile virus	T	[8,9]
Parvovirus B19	T	[12,14]
Cytomegalovirus	P	[13]
Childhood HIV	P, T	[37]
Enteroviruses ^c		
Varicella zoster		
Genital herpes simplex virus		

Despite the use of IVIg in infectious diseases, several fundamental questions remain unanswered, including what are the appropriate indications, optimal dosage and frequency of

difficult. However, there are enough encouraging experimental and clinical data to maintain continuing interest in the IVIg field and demand further studies in infectious conditions for which IVIg has been found to be beneficial in uncontrolled studies (i.e. those that lack placebo-controlled clinical trials). Controlled trials, particularly with viral diseases and certain defined septic subgroups where IVIg represents a promising but unproven treatment, are imperative. It is evident, however, that IVIg preparations

IGIV – EFEITOS ADVERSOS

Minor (ritmo rápido de perfusão)

cefaleias, náuseas, vômitos, febre, arrepios, mialgias, artralgias, “flushing”, dor abdominal

Mais frequentes se

- Infecção aguda
- 1º tratamento
- ↑ intervalo entre perfusões (>4 sem.)
- Alteração da formulação
- Hiperosmolaridade

↓ ritmo de perfusão

pré tratamento com paracetamol ou AINE e/ou anti-histamínico

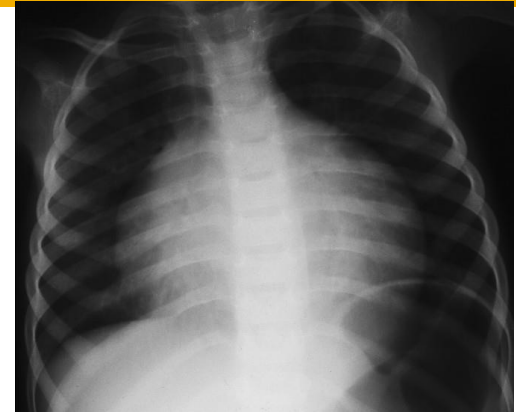
IGIV – EFEITOS ADVERSOS

- Anafilaxia (def. IgA – Ac Anti-IgA?)
- Fenómenos tromboembólicos
- Meningite asséptica
- Anemia Coombs+
- Insuficiência renal
- Sobrecarga volume

↑ risco com doses elevadas (0,8 – 2g/kg)

Doentes com síndromes de hiperviscosidade
IGIV de baixa osmolaridade
Hidratação prévia

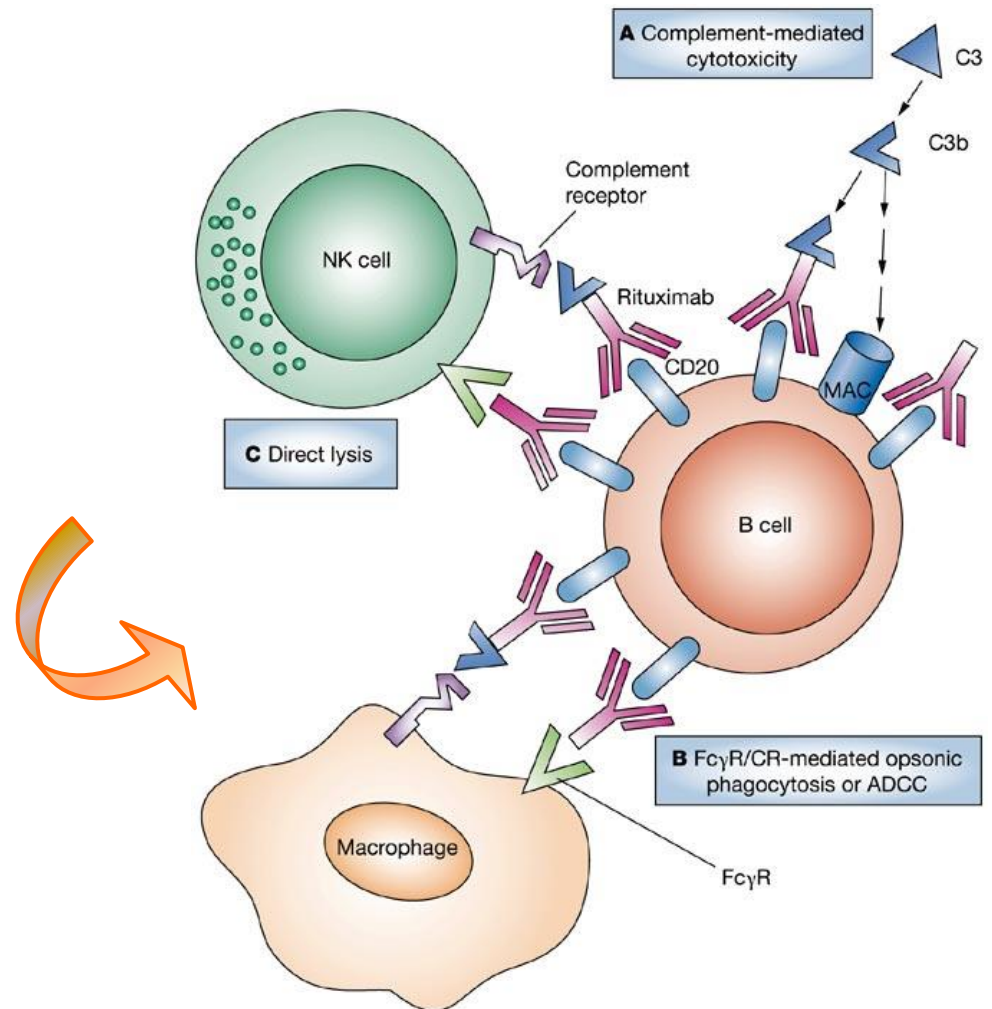
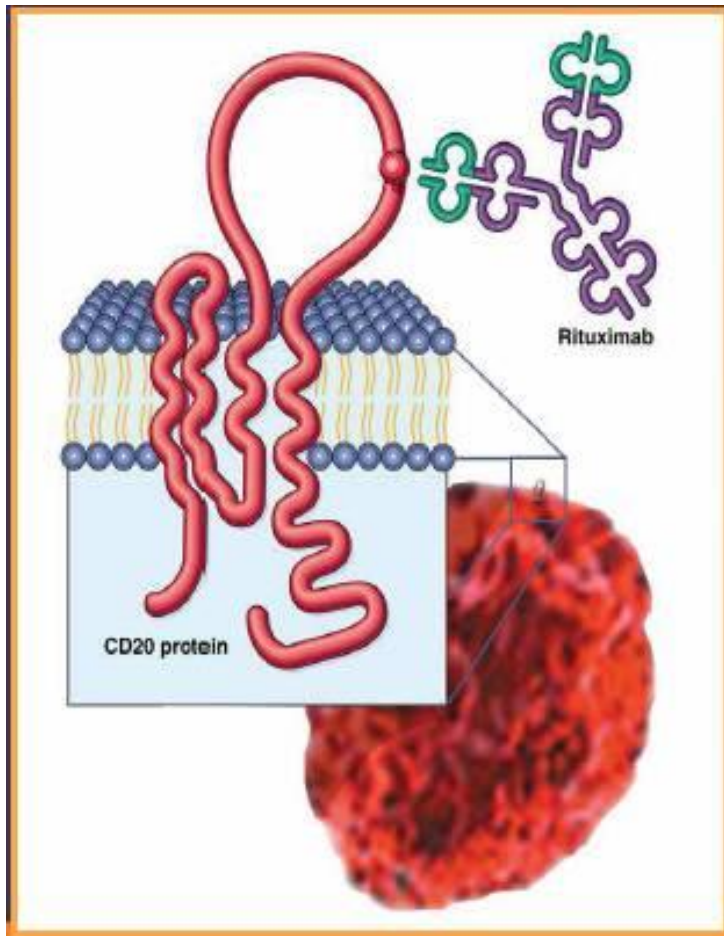
Transmissão infecções



IVIG 10%
< teor Na e Albumina

RITUXIMAB

Ac monoclonal quimérico
ratinho / humano anti-CD20



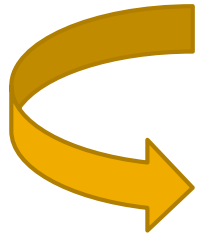
Adapted from: Nature Immunology Reviews, 2007

RITUXIMAB – INDICAÇÕES Tx HABITUAIS

- Neoplasias de Cels B: LLC
 - Linfoma difuso de grandes células
 - Linfoma folicular
- Dcs autoimunes: Artrite reumatóide
 - PTI
 - Anemia hemolítica
- Vasculites
- Esclerose múltipla
- Transplantação: profilaxia da rejeição (rim)
 - Tx de complicações associadas ao EBV

RITUXIMAB – adjuvante nas infecções

- Infecção a **EBV complicada** em doente de risco (doentes com XLP, outras formas de ID, ou receptores de transplante) com necessidade de ↓↓ rápida da virémia
 - com síndrome hemofagocítico secundário
 - PTLD (*post-transplant lymphoproliferative disease*)
 - Linfoma de células B, EBV +



Avaliar a virémia + marcação de EBV em linfócitos B
(sangue periférico, biópsia ganglionar)

Outras indicações:

Trombocitopenia (PTT) associada ao VIH (refractário a outras Tx)

RITUXIMAB – EFEITOS ADVERSOS

- **Hipogamaglobulinémia** prolongada
- **Sind. de libertação de citocinas** (febre, calafrio, urticária, angioedema, dispneia, broncospasmo, hipóxia, hipotensão)
- **Anafilaxia**
- **Sind. de lise tumoral** (+ hiperuricémia, hipercaliémia, hipocalcémia, hiperfosfatémia, IRA, ↑LDH, pneumonite)
- EAM, arritmias, insuf. cardíaca
- Trombocitopénia, neutropénia
- LMP (vírus JC) e reactivação de VHB, VHC, CMV, parvovírus B19, HSV, VZV
- Perfuração e obst. intestinal

Modulating immunity as a therapy for bacterial infections

Robert E. W. Hancock¹, Anastasia Nijnik² and Dana J. Philpott³

Abstract | Despite our efforts to halt the increase and spread of antimicrobial resistance, bacteria continue to become less susceptible to antimicrobial drugs over time, and rates of discovery for new antibiotics are declining. Thus, it is essential to explore new paradigms for anti-infective therapy. One promising approach involves host-directed immunomodulatory therapies, whereby natural mechanisms in the host are exploited to enhance therapeutic benefit. The objective is to initiate or enhance protective antimicrobial immunity while limiting inflammation-induced tissue injury. A range of peptides have been proposed, including innate defence regulator peptides that are in clinical trials to treat bacterial infections.

Table 1 | Immunomodulatory therapies that target pattern recognition receptors to treat microbial infections

Drug	Target and activity	Application	Phase of development
Imiquimod ¹²¹	TLR7 agonist	Keratosis, basal cell carcinoma, HPV-associated genital warts	Clinical
MPL ^{122,123}	TLR4 agonist	Adjuvant in the Cervarix (GlaxoSmithKline) vaccine against HPV infections and associated cervical cancer	Clinical
Luivac (lysate of a combination of bacterial species) ^{18,19}	Agonist for various TLRs	Recurring respiratory tract infections	Clinical
CADI-05 (heat-killed <i>Mycobacterium indicus pranii</i>) ¹⁵	Agonist for various TLRs	Leprosy (in combination with antimicrobial drugs) and tuberculosis	Clinical and Phase III
CpG-7909 (REF. 16)	TLR9 agonist	Improving the efficacy of the anthrax vaccine BioThrax (Coley Pharmaceutical)	Phase II
DIMS-0150 (an oligonucleotide-based drug) ¹⁷	TLR9 agonist	Steroid-resistant ulcerative colitis	Phase III
E-5564 (eritoran)	TLR4 antagonist	Sepsis	Phase III
TAK-242 (resatorvid)	TLR4 antagonist	Sepsis	Suspended in Phase III
MF-59 (squalene and water emulsion) and MTP-PE (mifamurtide)	NOD2 agonist	HIV, influenza viruses	Phase I

HPV, human papillomavirus; MPL, monophosphoryl lipid A; MTP-PE, phosphatidylethanolamine-linked muramyl tripeptide; NOD2, oligomerization domain-containing 2; TLR, Toll-like receptor.

Terapêuticas adjuvantes na infecção

Table 2 | Innate defence regulator peptides that are in clinical trials to treat bacterial infections

Peptide	Sequence and/or structure	Activity	Potential clinical applications	Phase	Company
EA-230	4 amino acid peptide	Anti-inflammatory activity in experimental endotoxin challenge in healthy volunteers	Prevention of sepsis, and protection against renal failure following cardiac surgery	Phase I–II	Exponential Biotherapies
hLF1-11	11 amino acid cationic peptide, a fragment of lactoferrin	Direct antibacterial and antifungal activity, and stimulation of innate immunity	Prevention of infections in immunocompromised patients	Phase I	AM-Pharma
IC-31	Synthetic cationic peptide (KLKL, KLK) in combination with a synthetic oligonucleotide (ODN1a)	Potent adjuvant activity in formulation with immunostimulatory oligonucleotides in animal models	Component of an adjuvant formulation in a novel vaccine against tuberculosis	Phase I	Intercell
IMX-942	5 amino acid synthetic cationic peptide loosely derived from indolicidin and IDR1	Immunomodulatory, with no antimicrobial activity; shows protective effects in mouse models of antibiotic-resistant bacterial infections	Prevention of infections in immunosuppressed patients undergoing chemotherapy for cancer	Phase II	Inimex Pharmaceuticals
MSI-78	22 amino acid cationic peptide derived from magainin	Antibacterial activity; potential immunomodulatory activity unknown	Treatment of foot ulcers in patients with diabetes	Phase III	MacroChem
MX-226 (omiganan)	12 amino acid cationic peptide derived from indolicidin	Direct antimicrobial and immunomodulatory activity	Topical antiseptic for the prevention of catheter infections	Phase III	BioWest Therapeutics
Opebacan	21 amino acid peptide derived from BPI	Antibacterial and anti-inflammatory activity	Treatment of endotoxaemia and GVHD in patients receiving bone marrow transplantations	Phase I–II (terminated)	XOMA
PMX-30063	Small-molecule structural mimetic of defensin	Antibacterial activity against MRSA; potential immunomodulatory activity unknown	Treatment of acute <i>Staphylococcus aureus</i> skin infections	Phase II	PolyMedix
XOMA-629	9 amino acid peptide derived from BPI	Direct antibacterial activity; immunomodulatory activity unknown	Treatment of impetigo skin infections caused by <i>Staphylococcus aureus</i> and <i>Streptococcus pyogenes</i>	Phase IIA	XOMA

Table is modified, with permission, from REF. 67. BPI, bactericidal permeability-increasing protein; GVHD, graft-versus-host disease; IDR1, innate defence regulator peptide 1; MRSA, methicillin-resistant *S. aureus*.

Obrigada

