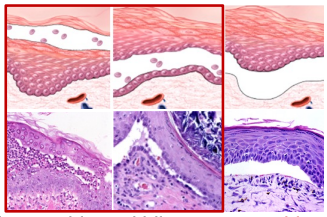
Autoimmune Diseases of the Basement Membrane

1

Autoimmune Blistering Diseases (AIBDs)

- blister [blis'ter]: a local swelling of the skin that contains watery fluid
- autoimmune: due to an immune response to self-antigens

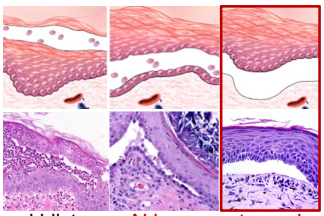


intra-epidermal blisters = pemphigus

2

Autoimmune Blistering Diseases (AIBDs)

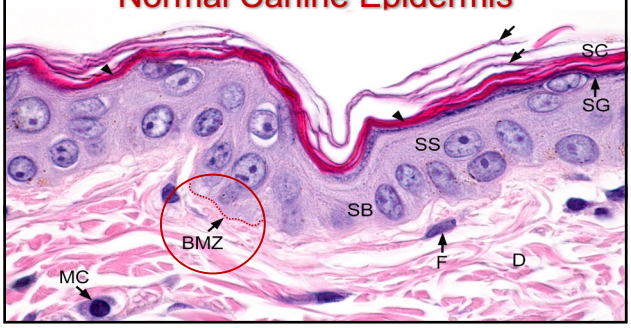
- blister: a small pocket of body fluid within the upper layers of the skin
- autoimmune: due to an immune response to self-antigens



sub-epidermal blisters = AI basement membrane diseases

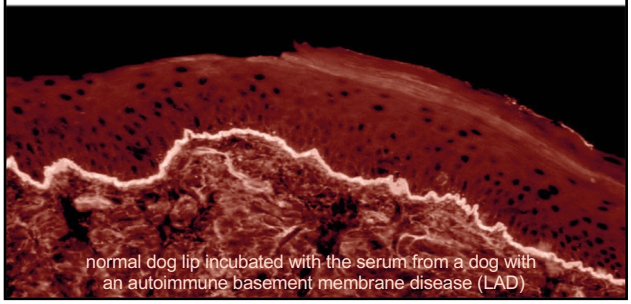
3

Normal Canine Epidermis



4

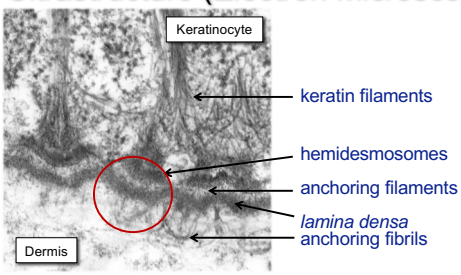
Epidermal Basement Membrane



normal dog lip incubated with the serum from a dog with an autoimmune basement membrane disease (LAD)

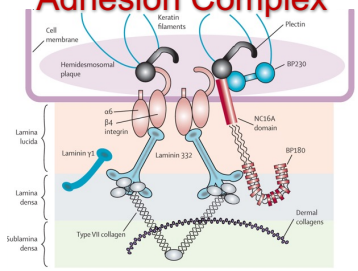
5

Epidermal Basement Membrane
Ultrastructure (Electron Microscopy)



6

Hemidesmosome-Anchoring Fibrils Adhesion Complex



(Schmidt, Lancet 2012)

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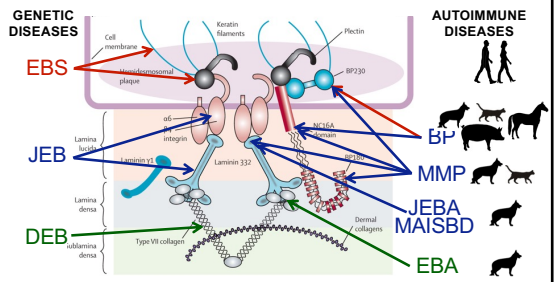
Basement Membrane Skin Diseases



(Schmidt, Lancet 2012)

8

AI Subepidermal Blistering Diseases

100			77		
BP	69 %	81%	MMP	48 %	74%
MMP	12 %		EBA	26 %	
LAD	5 %		BP	10 %	
PG	4 %		LAD	3 %	
EBA	2 %		PG	1 %	
BSLE	2 %		BSLE	1 %	
other or ?	6 %		other or ?	11 %	

(Bernard, Arch Dermatol 1995) (Olivry, Vet Dermatol 2014)

9

Mucous Membrane Pemphigoid (MMP)

10

AI Subepidermal Blistering Diseases

	100			77	
	BP	69 %		MMP	48 % #1
#2	MMP	12 %		EBA	26 %
	LAD	5 %		BP	10 %
	PG	4 %		LAD	3 %
	EBA	2 %		PG	1 %
	BSLE	2 %		BSLE	1 %
	other or ?	6 %		other or ?	11 %

(Bernard, Arch Dermatol 1995) (Olivry, Vet Dermatol 2014)

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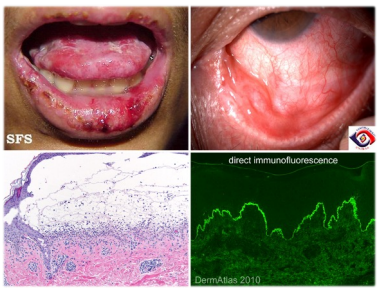
Human MMP



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Canine MMP
Historical Perspective

1984 report of German shepherd dog with "BP" but with MMP phenotype (Alhaidari, Point Vet 1984)

1986 recognition of MMP phenotype as most common variant of canine "BP" (Olivry, DrVet Thesis 1986)

2001 1st report of MMP in 17 dogs with characterization of autoantigens targeted (Olivry, J Autoimmunity 2001)

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Canine MMP
Signalment

– breed predisposition?
- German Shepherds dogs: 18/62 (29%)

– sex distribution:
- female-to-male ratio: 1.1

– age of onset:
- median (range): 5 yrs (1-15)
- young adulthood (1-3 yrs): 25%
- mid-adulthood (4-7 yrs): 47%
- old age (> 8 yrs): 28%

(Bizikova, BMC Vet Res 2023)

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Canine MMP

ulcers: 49/50 (98%)

15

Canine MMP

vesicles and bullae: 21/50 (42%)

16

Canine MMP

scarring: 10/54 (19%)

17

Canine MMP
First Areas Affected

– oral or perioral: 28/50 (56%)

– nasal or perinasal: 17/50 (34%)

– ocular or periocular: 10/50 (20%)

– genital or perigenital: 8/50 (16%)

– ears: 8/50 (16%)

note: lesions sometimes arose simultaneously at several locations

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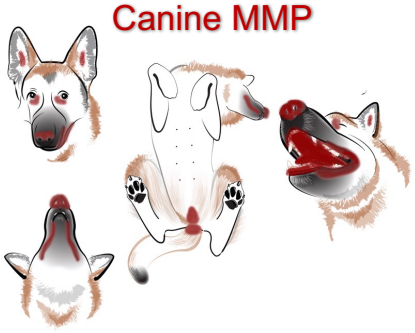
Canine MMP



(Bizikova, BMC Vet Res 2023)

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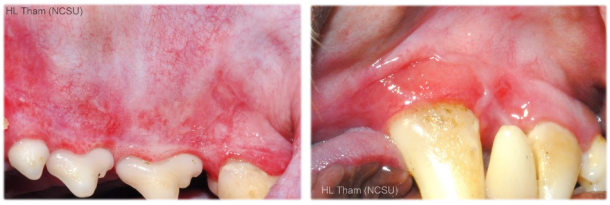
Canine MMP



oral cavity: 34/54 (63%)
gingivae: 31/34 (91%)

(Bizikova, BMC Vet Res 2023)

20

Canine MMP

oral cavity: 34/54 (63%)
gingivae: 31/34 (91%)

(Bizikova, BMC Vet Res 2023)

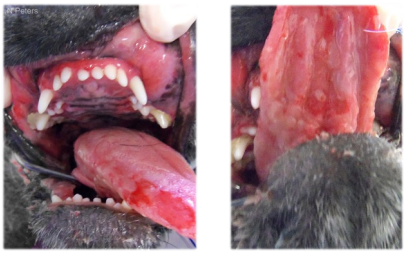
21

Canine MMP

oral cavity: 34/54 (63%)
palate: 24/34 (71%)

22

Canine MMP



oral cavity: 34/54 (63%)
tongue: 9/34 (26%)

23

Canine MMP

nasal/perinasal: 29/54 (54%)

24

Canine MMP

nasal/perinasal: 29/54 (54%)

25

Canine MMP

nasal/perinasal: 29/54 (54%)

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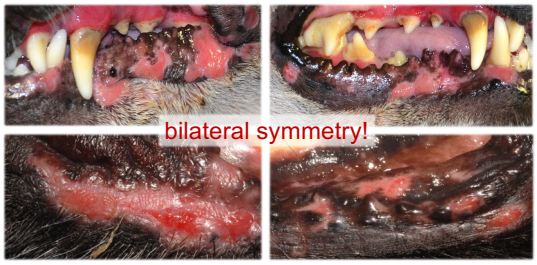
Canine MMP



labial/perilabial: 29/54 (54%)

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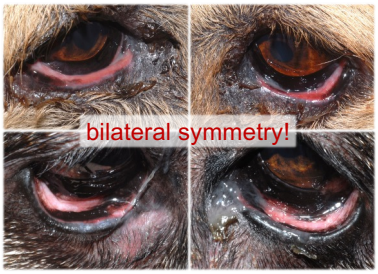
Canine MMP



ocular/periocular: 24/54 (44%)

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Canine MMP

ocular/periocular: 24/54 (44%)

29

Canine MMP

concave pinnae: 19/54 (35%)

30

Canine MMP

genital/perigenital: 20/50 (40%)

31

Canine MMP

anal/perianal: 11/50 (22%)

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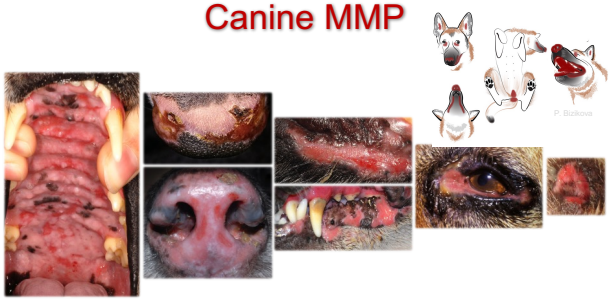
Canine MMP



oral > nasal > labial > ocular > anogenital

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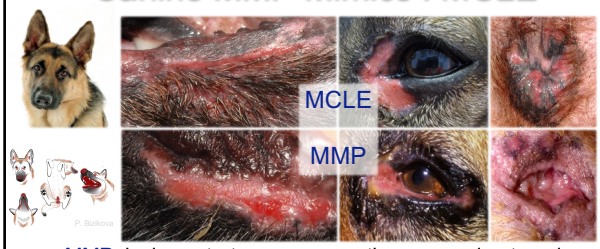
Canine MMP Mimics : MCLE



MMP: lesions start on mucosae, then expand outward
MCLE: lesions start perimucosal, rarely expand inward
scarring: MMP >>> MCLE

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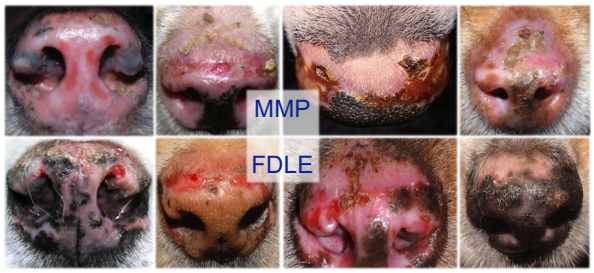
Canine MMP Mimic 2: Facial DLE



☞ *nasal MMP and FDLE are difficult to tell apart = look at other mucosae!*

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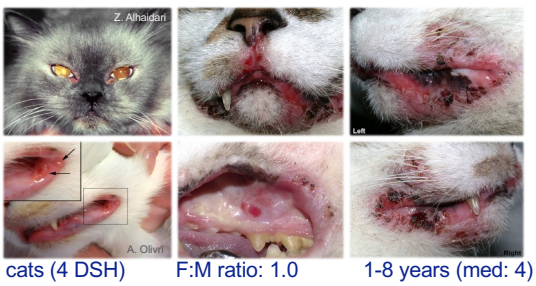
Feline MMP



6 cats (4 DSH) F:M ratio: 1.0 1-8 years (med: 4)

2 cats with high elevation of ALT!

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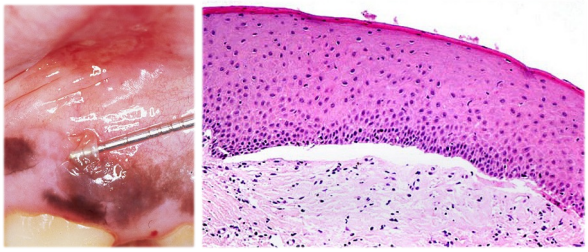
Canine MMP



subepidermal clefting: 50/56 (89%)

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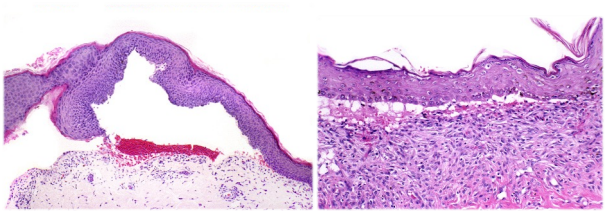
Canine and Feline MMP



subepidermal clefting with or without dermal fibrosis

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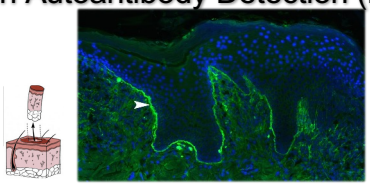
Canine MMP
Skin Autoantibody Detection (Direct IF)



linear deposition at the basement membrane zone

IgG	C3	IgM	IgA
52/56	33/44	19/40	13/30
93%	75%	48%	43%

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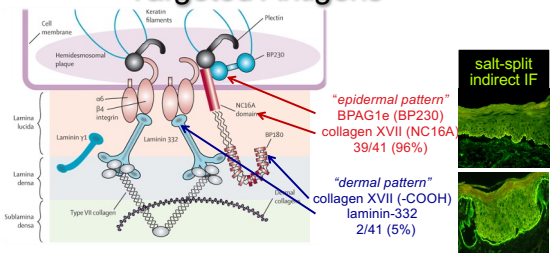
Canine MMP
Targeted Antigens



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Canine MMP
Treatment & Outcome

- –spontaneous remission: 0/23 (0%)
- –complete remission: 19/23 (83%)
- –treatment leading to complete remission:
  - prednisone alone: 1/15 (7%)
  - dapsone alone: 1/15 (7%)
  - cyclin + niacinamide ± other 9/15 (60%)
- –time to complete remission:
  - median: 31 weeks
  - range: 4 to 64 weeks

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Canine MMP
Treatment & Outcome

April 2002 February 2003

1. niacinamide + tetracycline for 5 months: no effect
2. prednisone + topical betamethasone 0.1% for 2 months: partial remission (50%)
3. prednisone + topical tacrolimus 0.1% for 3 months: complete remission

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Canine MMP
Treatment & Outcome

1. no response to prednisone, azathioprine, cyclosporine, colchicine
2. complete remission within 1 year of tetracycline and niacinamide

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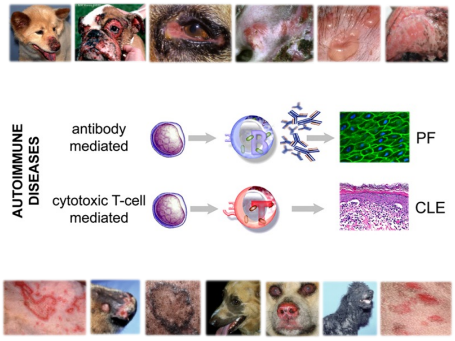

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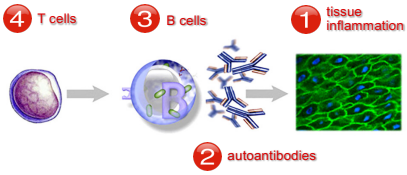
Therapeutic Targets
Antibody-Dependent Diseases



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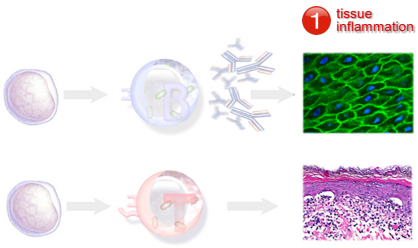
Therapeutic Targets



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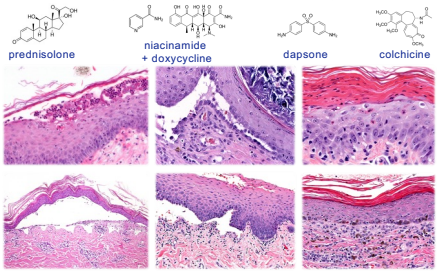
Therapeutic Targets
Tissue Inflammation



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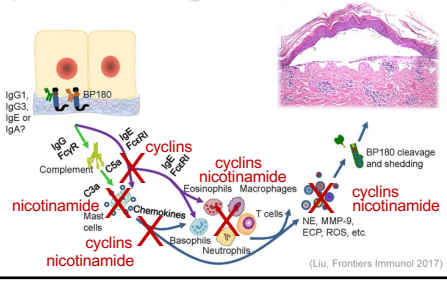
Human Bullous Pemphigoid
Proposed Pathogenesis: Skin Lesions



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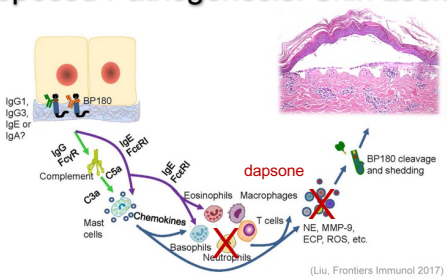
Human Bullous Pemphigoid
Proposed Pathogenesis: Skin Lesions



(Liu, Frontiers Immunol 2017)

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Canine and Feline MMP
Clinical Summary

- most common autoimmune subepidermal blistering disease in dogs and cats
- German shepherd dogs are likely predisposed
- vesicles, ulcers ± scarring affect principally the oral mucosa and other mucosae junctions
- chronic evolution with frequent recurrences
- complete remission achievable with combination therapy with cyclin antibiotics
- outcome appears favorable

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Epidermolysis Bullosa Acquisita (EBA)

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AI Subepidermal Blistering Diseases

	100		77		
	BP	69 %	MMP	48 %	
	MMP	12 %	EBA	26 %	#2
	LAD	5 %	BP	10 %	
	PG	4 %	LAD	3 %	
#5	EBA	2 %	PG	1 %	
	BSLE	2 %	BSLE	1 %	
	other or ?	6 %	other or ?	11 %	

(Bernard, Arch Dermatol 1995) (Olivry, Vet Dermatol 2014)

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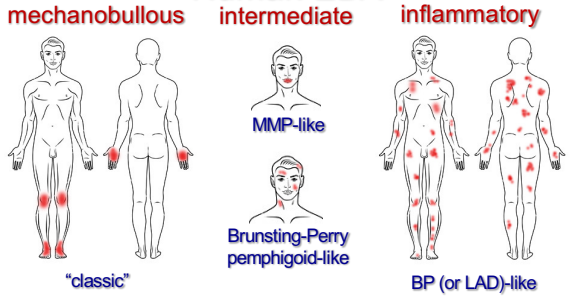
Human EBA



(inspired from Kim, J Eur Acad Dermatol Venereol 2013)

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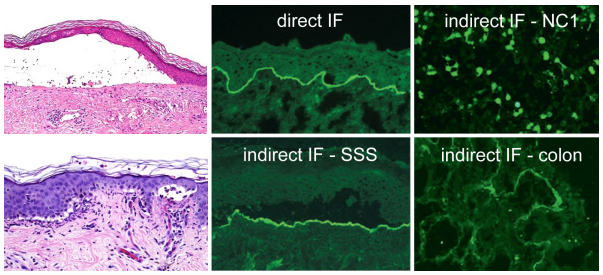
Human EBA

54

Human EBA



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Canine EBA
Historical Perspective

1998 1st report of inflammatory EBA in a great Dane
(Olivry, Vet Dermatol 1998)

2000 1st report of Brunsting-Perry localized EBA in a German shorthaired pointer (Olivry, Vet Rec 2000)

2015 report of 20 dogs (11 great Danes) with EBA
(Bizikova, Vet Dermatol 2015)

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Canine EBA
Signalment

– 24 dogs (USA: 19, Canada: 1, Europe: 4)
- 14 great Danes (58%)
- 3 German shorthaired pointers (13%)

– median (range) age of onset: 1.2 yr (0.3-8.0)
- 9 dogs had signs before 1 year of age (45%)

– male-to-female ratio: 2.3

(Bizikova, BMC Vet Res 2023)

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Canine EBA
Lesion Distribution

oral mucosal, areas of friction ± footpads

(Bizikova, BMC Vet Res 2023)

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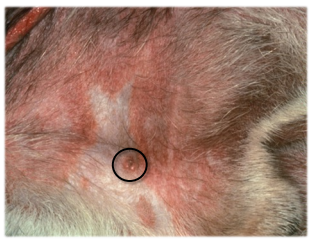
Canine Generalized Inflammatory EBA



erythematous macules and patches: 18/24 (75%)
erythematous papules and wheals: 10/24 (42%)

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Canine Generalized Inflammatory EBA

vesicles and bullae: 22/24 (92%)

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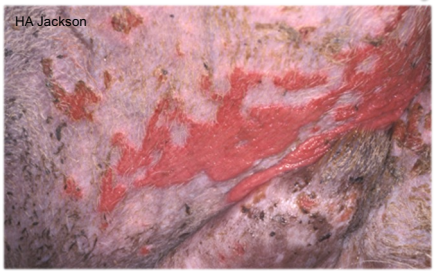
Canine Generalized Inflammatory EBA



deep erosions and ulcers: 24/24 (100%)

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Canine Generalized Inflammatory EBA

oral cavity: 22/24 (92%) lips: 19/24 (79%)

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Canine Generalized Inflammatory EBA

pinnae: 19/24 (79%)

63

Canine Generalized Inflammatory EBA

axillae, groin, pressure points, friction areas: 22/24 (92%)

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Canine Generalized Inflammatory EBA

footpads: 17/24 (71%)

65

Canine Generalized Inflammatory EBA

nasal planum: 12/20 (60%)

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Canine Localized EBA
"Brunsting-Perry Pemphigoid-Type"

German Shorthaired Pointer, M, 10 months

(Olivry, Vet Record 2000)

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Canine EBA

– presence of systemic signs: 17/18 dogs (94%)

- lethargy: 14/18 dogs (78%)
- fever: 7/18 dogs (39%)
- lymphadenopathy: 5/18 dogs (28%)
- anorexia: 4/18 dogs (22%)

(Bizikova, Vet Dermatol 2015)

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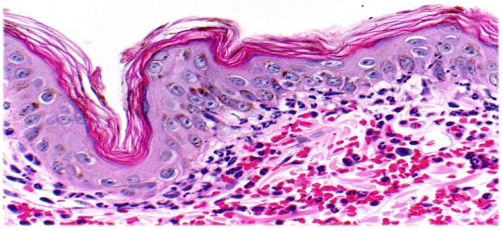
Canine EBA
Histopathology (Early Lesions)



alignment of neutrophils along the dermo-epidermal junction

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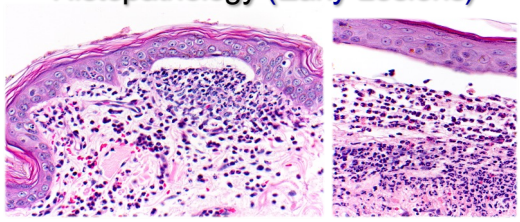
Canine EBA
Histopathology (Early Lesions)



perivascular to interstitial neutrophilic dermatitis: 17/17 (100%)
intravesicular neutrophils: 16/17 (94%)
intravesicular eosinophils: 7/17 (41%)

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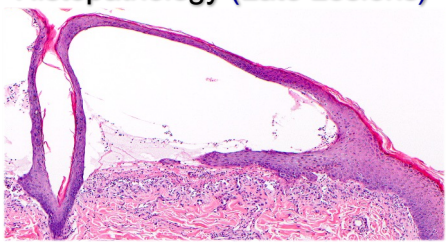
Canine EBA
Histopathology (Late Lesions)



subepidermal vesiculation with inflammation: 17/17 (100%)

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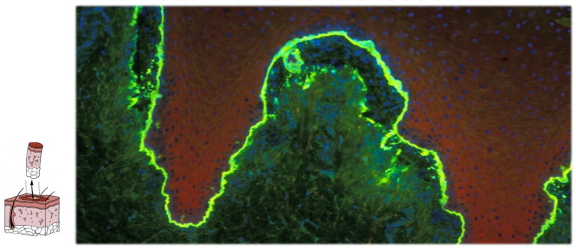
Canine EBA
Direct Immunofluorescence



IgG deposition along the basement membrane: 17/20 (85%)

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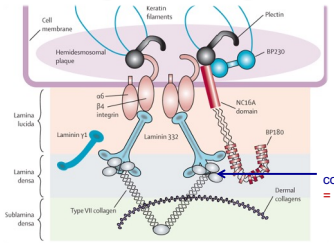
Canine EBA
Targeted Antigen



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Canine EBA
Treatment & Outcome

– spontaneous remission: 0/24 (0%)

– complete remission: 17/24 (71%)
- prednisone alone: 3/17 (18%)
- prednisone + immunosuppressant: 6/17 (36%)
- prednisone + colchicine: 1/17 (6%)
- prednisone + immunosup. + colchicine: .5/17 (29%)
- prednisone + immunosup + doxycycline: 1/17 (6%)
- dexamethasone + doxycycline: 1/17 (6%)

– median dosage of prednisone (mg/kg/d):
- as monotherapy: 4.0
- with adjuvant immunosuppressant: 2.7

(Bizikova, BMC Vet Res 2023)

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Canine EBA
Treatment & Outcome

– time to complete remission:
- median: 58 days
- range: 26 to 140 days

– long-term outcome:
- complete remission; off-medication: 8/17 (47%)
- complete remission; on colchicine: 7/14 (50%)
- complete remission; on azathioprine: 1/14 (7%)
- complete remission; on doxycycline: 1/14 (7%)

– euthanasia: 6/24 (25%)
- immediately after diagnosis: 1/6 (17%)
- because of lack of response to treatment: 5/6 (83%)

(Bizikova, BMC Vet Res 2023)

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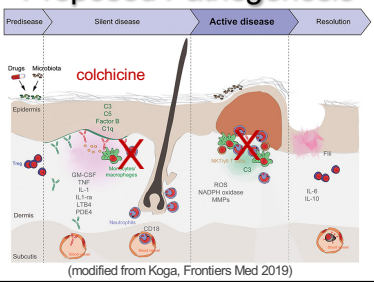
Human EBA
Proposed Pathogenesis



(modified from Koga, Frontiers Med 2019)

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Canine EBA
Summary

– 2nd most common canine autoimmune subepidermal blistering disease

– young adult male great Danes are likely predisposed

– blisters and erosions/ulcers affect the oral mucosa and areas of friction including footpads

– blister and dermal inflammation is rich in neutrophils

– treatment outcome appears more favorable than first reported

– add colchicine to EBA's treatment regimen!

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AI Subepidermal Blistering Diseases

① *look at your patient!*
- signalment (breed, age of onset)
- type of lesions (blisters, scars)

② *take multiple skin biopsies!*
- degree of blister/dermal inflammation (acellular, cell-rich)
- type of inflammation (neutrophils, eosinophils)
- degree of scarring

☞ *play the odds for the most likely diagnosis!*

☞ *treat accordingly*!

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Veterinary Dermatology

Vet Dermatol 2014; **25**: 316–318 DOI: 10.1111/vde.12152

An autoimmune subepidermal blistering skin disease in a dog? The odds are that it is not bullous pemphigoid

Thierry Olivry, *Vet Dermatol* 2014

In summary, for diagnosing AISBDs in dogs, as in other species, clinicians are to remain kings for years to come! The diagnosis of these diseases shall not, and never will be made from a blood test result.

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Bizikova *et al. BMC Veterinary Research* (2023) 19:55
https://doi.org/10.1186/s12917-023-03597-1

BMC Veterinary Research

REVIEW Open Access

Spontaneous autoimmune subepidermal blistering diseases in animals: a comprehensive review

Petra Bizikova[1*], Thierry Olivry[1], Keith Linder[2] and Jan Rybnicek[3]

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