



## Review of Immunosuppressive Therapies: Indications, Monitoring, and Risks

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Continuing EDUCATION

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## Presentation Outline

- General Use of Immunosuppressive Drugs:
  - When should I use immunosuppressives? (*indications*/disease processes)
  - How should I monitor patients on them and taper immunosuppressives?
  - When shouldn't I use them? (*contraindications*)
- Getting to Know the Major Players:
  - Drug-specific dosing and formulations
  - Evidence-based indications
  - Drug-specific side effects and monitoring strategies



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## Immune-Mediated Disease Definition


- Immune system functions → Preserve body integrity
  - Pathogen defense
  - Recovery from tissue trauma or infection
  - Recognition of "self" and "non-self"
  - Cancer surveillance
- Immune dysregulation
  - Genetic factors
  - Environmental triggers
- Autoimmune disease
  - Loss of self-tolerance
  - Antibodies, T cells directed against self-antigens

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## Immunosuppressive Drug Use: Indications

<p><b>Autoimmune Disease</b></p> <ul style="list-style-type: none"> <li>• IMHA</li> <li>• ITP</li> <li>• IMPA</li> <li>• IMN</li> <li>• PLN/ICGN</li> <li>• PIMA/PRCA</li> <li>• SLE</li> </ul>	<ul style="list-style-type: none"> <li>• PF, PV, DLE, SLO, vasculitis</li> <li>• Polymyositis, MMM, MG</li> <li>• SRMA, GME, MUE</li> <li>• UVD, KCS</li> <li>• Stomatitis</li> </ul>
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## Immunosuppressive Drug Use: Indications

### Chronic Inflammatory Disorders

- IBD/PLE
- Chronic hepatitis/cholangitis
- Feline asthma
- Chronic rhinitis
- Atopic dermatitis
- Colorectal inflammatory polyps
- Chronic pancreatitis?



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## Immunosuppressive Drug Use: Goals



- Timing
  - After diagnosis is achieved!
  - Collect samples and complete work-up
  - Immunosuppressive drugs have risks
  - Steroids impact test results
- Achieve remission
  - Clinical
  - +/- Diagnostic
  - Ideal vs reality – case-specific considerations

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## Immunosuppressive Drug Use: Goals

- Taper and recheck
  - 25% (or 33%?) rule
  - Recheck q2-4 weeks
  - Discontinue immunosuppression vs lowest effective dose
  - Relapse
- Minimize side effects
- Steroids vs 2<sup>nd</sup> line immunosuppressives?
  - Disease severity
    - Clinical presentation, prognostic factors
  - Unable to achieve/sustain remission
  - Intolerable steroid side effects

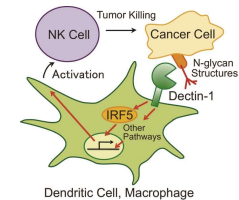


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## Immunosuppressive Drug Use: Contraindications

- Infectious disease
  - Newly acquired/secondary infections – UTIs, pyoderma
  - Pre-existing – Toxoplasmosis, Babesia, FHV
  - Caution with cyclosporine
- Increased risk of neoplasia?
  - Impaired tumor surveillance
  - Decreased oncogenic virus immunity
  - Renal transplant cats → increased risk of malignancy/lymphoma



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## Immunosuppressive Drug Use: Contraindications

- Comorbidities
  - Endocrinopathies
  - Liver or renal disease
  - Neoplasia
  - Immunocompromised
  - Other immunomodulatory meds
- Patient factors
  - Drug choice
  - Breed
- Owner considerations
  - Financial limitations
  - Noncompliance
  - Client health



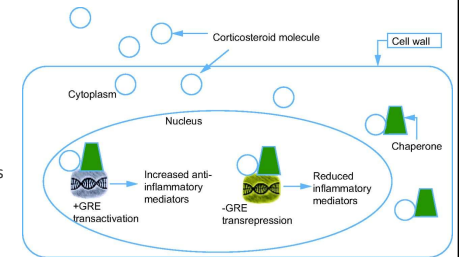
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## Glucocorticoids

### Mechanism of Action

- Bind to intracellular GC receptors
- Act in the nucleus to affect gene transcription
  - → Inhibit pro-inflammatory mediators (phospholipase A2, COX-2)
  - → Increase anti-inflammatory mediators
- Dose-dependent effects
- Wide-ranging indications



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## Glucocorticoids

Glucocorticoid (Species)
Prednisone/prednisolone (dog)
Prednisolone (cat)
Methylprednisolone (dog)
Methylprednisolone (cat)
Methylprednisolone acetate (cat)
Dexamethasone (dog)
Dexamethasone (cat)
Triamcinolone (dog)
Triamcinolone injectable (dog)
Triamcinolone (cat)
Triamcinolone injectable (cat)

### Forms and Dosing

- Different forms, different potencies, durations, and indications
- Prednisone/prednisolone:
  - Immunosuppressive: 2 – 4 mg/kg/day
  - Or 2 – 3 mg/kg/day to start → quickly reduce to 2mg/kg/d or less
- Anti-inflammatory: 0.5 – 1.0 mg/kg/day
- Physiologic: 0.1 – 0.25 mg/kg/day



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## Glucocorticoids

### Pros

- Fast and effective
  - GCRs are ubiquitous
- Prolonged effects
- Predictable dosing
- Inexpensive \$

### Cons

- High rate of significant side effects
  - PU/PD, +/- urinary incontinence
  - Polyphagia
  - Panting
  - Muscle mass loss
  - Behavior changes
  - Haircoat/skin changes
  - GI ulceration
  - Insulin resistance
  - CHF
  - Hypercoagulability
- Need to taper



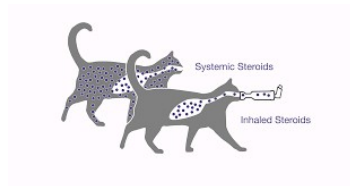
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## Glucocorticoids

### Monitoring

- PE, baseline chemistry, UA, +/- UCS q8-12 weeks
- Consider occasional CBCs to screen for anemia
- Cats: RR/RE, BG



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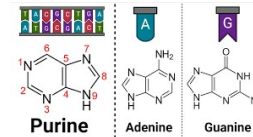
## Azathioprine

### Mechanism of Action

- Purine analog → inhibits DNA and RNA synthesis → inhibits lymphocyte proliferation, macrophage function, antibody production
- Active metabolite 6-MMP
- Slower onset

### Indications

- Used extensively
- IMHA, ITP, IBD, CH, ICGN, IMPA, transplants



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## Azathioprine

### Forms and Dosing

- Generic or Imuran
  - 50mg tablets
- 2mg/kg PO q24- 48hr
- \$\$
- Don't use with:
  - Mycophenolate
  - ACEIs
  - Allopurinol
  - Sulfasalazine



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## Azathioprine

### Side effects

- GI signs + pancreatitis
- Hepatotoxicity
  - 6-MMP accumulation
  - Reversible increase in ALT (2-5x)
  - No clinical signs, 2-3 weeks
  - 15%, higher risk in GSDs
- Myelosuppression
  - 8%
  - NR anemia, 4-16 weeks

### Monitoring

- Liver enzymes q2 weeks x 2 months
- CBCs q2 weeks x 2 months, then q1-2 months throughout treatment



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## Azathioprine

### In Cats?

- No!
- TPMT deficiency
- Severe myelosuppression, especially neutropenia



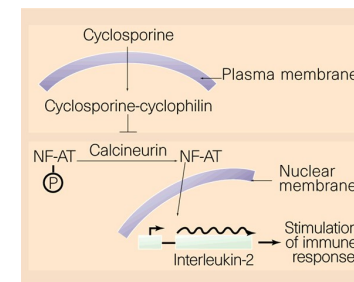
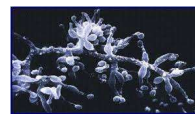
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## Cyclosporine

### Mechanism of Action

- Cyclosporine A derived from fungus (*Tolypocladium inflatum*)
- Atopy, PF, renal transplants, IBD, IMHA, ITP, asthma, CH, etc
- Calcineurin inhibitor, prevents IL-2 production
- Inhibits T-cell function and cell-mediated immunity



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## Cyclosporine

### Formulations

- Ultramicroemulsified/modified, microemulsion formulation
  - On empty stomach
- Atopica
  - 10mg, 25mg, 50mg, 100mg capsules
  - 100mg/ml liquid
- Cycloavance (100mg/ml) – dogs
- Modulus (100mg/ml) – cats
- Tacrolimus: topical only
  - Perianal fistulas, KCS



### Dosing

- 5mg/kg q12 in dogs, 7mg/kg in cats
- Large individual variability

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## Cyclosporine

### Drug Monitoring

- Pharmacokinetic monitoring of cyclosporine levels
  - Peak: .15-2hrs post pill → toxicity
  - \*Trough: BND, 11-12hrs post pill (for BID dosing) → efficacy
- Auburn:
  - Immune-mediated disease: peak 800-1400ng/ml, trough 400-600ng/ml
  - Inflammatory disease: trough 250ng/ml
  - Renal transplantation: peak 2600-3000ng/ml, trough 750ng/ml



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- Pharmacodynamic monitoring
  - IL-2, IL-4, IF-gamma expression
  - 2hrs post-pill
- MS State closed!

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## Cyclosporine

### Drug Interactions

- Cytochrome P450 enzyme metabolism
  - Inhibitors → increase CsA
  - Inducers → decrease CsA

TABLE 1.  
Important Drugs That Affect Cyclosporine Concentrations in Blood

DRUG TYPE	MAY INCREASE CYCLOSPORINE CONCENTRATION	MAY DECREASE CYCLOSPORINE CONCENTRATION
Antibacterials	Azithromycin Chloramphenicol Ciprofloxacin Clarithromycin	Enrofloxacin Erythromycin Imipenem Metronidazole
Antifungals	Fluconazole Itraconazole	Ketoconazole Terbinafine
Gastroprokinetics Gastroprotectants	Cimetidine Cisapride	Metoclopramide Omeprazole Famotidine
Other Drugs	Calcium channel blockers Digoxin ( <b>cardiac glycoside</b> ) Estrogens ( <b>hormone</b> ) Flavonoids in grapefruit juice	Azathioprine ( <b>immunosuppressive</b> ) Phenobarbital ( <b>anticonvulsant</b> ) Phenytoin ( <b>anticonvulsant</b> ) Cyclophosphamide ( <b>chemotherapeutic</b> )

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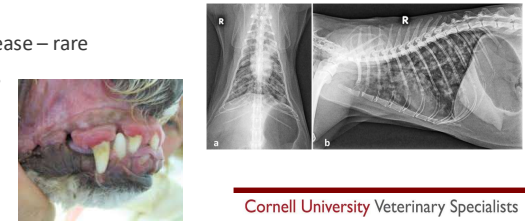
## Cyclosporine

### Side Effects

- GI signs
- Gingival hyperplasia, hypertrichosis
- Hepatotoxicity and lymphoproliferative disease – rare
- Opportunistic infections
- Hypercoagulability
- Insulin resistance

### Monitoring

- PE most important
- +/- Chem, UCS



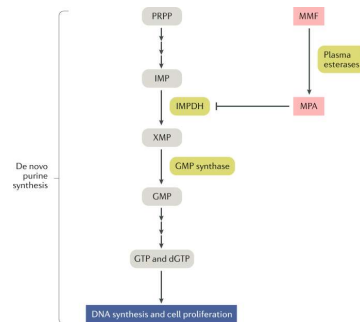
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## Mycophenolate

### Mechanism of Action

- Inhibitor of IMPDH → prevents purine synthesis → inhibits lymphocytes and cell-mediated immunity
- Prodrug of MPA
- Don't give with: azathioprine



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## Mycophenolate

### Indications

- Dogs: IMPA, IMHA, ITP, PF, CH
- Cats?
  - Pharmacodynamic studies not supportive of efficacy
  - IMHA and IMPA

### Forms and Dosing

- CellCept, generic
  - 250mg capsules, 500mg tablets
  - Compounding necessary
- 10mg/kg q12hr
- \$\$\$



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## Mycophenolate

### Side Effects

- Severe ulcerative colitis
- Rare: cytopenias, skin reactions



### Monitoring

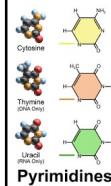
- CBC
- TDM (Auburn)

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## Leflunomide

### Mechanism of Action

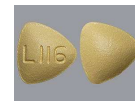


- Pyrimidine analog → inhibits lymphocyte proliferation, antibody production, macrophages, and neutrophils

- **Indications:** IMPA, IMHA, ITP, transplants, colorectal polyps
- FHV in cats?

### Forms and Dosing

- Arava, generic
- 10mg, 20mg tablets
- 2 (to 4) mg/kg q24hr
- \$\$



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## Leflunomide

### Side Effects

- Diarrhea
- Lethargy
- Hepatotoxicity
- Myelosuppression
- Spontaneous hemorrhage
- Higher risk in Mini Dachshunds

### Monitoring

- CBCs and liver enzymes q2 weeks x 2 months, then q 1-2 months
- TDM (Auburn)



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## Chlorambucil

### Mechanism of Action

- Alkylating agent → cross-links DNA and RNA
- Chemotherapeutic and immunosuppressive
  - Targets rapidly dividing lymphocytes (B cells)
- **Indications:**
  - Cats!
  - PLE/IBD, PF, ICGN, ITP

### Forms and Dosing

- Leukeran 2mg tablets
- Compounded tablets
  - Never liquid
- Dogs: 2-4mg/m<sup>2</sup> (0.1-0.2mg/kg) q24-48hr
- Cats: 2mg q48-74hr



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## Chlorambucil

### Side Effects

- GI toxicity
- Myelosuppression
  - Reversible
- Rare: neurotoxicity, acquired Fanconi syndrome, alopecia

### Monitoring

- CBCs at 2 and 4 weeks, then q3 months
- UA in cats



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## Summary

### Take Home Points

- Autoimmune and chronic inflammatory diseases are common
  - Immunosuppressive drugs have numerous indications and uses
  - Nonsteroidal immunosuppressive drug use is growing
- General immunosuppressive use:
  - 1) complete work-up, 2) monitor for adverse effects and remission, 3) taper and follow-up
- Caution in patients with: infectious disease, cancer, endocrinopathies
  - Consider patient- and owner-specific factors
- Azathioprine and mycophenolate don't mix
- Monitor patients closely, consider TDM
- Drug side effects:
  - Azathioprine: GI, hepatotoxicity, myelosuppression
  - Cyclosporine: GI signs, opportunistic infections
  - Mycophenolate: severe colitis
  - Lefunomide: diarrhea, hepatotoxicity, hemorrhage
  - Chlorambucil: GI, myelosuppression



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## Questions?



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