

Supplementary File 1. Detailed PEDIAS In & Out framework for differential diagnosis in small animal practice

1. PEDIAS-OUT: External / Exogenous Causes

Purpose

Rapid identification and exclusion of causes originating outside the body before progressing to internal disease reasoning.

P – Physiological / Psychological / Behavioral

Examples:

- Growth-related polyphagia in puppies
- Estrus-related behavioral changes
- Stress-induced vomiting or diarrhea
- Fear or anxiety causing anorexia, aggression, or panting
- Motion sickness (e.g., travel-related vomiting)
- Rapid eating leading to regurgitation or vomiting

E – Environment / Weather / Exposure

Examples:

- Heat stroke due to high ambient temperature
- Cold exposure leading to hypothermia
- Environmental allergens (pollens, dust)
- Smoke inhalation
- Flea or tick exposure
- Insects and bugs (bites, stings, or ingestion)
- Envenomation (snake venom or insect toxins)
- Exposure to contaminated water or spoiled environmental sources

D – Diet / Drugs / Chemicals / Toxins (Oral Intake)

Examples:

- Sudden diet change causing gastroenteritis
- Dietary indiscretion (garbage ingestion)
- Food intolerance or allergy
- Chocolate, xylitol or toxin ingestion
- NSAID-induced vomiting or ulceration
- Antibiotic-associated GI upset
- Toxic plant ingestion
- Supplement imbalance
- Overnutrition / obesity-related imbalance

Foreign Material / Ingestion Risks:

- Linear and non-linear foreign bodies
- Bones, toys, fabric ingestion
- Gastric irritation from ingested material

Clinical Note: These ingestion-related causes may mimic internal disease and should always be ruled out early.

I – Iatrogenic / Induced

Examples:

- Sedation-related ataxia
- Injection site reaction
- Post-surgical complications (infection/inflammation)
- Drug side effects (e.g., steroids → polyuria/polydypsia, NSAIDs → GI signs)
- Chemotherapy-induced vomiting
- Handling-related trauma

A – Activity-related

Examples:

- Lameness after excessive exercise
- Muscle strain or ligament injury
- Exertional stress
- Reproductive stress

- Exertional myopathy/myoglobinuria following intense activity
- Heat/exercise-induced collapse

S – Signalment

(Species, breed, age, sex, reproductive status [intact vs neutered/spayed])

Examples:

- Brachycephalic airway disease (breed-related)
- Large breed predisposition to Gastric Dilatation and Volvulus
- Small breed predisposition to mitral valve disease
- Geriatric endocrine disease (e.g., diabetes mellitus, Cushing's disease)
- Young animals → parasites, parvovirus, congenital disorders
- Non-spayed females → pyometra, mammary gland tumors
- Breed-specific disorders (e.g., Intervertebral Disc Disease, cardiomyopathy)

Clinical Note:

Signalment is a powerful external filter that significantly narrows differentials early in the diagnostic process by incorporating species, breed, age, and reproductive status–associated risks.

Clinical Value of PEDIAS-OUT

- High diagnostic yield
- Frequently reversible causes
- Prevents unnecessary diagnostics
- Anchors reasoning in history and context

2. PEDIAS-IN: Internal / Endogenous Disease Processes

Purpose

Systematic evaluation of internal disease processes after exclusion of external causes.

P – Perfusion / Hemodynamic Disorders

Examples:

- Hypovolemic shock
- Cardiogenic shock

- Dehydration
- Anemia
- Thromboembolism
- Sepsis-related hypoperfusion

Key Principle:

Perfusion abnormalities are time-critical and can affect all organ systems.

E – Endocrine / Metabolic Disorders

Examples:

- Diabetes mellitus / diabetic ketoacidosis
- Hypothyroidism (dogs)
- Hyperthyroidism (cats)
- Hyperadrenocorticism
- Hypoadrenocorticism
- Electrolyte imbalance
- Uremia (renal disease)
- Hepatic metabolic dysfunction

D – Degenerative Disorders

Examples:

- Osteoarthritis
- Intervertebral disc disease
- Cognitive dysfunction
- Chronic kidney disease
- Chronic liver disease
- Degenerative cardiac disease

I – Infection / Inflammation (System-Based Scan)

A structured organ-system evaluation:

Systems Reviewed:

Head, eyes, ears, nose, and throat (including oral/dental), respiratory, cardiovascular,

gastrointestinal, hepatobiliary, renal/urinary, neurologic, musculoskeletal, reproductive, dermatologic, hematologic

Examples by System:

- **Respiratory:** pneumonia, bronchitis
- **Cardiovascular:** mitral valve disease, cardiomyopathy, heartworm disease
- **Gastrointestinal:** gastroenteritis, pancreatitis, inflammatory bowel disease, peptic ulcer
- **Oral/Dental:** periodontal disease, gingivitis, stomatitis
- **Urinary:** cystitis, pyelonephritis, Feline Lower Urinary Tract Disease
- **Skin:** pyoderma, fungal infection, parasitic disease
- **Neurologic:** meningitis, encephalitis
- **Systemic infectious causes:**
 - Viral (parvovirus, FeLV, FIV)
 - Bacterial (salmonella, sepsis)
 - Parasitic (roundworms, Giardia)
 - Fungal / oomycete (histoplasmosis, pythiosis)

Masses / Neoplasia (Within Systematic Review)

- Oral tumors
- Gastrointestinal neoplasia (e.g., lymphoma)
- Abdominal masses (hepatic, splenic)
- Cutaneous tumors
- Lymphadenopathy

Clarifying Principle:

Neoplasia is not treated as a separate category but must be actively assessed during organ-system evaluation.

A – Autoimmune / Allergic Disorders

Examples:

Immune-mediated systemic:

- Immune-mediated hemolytic anemia

- Immune thrombocytopenia
- Immune-mediated polyarthritis

Allergic conditions:

- Atopic dermatitis
- Food allergy
- Hypersensitivity reactions

Autoimmune dermatologic disorders:

- Pemphigus complex
- Systemic lupus erythematosus

S – Syndromes / Specific Disorders / Diseases

Examples:

- Idiopathic epilepsy
- Feline hyperesthesia syndrome
- Feline high-rise syndrome
- Brachycephalic airway syndrome
- Chronic vomiting syndrome
- Bilious vomiting syndrome
- Multifactorial dermatologic disease
- Functional GI disorders (e.g., ileus, dysautonomia)

3. Mnemonic Aids

PEDIAS-OUT Mnemonic

*“A **Psycho** living in an **Environment** of **Drugs** and **Iatrogenic Activity**, indicating a **Signal**.”*

- **P – Psycho** → **Physiological / Psychological / Behavioral**
- **E – Environment** → **Environment / Weather / Exposure**
- **D – Drugs** → **Diet / Drugs / Chemicals / Toxins**
- **I – Iatrogenic** → **Iatrogenic / Induced**
- **A – Activity** → **Activity-related**

- **S – Signal → Signalment**

PEDIAS-IN Mnemonic

“Perfused End of Degeneration and Infection through Auto-Syndrome.”

- **P – Perfused → Perfusion / Hemodynamic**
- **E – End → Endocrine / Metabolic**
- **D – Degeneration → Degenerative**
- **I – Infection → Infection / Inflammation**
- **A – Auto → Autoimmune / Allergic**
- **S – Syndrome → Syndromes / Specific Disorders / Diseases**

4. Table 1. Structured PEDIAS In & Out Clinical Application

Framework

Stage	P	E	D	I	A	S
PEDIAS-OUT	Physiological / Psychological / Behavioral	Environment / Exposure	Diet / Drugs / Toxins	Iatrogenic / Induced	Activity-related	Signalment
PEDIAS-IN	Perfusion / Hemodynamic	Endocrine / Metabolic	Degenerative	Infection / Inflammation (system-based)	Autoimmune / Allergic	Syndromes / Specific Diseases

5. Example – Vomiting (Structured PEDIAS Clinical Application)

When a patient presents with vomiting, a clinician should first apply **PEDIAS-OUT** to systematically rule out external and reversible causes before proceeding to internal disease processes using **PEDIAS-IN**.

PEDIAS-OUT (External Causes to Rule Out First)

- **P – Physiological / Psychological / Behavioral**

Rule out stress, fear, anxiety, motion sickness, or behavioral causes such as rapid eating or dietary indiscretion.

- **E – Environment / Exposure**

Assess for environmental triggers including heat exposure, husbandry related

- **D – Diet / Drugs / Toxins**

Evaluate recent diet change, spoiled food ingestion, food intolerance, foreign material ingestion, medications (e.g., NSAIDs, antibiotics), or toxins (e.g., chocolate, xylitol).

- **I – Iatrogenic / Induced**

Consider recent drug administration, anesthesia, chemotherapy, vaccination, or medical procedures.

- **A – Activity-related**

Assess recent exertion, travel, or stress-related triggers.

- **S – Signalment**

Consider age (young → parasites, parvovirus; older → neoplasia), breed predisposition, and species-specific risks, and reproductive status (spayed or intact).

If no clear external cause is identified, proceed to PEDIAS-IN

PEDIAS-IN (Internal Disease Processes)

- **P – Perfusion / Hemodynamic**

Evaluate for shock, dehydration, anemia, or systemic compromise affecting perfusion.

- **E – Endocrine / Metabolic**

Rule out:

- Uremia (renal disease)
- Diabetic ketoacidosis
- Hypoadrenocorticism
- Hyperthyroidism (cats)
- Electrolyte imbalances

- **D – Degenerative**

Consider chronic organ dysfunction:

- Chronic kidney disease
- Chronic hepatobiliary disease
- Chronic GI degeneration or motility disorders

- **I – Infection / Inflammation (System-Based)**

Include both gastrointestinal and systemic causes:

Gastrointestinal:

- Gastroenteritis
- Inflammatory bowel disease
- Pancreatitis
- Peptic ulcer disease

Infectious:

- Viral (e.g., parvovirus)
- Bacterial (e.g., salmonella)
- Parasitic (e.g., roundworms, Physaloptera)
- Fungal / oomycete (e.g., histoplasmosis, pythiosis)

Extra-GI inflammatory:

- Peritonitis
- Sepsis

- **A – Autoimmune / Allergic**

Consider:

- Food hypersensitivity
- Immune-mediated gastrointestinal disease

- **S – Syndromes / Diseases**

- Bilious vomiting syndrome
- Ileus / dysautonomia
- Motility disorders

Key Advantages

- Reduces missed external causes

- Improves diagnostic efficiency
- Decreases cognitive load
- Standardizes reasoning
- Enhances teaching