# Welcome

## We're so glad you're here!

MEDVET

CONFERENCE

# Autoimmune Disease: Review of Immunosuppressive Strategies

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MedVet Salt Lake City

# Intro to Autoimmune Disease

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# What Causes Autoimmunity?

Genetics

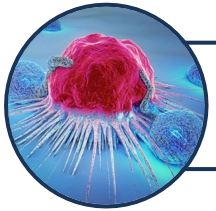
*Autoimmunity*

Environment

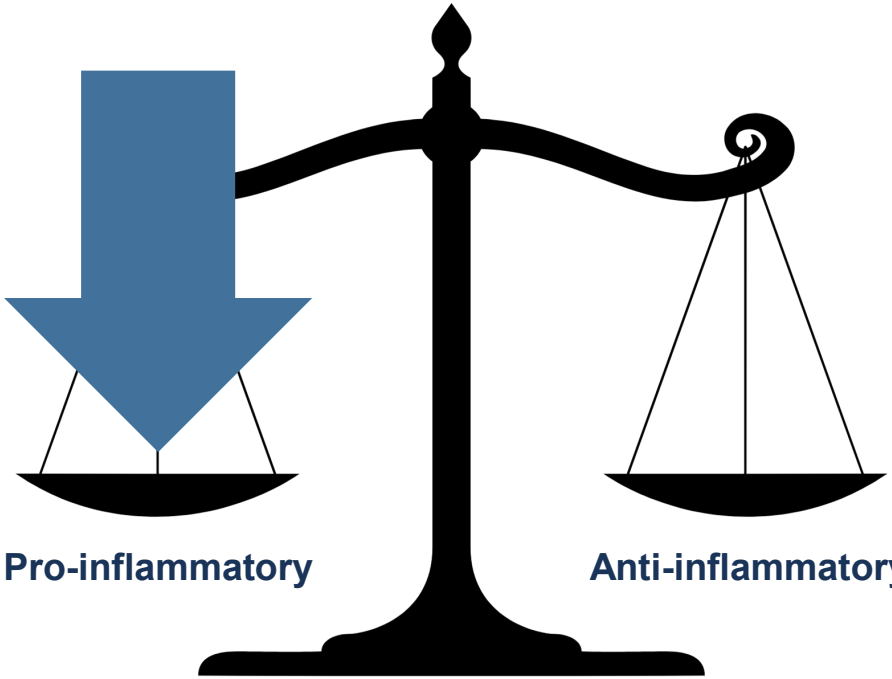
Systemic

Vaccination

Infection



Neoplasia

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Genetics

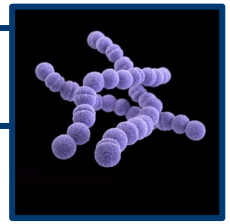
Environment

Immune system

Self-antigen

Molecular mimicry

Eg Post-streptococcal disorder

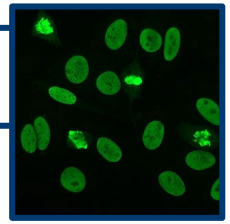


Hapten formation

Eg Poison ivy

Cryptic antigens

Eg Anti-nuclear antibodies



Unbalanced response

Eg Vaccine adjuvants

Semple 2006, Fagiolo 2003

# Challenges of Autoimmunity

***Diagnostic criteria for IMHA***

Positive Coombs
*OR*
Autoagglutination
*OR*
Spherocytosis

+

Rule out all secondary causes

# Common Autoimmune Diseases

- IMHA and variants
- ITP
- IM neutropenia
- IMPA
- Skin diseases
- Systemic lupus erythematosus
- CNS disease
- Muscular disease
- Autoinflammatory diseases

Mechanistic approach to treatment

*Understanding what mediates the disease means we can target specific immune responses*

# Common Autoimmune Diseases

- Faster response to therapy
- Decreased side effects
- Better long-term control and maintenance
- Reduced risk of complications

Mechanistic approach to treatment

*Understanding what mediates the disease means we can target specific immune responses*

# Common Autoimmune Diseases

- IMHA and variants
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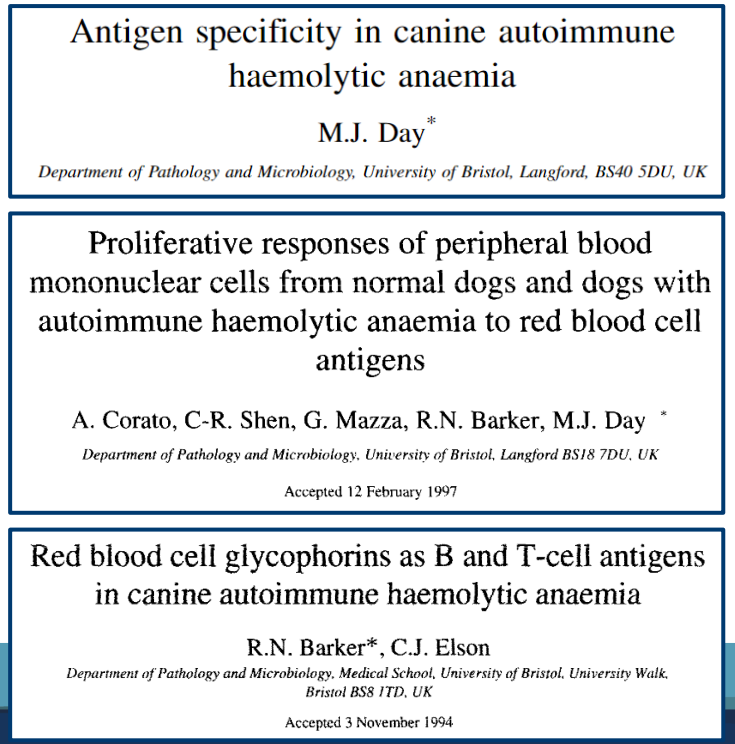
Mechanistic approach to treatment

*Understanding what mediates the disease means we can target specific immune responses*

# IMHA|What We Know



Antigen specificity in canine autoimmune haemolytic anaemia

M.J. Day*

*Department of Pathology and Microbiology, University of Bristol, Langford, BS40 5DU, UK*

Proliferative responses of peripheral blood mononuclear cells from normal dogs and dogs with autoimmune haemolytic anaemia to red blood cell antigens

A. Corato, C-R. Shen, G. Mazza, R.N. Barker, M.J. Day *

*Department of Pathology and Microbiology, University of Bristol, Langford BS18 7DU, UK*

Accepted 12 February 1997

Red blood cell glycophorins as B and T-cell antigens in canine autoimmune haemolytic anaemia

R.N. Barker*, C.J. Elson

*Department of Pathology and Microbiology, Medical School, University of Bristol, University Walk, Bristol BS8 1TD, UK*

Accepted 3 November 1994

## Key Points

- PMNs respond to RBC membranes, glycophorin, spectrin
- IMHA **and** healthy dogs
- Antibody driven destruction of RBCs by the reticuloendothelial system
- Complement +/-

## Goals of therapy

- Reduce Ab production
- Reduce RE/phagocyte activity
- Remove or neutralize autoantibodies
- Reduce risk of complications

# Common Therapies

# Common Therapies

- Glucocorticoids
- Purine antagonists
- Pyrimidine antagonists
- Alkylating agents
- Cell signaling blockade
- Monoclonal antibodies

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- **Glucocorticoids**
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Throughout this textbook the reader will find GCs are considered first-line therapy for most immune diseases despite a lack of clinical trial-generated evidence to support their use. GCs are widely available and inexpensive. The

Dose: 1-2 mg/kg/day
Max dose: ~80 mg/day

- Alter gene expression
- Induces apoptosis in lymphocytes
- Inhibit lymphocyte activation
- Reduced production of lymphocytes
- Reduced cell adhesion
- Reduced pro-inflammatory cytokines
- Dampen effects of PRRs, cytokine receptors, and Fc receptors
- Reduced degranulation of some cells
- *In some scenarios, glucocorticoids may be pro-inflammatory*
- *One of the only therapies we use which more directly affects the innate immune response*

Cain and Cidlowski 2017
Ettinger 2017
Coutinho and Chapman 2011

# Common Therapies

- Glucocorticoids
- **Purine antagonists**
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- Cell signalling blockade
- Monoclonal antibodies

**Azathioprine, 6-MP** (1st gen)

- Purine analog results in non-functional DNA and inhibits further synthesis
- Prevents cell division
- Induces apoptosis

**Mycophenolate** (2nd gen)

- Reversible enzyme inhibition
- More selective for activated lymphocytes
- Induces T cell apoptosis
- Decreases cell adhesion
- Decreases antibody production

Allison, Eugui 2000
Ettinger 2017

# Common Therapies

2 mg/kg q24 hrs for two weeks
Then q48 hrs for maintenance

Monitor CBC and liver enzymes q2 months
Watch for signs of pancreatitis

10 mg/kg q12 hrs

Monitor CBC occasionally
Idiosyncratic hemorrhagic colitis is rare

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Allison, Eugui 2000
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Plumb's Veterinary Drug Handbook

# Common Therapies

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## Leflunomide

- Non-functional DNA (cell division)
- Limits pyrimidine production
- Limits T-cell proliferations and antibody production from B-cells
- Possible anti-platelet effect

2-4 mg/kg q24 hrs

CBC and liver enzymes q2 months
Idiosyncratic hemorrhagic colitis is rare

Ettinger 2017
Plumb's Veterinary Drug Handbook

# Common Therapies

- Glucocorticoids
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- **Alkylating agents**
- Cell signaling blockade
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**Alkylating agents are generally no longer recommended as first-line immunosuppressives**

## Cyclophosphamide

- Historical use in IMHA, some niche cases of glomerulonephritis

## Chlorambucil

- Possible use in refractory IBD
- Empirical treatment of moderate-severe IBD in cats

Ettinger 2017
Plumb's Veterinary Drug Handbook

# Common Therapies

- Glucocorticoids
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## Cyclosporine

- Calcineurin inhibitor
- Blocks cell signalling cascade which normally results in T-cell activation
- Possible procoagulant effects
- Questionable bioavailability of generic

## Tacrolimus

## Apoquel

Ettinger 2017
Plumb's Veterinary Drug Handbook

# Common Therapies

5 mg/kg q12-24 hrs

Not generally considered myelosuppressive
Risk of lymphoid neoplasia in people

*Watch this space...*

## Cyclosporine

- Calcineurin inhibitor
- Blocks cell signaling cascade which normally results in T-cell activation
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## Tacrolimus and Apoquel

Ettinger 2017
Plumb's Veterinary Drug Handbook

# Common Therapies

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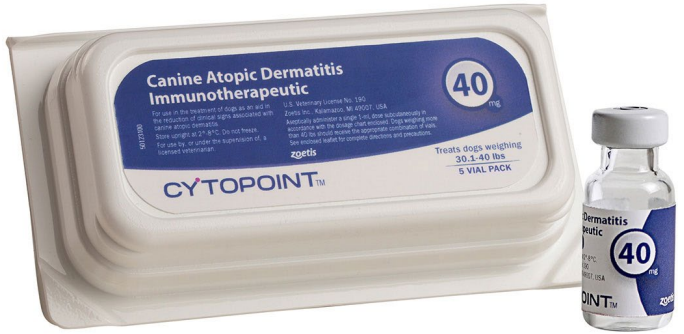



- Chimeric monoclonal antibody
- Targets IL-31
- Not an anti-inflammatory
- Not an immunosuppressive
- Not for use in cats

Zoetisus.com
Plumb's Veterinary Drug Handbook

# Fringe Therapies

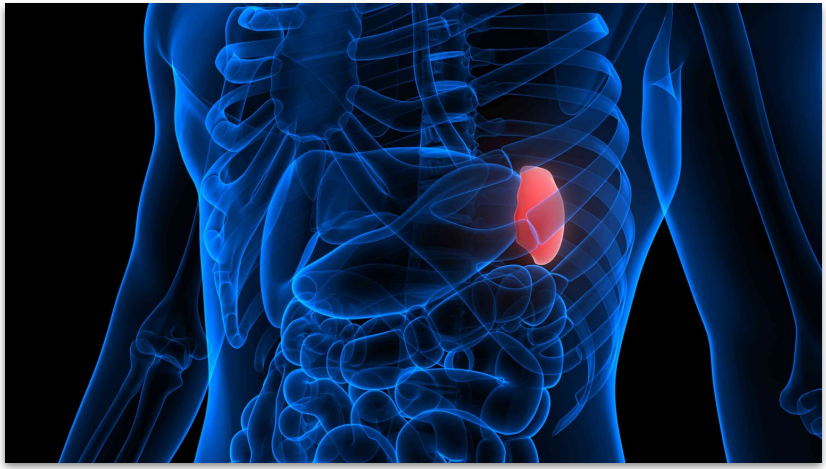
# Fringe Therapies|IV Immunoglobulin

- Polyclonal mixture of immunoglobulins from many donors
- Expensive
- Not well studied
- Likely beneficial
- Best used in antibody-mediated (humoral) diseases


Ettinger 2017
Whelan 2009
Ballow 2014
Swann 2019

# Fringe Therapies|Splenectomy

- The spleen houses a large population of Th-cells and antigen presenting cells
- Reticuloendothelial cells active in hematologic diseases
- Second-line treatment in people for many diseases
- Evidence suggests it's highly effective in dogs with IMHA



Ettinger 2017
Swann 2019

# Fringe Therapies|Plasma Exchange

- Removal of harmful proteins and substances in the plasma
- Half life of IgG >1 week
- Described for IMHA, ITP, and more.
- Reported >90% survival


**Now available at MedVet SLC**

# Examples of Indications for TPE

## IMHA

- Autoagglutination
- Intravascular hemolysis
- Elevated BUN, tbili
- High transfusion requirement

## ITP

- Clinical bleeding, especially pulmonary, CNS
- Unresponsive in 2-3 days

Other diseases that may benefit include MG, SLE, pemphigus, Lyme nephritis, MUE, Coonhound paralysis

# Novel Therapies

# Novel Therapies

- New monoclonal antibodies
- New small molecule inhibitors
- Immunomodulatory proteins
- Hemoperfusion
- Adoptive cell therapy

HUMIRA®
adalimumab

Enbrel®
etanercept

# Disease Management

## IMHA

# IMHA|How I Do It

## Mild

- Mild-moderate anemia
- No agglutination
- No intravascular hemolysis
- No other lab abnormalities

## Treatment

- Prednisone 2 mg/kg/day
- Clopidogrel 1-4 mg/kg SID
- Second agent unlikely

## Monitoring

- Document regeneration
- PCV q2 weeks until >30%
- Taper pred 25% q2 weeks
- Monitor PCV each dose
- If started, continue 2nd agent

Ettinger 2017

## Mild cases can be difficult to diagnose

- Agglutination, hemolysis, spherocytosis, Coomb's + may not be present
- You may only have mild-moderate regenerative anemia and minimal systemic signs of illness

## Mild cases can be outpatient

- Vigilant monitoring required of client
- May progress to more severe form of disease

## Regardless of severity, client compliance is key

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Ettinger 2017

## Antithrombotic therapy

- Clopidogrel is recommended over Aspirin
- Heparin is recommended over oral for more severe cases
- First two weeks are the most important
- Continue oral therapy until pred is discontinued

## When to discontinue a second agent

1. Cold turkey after pred is discontinued
2. Tapered after pred is discontinued
3. Continuous low-dose in perpetuity

# IMHA|How I Do It

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- Taper pred 25% q2 weeks
- Monitor PCV each dose
- If started, continue 2nd agent

## Moderate

- Moderate-severe anemia
- Agglutination +/-
- Intravascular hemolysis +/-
- Elevated BUN/ALP/Tbili

## Treatment

- Dex SP 0.2 mg/kg/day
- Mycophenolate 10 mg/kg BID
- Clopidogrel 1-4 mg/kg SID
- Transfusion as needed

## Monitoring

- Watch for PTE or similar
- Transfusion reactions
- Persistent agglutination, hemolysis, progressive anemia

## Severe

- Severe anemia
- High transfusion dependence
- Persistent agglutination and hemolysis
- Severe lab abnormalities
- Kernicterus

## Treatment

- Dex SP 0.2 mg/kg/day
- Mycophenolate 10 mg/kg BID
- Clopidogrel 1-4 mg/kg SID
- Heparin +/-
- Transfusion as needed
- **Therapeutic plasma exchange**

Ettinger 2017

# Other Autoimmune Diseases

## Treatment typically follows the same pattern...

1. Prednisone
2. Second agent +/- depending on severity
3. Long-term therapy with slow taper

## Variations on a theme

- Leflunomide and NSAIDs for IMPA
- Budesonide for IBD
- Chlorambucil for refractory IBD
- Cytosar for MUE
- IVIG or splenectomy for hematologic disease
- TPE for antibody-mediated disease

# Questions?

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- MedVet will then submit your proof of attendance to the AAVSB where they will centrally record and track your RACE CE credits for your license renewal using your license number and state of license. Now that the AAVSB is utilizing RACEtrack for all veterinarians and technicians, MedVet is no longer providing certificates. RACEtrack provides an easy way for you to communicate your CE to your licensing agencies.

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