Septic Peritonitis

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Anatomy

Peritoneal cavity

- Sterile potential space lined with peritoneum
  - Serous membrane composed of single layer of mesothelial cells and thin layer of connective tissue – supports nerves, lymphatics, blood vessels
    - Visceral, parietal
- Peritoneal lining has a vast surface area (100-150% of BSA) and can result in substantial production and absorption of fluid
- Fluid production is due to hydrostatic and oncotic pressures of abdominal vasculature and mesothelial reflection coefficient
- Lymphatics in the diaphragm drain fluid to the thoracic duct
- Peritoneal capillaries and mucosal lining allow WBC, fibrin, fibronectin, fluid to enter abdominal cavity

Peritonitis Defined

- Aseptic peritonitis
  - Exposure to sterile abdominal fluids – bile, urine, gastric, pancreatitis enzymes, foreign material
  - Micro/macroscopic material – surgical glove powder, cotton swabs, sponges, hair, sticks, plant material, metal – may elicit a granulomatous response

- Primary peritonitis
  - Spontaneous inflammation in the absence of underlying pathology or penetrating injury
  - Hematogenous/lymphatic spread of infectious agents possible; transmural migration of bacteria from GIT
  - Facilitated by impaired host immune defense
    - FIP wet form most common
    - Case reports of salmonella, chlamydia, actinomyces, blastomyces, clostridium, candida, bacteroides

Peritonitis Defined

- Secondary peritonitis
  - Most common; polymicrobial
  - Intraperitoneal leakage of bacteria → GIT – ulceration (NSAID, steroids, neoplasia/non neoplastic infiltrative disease, gastrinoma, hepatic disease), FB perf, neoplasia, trauma, ischemic damage, dehiscence most common
    - Enterotomy – 3-12% dehiscence
    - R&A – 6-16% dehiscence
      - Increased risk for intestinal anastomosis leakage: Alb < 2.5, preoperative peritonitis, intestinal FB, intraop hypotension
    - Neoplasia LSA or carcinoma
      - 25% in cats
    - Linear FB 41%
  - Septic bile peritonitis, hepatic abscess, pyometra, septic uroabdomen, penetrating trauma, etc

Peritonitis Defined

- Culp JAVMA 2009 – Primary vs Secondary Peritonitis
  - Dogs
    - Primary:
      - Diarrhea more common
      - More gram-positive infections
      - If underwent surgery, were less likely to survive
    - Secondary:
      - Effusions more exudative
  - Cats
    - Primary:
      - More painful than in secondary peritonitis
      - More likely to have hypoproteinemia and hypoAlb
  - Survival
    - Primary: dogs 47%; cats 44%
    - Secondary: dogs 70%; cats 36%
    - No significant difference in survival rates

- <u>Tertiary peritonitis</u>
  - Persistent or recurrent peritonitis after adequate attempt has been made to control primary or secondary peritonitis

Pathophysiology

- Localized, mild, early cases – associated with local manifestations
  - Peritoneum, immune system, digestive systems involved
- Severe cases – local and systemic manifestations
  - Cardiovascular, urinary, endocrine systems also involved
- Locally – release of vasoactive substances (histamine, serotonin, cellular proteases, endotoxin) → increased capillary permeability and vasodilation, damage to peritoneum
- Inflammation results in fibrin deposition around site of injury and in within peritoneum + isotonic fluid shifts (3^{rd} spacing) → hemoconcentration
- Increased fluid volume has negative effect on bacterial clearance (leading to increased proliferation)
- Omentum moves toward areas of inflammation to increase oxygen tension, deliver WBC, absorb bacteria/debris/foreign material, isolate source of contamination
- SNS stimulation inhibits peristalsis → protective to prevent movement of contaminants within peritoneal cavity

Pathophysiology

- Intraperitoneal substances (gastric mucin, bile salts, Hgb) can worsen local or systemic inflammatory response
- Humoral opsonins, Abs, complement are activated with increased severity of the inflammatory response
- TNFa, IL1, IL6, PGE2, PAF released → leads cardiovascular consequences of SIRS/sepsis
- Acidosis can result from increased lactate production, decreased GFR, and hypoventilation from abdominal pain
- Lytes: hyperK, hypoNa
  - HyperK – secondary to cell death, NaK ATPase pump failure, respiratory/metabolic acidosis, decreased GFR
  - HyopNa – fluid shifts in abdomen, cellular sequestration, dilution of circulating blood volume (vasopressin – volume takes precedence over osmolality)
- More on SIRS, MODS, DIC elsewhere …

Sepsis Associated Pathophys – Cholestasis of Sepsis

- Liver has role in endotoxin and bacteria scavenging, detox, synthesizing proteins for metabolic, immune, coag function
  - Kupffer cells, hepatocytes, sinusoidal endothelial cells all play a role
- Septic shock – hepatocytes shift metabolic pathway to upregulation of inflammatory response, increase in APPs mediated by IL6
- Liver hypermetabolism - increased AA uptake and glycogenolysis and gluconeogenesis occurs
- Kupffer cells
  - Scavenge bacteria and endotoxin – liver has 80% of macrophage in body
    - Liver disease = decreased clearance
  - Produce various pro-inflam mediators and production of NO; induced by LPS
  - Can induce hepatocellular dysfunction, apoptosis
  - Interact with platelets, RBCs, leukocytes → NP recruitment to sinusoids and enhancing pro-inflam response
    - Hepatic injury can be worsened through adhesion of NPs to sinusoidal endothelial cells, promoting thrombi formation in sinusoids and impairing microvascular perfusion

Sepsis Associated Pathophys – Cholestasis of Sepsis

Causes of liver injury in sepsis:

- Hypoxic hepatitis
  - Compromised hemodynamics resulting in decreased CO and DO2, VO2
  - IRI can lead to oxidative stress → activation of KCs and recruitment and activation of systemic neutrophils that can perpetuate injury → sharp but unsustained increased in ALT and AST

Sepsis Associated Pathophys – Cholestasis of Sepsis

Causes of liver injury in sepsis…

- Cholestasis
  - Gram negative bacterial sepsis, septic shock
  - Bile acids play important role in maintaining get barrier integrity
  - Bile formation is oxygen intense and osmotically driven process → organic and inorganic molecules are moved through canalicular membrane and then water passively follows; correct functioning of integral membrane proteins is needed to excrete bile into canaliculi
    - Process impaired in sepsis because of lack of energy (hypoxia/hypoperfusion)
  - Endotoxin/pro-inflam cytokines cause direct impairment of bile flow through alterations of gene expression of acid transporters resulting in down regulation, direct inhibit of transporters, and alteration of cytoskeleton structure of hepatocytes resulting in disturbance of bile flow = intrahepatic cholestasis / hyperBili
  - Can lead to intestinal atrophy depriving gut of bacteriostatic neutralizing effects = increased endotoxin = viscous cycle
- HyperTbili reported in dogs and cats with SIRS and sepsis (Traboada JVIM 1989, Klainbert JAVMA 2017)
- Tx: none; ensure good perfusion, steroids may be helpful in restoring bile transport; enteral nutrition, ursodiol maybe

Sepsis Associated Pathophys – Sepsis Induced AKI

- Pre-renal and renal causes – abnormal renal blood flow, decreased GFR, ROS, tubular injury have been implicated
- AKI documented to occur in 12% of dogs with septic peritonitis – 14% of those surviving to discharge (Kenney JAVMA 2010)
  - Humans 47%
  - Failure to recognize in veterinary medicine
- Human literature – 3 grading/classification systems (RIFLE → modified to create AKIN → AKIN + RIFLE = KIDGO for unified criteria)
- IRIS – vet med
- AKI in sepsis shows marked reduction in kidney function with mild histo changes (patchy tubular changes with little evidence of necrosis – compared to ischemia or nephrotoxin induced AKI)

	Serum Creatinine	Urine output
STAGE 1	↑ sCr × 1.5–1.9 from baseline or > 26.5 µmol/L (>0.3 mg/dL)	<0.5 mL/kg/h for 6–12 h
STAGE 2	↑ sCr × 2–2.9 baseline	<0.5 mL/kg/h for ≥12 h
STAGE 3	↑ sCr × 3 baseline *or* ↑ sCr ≥353.6µmol/L (≥4.0 mg/dL) or initiation of renal replacement therapy	<0.3mL/kg/h for ≥24 h or Anuria for≥ 12 h

Sepsis Associated Pathophys – Sepsis Induced AKI

Causes (Keir JVECC 2015):

- Poor perfusion
  - Traditionally thought that low flow states due to cardiogenic, hemorrhagic, septic shock → global ischemia of kidneys
  - Global kidney perfusion may be normal or even increased but there may be abnormal distribution of blood flow within the kidney (flow favoring the cortex)

- Inflammation
  - Cells release DAMPs at site of sepsis → promote further proinflammatory response in DISTANT organs → activates immune cells in these organs (T cells, dendritic cells)

- Oxidative stress
  - ROS generated in sepsis can cause tubular injury
  - IRI

Sepsis Associated Pathophys – Sepsis Induced AKI

Causes…

- Epithelial dysfunction
  - Tubular dysfunction due to inflammatory response can result in LACK of NaCl resorption in the PCT → detected as increase in Na and Cl delivery to the macula densa in DCT → tubuloglomerular feedback results in widespread VASOCONSTRICTION (due to Cl in macula densa) in the afferent arteriole and subsequent drop in GFR
  - Disruption of tight junctions between renal tubular epithelial cells = back leakage of tubular fluid across epithelium → interstitial edema in kidney
  - Cell injury can result in loss of adhesion to basement membrane and shedding of epithelial cells into the tubular lumen → casts - can block renal tubules
    - Widespread tubular injury would need to be seen on histo and typically isn't
- Sublethal injury
  - If repair process is incomplete there may be persistent inflammation and the development of tubulointerstitial fibrosis → CKD

Sepsis Associated Pathophys - Hypocalcemia

Cause not fully understood but suspected to be related to:

- Hypoparathyroidism secondary to parathyroid gland dysfunction
- Cytokine-mediated suppression of PTH
- HypoMg
- Alkalosis
- Elevated procalcitonin concentrations
- Accumulation of Ca within tissues
- Intracellular redistribution of calcium
- Chelation with lactate, bicarb, other anions, chelation with phos
- Inhibition of renal 1α-hydroxylase due to increased phos concentrations → decreasing calcitriol synthesis and intestinal Ca absorption

Sepsis Associated Pathophys - Hypocalcemia

- Complications: myocardial depression, hypotension, arrhythmias, muscle weakness, coagulopathy
- Present in 16% of critically ill dogs, more likely to occur in dogs with sepsis, and associated with long hospitalization and ICU stays (Holowaychuk JVIM 2009)
- Present in 24% septic dogs and associated with increase in mortality (Luschini JVECC 2010)
- Associated with longer LOH and ICU stay but not overall survival to discharge, prevalence of hypotension, coagulopathy, or arrhythmias in cats; failure to normalize iHCa was a negative prognostic indicator (Kellett-Gregory JVECC 2010)

Sepsis Associated Pathophys - CIRCI

- Inadequate cellular corticosteroid activity for the severity of a patient's illness – recognized by persistent hypotension in euvolemic patients despite appropriate vasopressor therapy
  - Cortisol has important homeostatic effects on catecholamine production, adrenergic receptor function, and the immune system
- Basal serum cortisol concentration within or above the reference range but a blunted cortisol response after ACTH administration -- suggests that the adrenal cortex can make and release cortisol
  - Quantity of cortisol produced is inadequate for the degree of physiologic stress
- Suppression of the HPA axis by cytokines such as TNFa, IL6, corticostatic substances circulating in sepsis, or adrenal microvascular thrombi and hemorrhage
- Delta cortisol < 3mcg/dL after cosyntropin was associated with systemic hypotension and decreased survival in septic dogs (Burkitt JVIM 2007)
- See previous CIRCI BR notes…

Sepsis Associated Pathophys – Neutrophil Dysfunction

- Webb JVIM 2007
  - Decreased phagolysosomal oxidative burst from a heterogenous group of dogs with sepsis but increased opsonization of E.coli
  - Dichotomous role not fully understood - hypoinflammatory state may decrease the patient's ability to clear the offending microbes or it may protect the patient from an otherwise exaggerated and damaging inflammatory response

Sepsis Associated Pathyphys – Lipid Dysmetabolism

- Lipoproteins/HDL binds LPS and lipotechoic acid neutralizing it and preventing it from stimulating inflammatory cytokines from macrophage; maintains endothelial function and repair; mediates inflammatory response; prevents peroxide damage; stimulates eNOS
  - Endotoxemia results in rapid and marked decline in serum cholesterol
- Hypocholesterol during critical illness is multifactorial and due to downregulation of hepatic synthesis, dilutional effects, increased consumption
- Hepatic exposure to TNFa, IL6, IL-1, IL10 leads to decrease in synthesis of apoproteins; accelerated clearance of lipoproteins
- Apolipoprotein A1 (Apo-A1) is a major component of HDL and determinant of HDL formation – directly inactivates bacterial endotoxin
- Humans with sepsis – HDL are shifted to acute phase HDL which are enriched with SAA and depleted of cholesterol and Apo-A1 → decreased Apo-A1 (and hypocholesterolemia) has been associated with greater illness severity, lethality, susceptibility

Sepsis Associated Pathyphys – Lipid Dysmetabolism

- Hardy JVECC 2018
  - Mixed sepsis sample – 41% GI perf; 55% survival
  - Survivors had significantly higher cholesterol compared to nonsurvivors (245mg/dL vs 167 mg/dL)
  - Cholesterol cut-off 174mg/dL (Se 75%, Sp 50%)
  - Number of dysfunctional organs and cholesterol concentration were most significant predictors of survival
- Giunti Frontiers 2020
  - Mixed septic sample – parvo, peritonitis, pyo, misc
  - Serum Alb and Apo-A1 significantly lower in septic dogs – only dogs with septic peritonitis had lower Apo-A1 compared to healthy dogs
  - Overall survival 70% though septic peritonitis more likely to die
  - Lower Apo-A1 in non survivors compared to survivors (cut-off <0.96 g/L – 55.6% Se and 89.1% Sp to predict mortality)
  - Apo-A1 seems to behave as a negative acute phase protein
- Yilmaz JSAP 2007
  - Dogs with CPV had cholesterol, HDL, and LDL levels that were significantly lower than controls
  - HDL and cholesterol level were lower in non-surviving dogs than control
  - HyperTG in dogs with CPV but did not differ in survivors/nonsurvivors

Sepsis Associated Pathophys - MODS

- Kenney JAVMA 2010 – MODS in dogs with septic peritonitis
  - Renal, CV, resp, hepatic, hematologic, neurologic, GI, endocrine, immune systems affected - MODS = >2 organ systems affected
  - 57.9% dogs had sepsis due to primary nonneoplastic GI leak/perforation; 52.6% survival to discharge
  - Median number of organ systems affected 2; 78.1% had at least 1 system affected
  - MODS (>2) was diagnosed in 50%; mortality rate was 70% compared to 25% for dogs with <2 organ systems affected
  - Odds ratio for death increased as number of dysfunctional organ systems increased; odds of death significantly higher in dogs with >1 dysfunctional organ system than without organ system dysfunction
    - 60.5% had coag dysfunction; 49.1% hepatic dysfunction; 31.6% resp dysfunction; 17.5% had CV dysfunction; 12.3% had renal
  - Dysfunction of the resp, CV, renal, coag system significantly increased odds of death
  - Age, sex, GIT perf, hepatic dysfunction not associated with outcome

Clinical Signs

- History:
  - Recent surgery, medications, etc
- Signalment:
  - Cats – bacterial cholangiohep common cause of sepsis, icterus, abdominal pain in cats
  - Shelties – mucocele with rupture common
  - Labs…
- Signs:
  - Systemically ill – anorexia, vomiting, dull, lethargic (most common in primary and secondary peritonitis)
  - Abdominal pain; prayer position (less consistent finding in cats)
  - Progressive states of hypovolemic and cardiovascular shock
    - Injected or pale MM, prolonged CRT, tachycardia, weak pulses, hyper/hypothermia
- Cats…
  - Icterus in a sick cat with signs of CV instability → cardinal feature of sepsis or SIRS
  - Cats with severe sepsis: lethargy, pale MM, diffuse abdominal pain, tachypnea, bradycardia, weak pulses, anemia, hypoAlb, hypothermia, icterus (Brady JAVMA 2000)
    - Bradycardia cats (16% of septic cats Costello JAVMA 2004; 66% Brady JAVMA 2000)
    - Bradycardia + hypothermia = negative prognostic indicator
- Uroabdomen = may still urinate normally

Diagnostic Tests

- CBC: neutrophilia, left shift
  - Normal or low neut count may be present
- Chem:
  - Hypoalbuminemia (3rd space, negative APP)
  - Hypoglycemia
  - Hypocalcemia
  - Hypocholesterolemia
  - Elevated liver enzymes, Tbili
  - Azotemia
  - Hyponatremia / chloremia
    - Hypochloremia maybe a negative prognostic indicator in septic/SIRS cats (DeClue JAVMA 2011)
- Spec cPL – if AUS shows pancreatitis, confirm with Spec to ensure

Diagnostic Tests

- AXR: peritoneal effusion, pneumoperitoneum (rupture of viscous organ, previous sx, penetrating trauma, gas forming bacteria) – horizontal beam
- CXR to rule out concurrent disease/metastasis
  - Bicavitary effusion: increases mortality odds by 3x
- AFAST
  - Peritoneal effusion: difficult to detect on PE if small volumes are present, or if an animal is dehydrated → serial AFAST
- AUS

Peritoneal Effusion Analysis

- Peritoneal fluid analysis
  - Single abdominal paracentesis - positive for septic peritonitis in only 20% of animals with effusion volume of 3 mL/kg, but in 80% of animals with an effusion volume of 10 mL/kg

- Septic abdomen
  - Paired glucose
    - Peritoneal BG < 20mg/dL of whole blood BG (Bonczynski Vet Surg 2003)
      - Chemistry analyzer
    - Difference >38mg/dL – specificity, PPV, and accuracy improved for plasma vs peritoneal fluid and plasma vs peritoneal fluid supernatant (Koenig JAVMA 2015)
      - Handheld glucometer
  - Effusion lactate > 2mmol/L of peripheral lactate (dogs, not cats) (Bonczynski Vet Surg 2003)
  - Effusion lactate > 2.5mmol/L (dogs, not cats) (Levin JAAHA 2004)

- Uroabdomen
  - Effusion Cr > 2x peripheral
  - Effusion K >1.4x peripheral (1.9x cats)

Peritoneal Effusion Analysis

- Urine dipstick leukocyte esterase – 60-75% sensitive; 91-92% specific for detecting bacterial peritonitis in dogs (69% PPV) (Thomovsky Vet J 2014)
  - Negative test = re-direct to alternative causes of peritoneal effusion
  - Positive further diagnostic tests necessary
- Diagnostic peritoneal lavage – 22mL/kg warmed sterile saline
- Fluid cytology and culture
  - Examine for neutrophils, organic debris, and bacteria
  - If bacteria is phagocytized = more than 2 hours after the insult
  - Septic exudates
    - WBC - 7,000 (often >10,000) /µL (normal: <2500 cells/µL)
    - Total protein – >3.0 g/dL (normal: <2.0 g/dL)

Table 3. Sensitivity and Specificity of Laboratory Results for the Diagnosis of Septic Peritonitis in Dogs and Cats

Study	Result	Sensitivity	Specificity
Bonczynski et al[a]	Abdominal effusion glucose concentration <55 mg/dL	57% (dogs)	100% (dogs)
Bonczynski et al[a]	Peripheral blood glucose concentration >20 mg/dL higher than the abdominal fluid glucose concentration	100% (dogs), 86% (cats)	100% (dogs and cats)
Levin et al[b]	Abdominal fluid lactate concentration >2.5 mmol/L	100% (dogs), 67% (cats)	91% (dogs), 67% (cats)
Bonczynski et al,[a] Levin et al[b]	>2.0 mmol/L difference in the lactate values of abdominal fluid and blood samples	63% to 100% (dogs)	100% (dogs)

[a]Bonczynski JJ, Ludwig LL, Barton LJ, et al. Comparison of peritoneal fluid and peripheral blood pH, bicarbonate, glucose, and lactate concentration as a diagnostic tool for septic peritonitis in dogs and cats. *Vet Surg* 2003;32(2):161-166.

[b]Levin GM, Bonczynski JJ, Ludwig LL, et al. Lactate as a diagnostic test for septic peritoneal effusions in dogs and cats. *J Am Anim Hosp Assoc* 2004;40(5):364-371.

Table 87.1 Fluid analysis findings in patients with peritonitis [8,12].

Diagnosis	Fluid cytology	Fluid analysis	Intervention indicated
Uroabdomen	Suppurative inflammation, presence of bacteria if UTI is present	Fluid creatinine:serum creatinine >2.0 Fluid [K+]:serum [K+] >1.4 (dogs) or 1.9 (cats)	Depending on location of urinary tract rupture: emergency surgery, bladder/urethral catheterization, percutaneous drainage, or combination
Hemoabdomen	Hemorrhage (with erythrophagocytosis if subacute or chronic)	Hemorrhagic effusion with PCV/TS dependent on chronicity and peripheral PCV/TS	Surgery usually not necessary in traumatic hemoabdomen; surgery indicated in spontaneous/neoplastic
Bile peritonitis	Suppurative inflammation with bile pigment within macrophages or in the background; may be septic if bacteria in biliary tree	Fluid bilirubin:serum bilirubin >2.0	Emergency surgery
Pancreatitis	Non-septic suppurative inflammation		Medical management; rarely surgery may be necessary if abscess present
Septic peritonitis	Septic suppurative inflammation with intracellular microbes	Fluid TNCC >13,000/μl Serum glucose:fluid glucose >20 mg/dL Fluid lactate:serum lactate >1.5 mmol/dL	Emergency surgery

PCV, packed cell volume; TNCC, total nucleated cell count; TS, total solids; UTI, urinary tract infusion.

Hemostatic Profiles

- Heterogenous group of dogs with sepsis (deLaforcade JVIM 2003)
  - Lower PC and AT at presentation but not related to survival compared to control
  - Decreased PT/aPTT and increased D-dimers and FDPs

- Dogs with septic peritonitis (Bentley JVECC 2013)
  - AT below reference interval for survivors and nonsurvivors pre-op
  - PC below reference for 91% non survivors, 13% survivors pre-op
  - Pre-op PC >60% and AT activity > 41.5% was a predictor of survival
    - Loss of PC and AT = loss of anti-coag and anti-inflammatory activity
  - TEG pre-op: more survivors where hypercoag (higher K, alpha angle, MA, CI) – predictive of survival with PC and AT
    - MA was most specific predictor of survival
  - Nonsurvivors – hemostatic profile more consistent with a consumptive, decompensated state (of both pro and anticoagulant factors)
  - Survivors – hypercoag, less depletion of AT → compensated procoagulant state

Hemostatic Profiles

- Feline coagulation parameters and sepsis (Klainbart JAVMA 2017)
  - Mixed septic sample; 63% survival rate
  - Prolonged aPTT, lower median AT and CP activity, higher D-dimers as compared to healthy controls
    - Not associated with nonsurvival
  - 4/22 (18%) were classified as being in DIC; not associated with survival

Biomarkers / Prognostic Indicators

- **HypoAlb** associated with mortality (Bentley JVECC 2007; Grimes JAVMA 2011)
- **HypoiCa**
  - Dogs
    - Found in 24% of septic dogs and associated with increase in mortality (Luschini JVECC 2010)
    - HypoiCa in critically ill dogs, more likely to be septic and associated with longer hospitalization and ICU stay (Holowaychuk JVIM 2009)
  - Cats (Kellett-Gregory JVECC 2010)
    - If hypoiCa did not normalize they were less likely to survive; overall survival 56%
    - HypoiCa was identified in 89% of cases at time of diagnosis and in 93% of cats at some time during hospitalization
    - LOH and duration of ICU stay correlated with lowest iCa during hospitalization
- **Lactate** (Cortellini JVECC 2014)
  - Lactate > 2.5mmol/L on admission was associated with mortality; >4 was significantly associated with mortality (92% specific for nonsurvival)
  - Inability to normalize lactate within 6 hours of admission was 76% sensitive and 100% specific for nonsurvival
  - Persistent post-op hyperlactatemia (>2) was associated with mortality; 46% sensitive and 88% specific for non survival
  - Lactate clearance < 21% at 6 hours and <42% at 12 hours prognostic indicator for nonsurvival

Biomarkers / Prognostic Indicators

- Hyperglycemia - Scotti JVECC 2019
  - Higher in non-surviving septic cats
- CRP - Gebhardt JVECC 2009
  - No difference in CRP levels in dogs with sepsis vs nonseptic SIRS
  - Surviving dogs showed significant decrease in CRP; change in CRP from day 0-2 predicted odds of survival; however false positive in 22%
- TNFa, IL6, IL10 - DeClue JVIM 2012
  - Plasma TNF, IL-6, CXCL-8, and IL-10 measured at ICU presentation do not appear to be valuable biomarkers to differentiate sepsis from nonseptic SIRS, or predict hospital outcome in dogs
- Ang-2 and VEGF – Konig JVIM 2018
  - Ang-2 could differentiate healthy from sick dogs (higher in nonsurvivors) but not from SIRS v septic; better at differentiating healthy from sick than VEGF
  - Ang-2 may be a promising diagnostic and prognostic biomarker

Biomarkers / Prognostic Indicators

- TNFa, IL6, IL1b, CXCL-8 - DeClue JAVMA 2011
  - TNFa higher in septic cats than healthy controls
  - IL6 higher in septic cats than cats with nonseptic SIRS; higher levels associated with nonsurvival
  - IL1b no different between septic and nonseptic SIRS cats, but increased concentrations were associated with nonsurvival
  - CXCL-8 not detectable is most cats

- Procalcitonin – Troia BMC Vet Res 2018
  - Dogs with sepsis had higher plasma PCT concentrations, though some overlap
  - May be more specific for severe sepsis or septic shock
  - High PCT clearance at 24hr and decreased PCT concentration from baseline was found in survivors
  - Clearance was low in nonsurvivors – persistently increased concentration may alert to possible treatment failure, persistent organ dysfunction, new infection

Biomarkers / Prognostic Indicators

- Procalcitonin, cell-free DNA nucleosomes, lactate, CCL2, IL6, IL10, glucose (Martiny Frontiers 2019)
  - The only significant difference in blood biomarker concentrations was for CCL2; significantly greater in dogs with SP compared to nonseptic ascites
  - Dogs with SP – concentration of glucose, cfDNA, nucleosomes, PCT, CCL2, IL-6, IL-10, and KC-like were significantly different between blood and effusion
    - Dogs with NSA - IL-6 and KC-like concentrations were different between blood and effusion
  - Dogs with SP had significantly greater effusion CCL2, IL-6, IL-10, and lactate concentrations than dogs with NSA
  - There was a high concentrations of cfDNA and nucleosomes in the peritoneal effusions of dogs with SP
    - Suggests NET release was occurring in the peritoneal cavities of these dogs
  - Blood-effusion concentration gradients of CCL2, glucose, IL-6, IL-10, and lactate were significantly different in dogs with SP compared to dogs with NSA
  - Effusion lactate concentration had the highest AUROC value → effusion lactate of 4.2 mmol/L was 72.2% sensitive and 84.2% specific for the diagnosis of SP

Biomarkers / Prognostic Indicators

- HMGB-1, CCL2, IL6, CXCL8, KC-like cytokines – Goggs JVECC 2019
  - Dogs with sepsis have significantly increased concentrations of HMGB-1, IL-6, CXCL8, and KC-like
  - Increased CCL2 concentration is a negative prognostic indicator in dogs with sepsis
- Cell free DNA - Letendre JVECC 2018
  - High cfDNA concentrations relative to neutrophil count are associated with nonsurvival
- Feline biomarkers of sepsis – Troia Frontiers 2020
  - IL-6, IL-8, KC-like, and RANTES were most discriminating for sepsis in cats but had no prognostic value, and they were not reflective of sepsis severity

Treatment

- Identify source / source control
- Fluid therapy:
  - Correct hypovolemia and metabolic changes (isotonic crystalloid; synthetic colloids – not recommended in septic humans)
  - Avoid volume overload – at risk due to vascular permeability, hypoproteinemia
- pRBC and plasma may be needed
  - Maintain PCV > 20-25%, Alb 3.5 g/dL and osmotic pressure > 16mmHg

Treatment - Fluids

Natural colloids

- FFP – large volume may be needed to provide albumin and oncotic support (20-25mL/kg to raise Alb 0.5mg/dL); costly
- Cryopoor plasma (CPP) for albumin replacement
  - Plasma partially thawed and spun – supernatant removed
    - No vWF, FVIII, FXIII, fibrinogen, fibronectin
  - Case report (Ropski JVECC 2017) – dog with septic peritonitis experiencing high rate of abdominal effusion
    - Developed low effective circulating volume and interstitial fluid overload with low UOP
    - Treated with HES, FFP, then CRI CPP → 1.1-2.2mL/kg/hr
      - 58 units over 9 days – 10.2L
  - CPP CRI in critically ill, hypoalbuminemic dogs (Culler JVECC 2019)
    - 70% of patients were septic; 71% of those had septic peritonitis (5/7)
    - Median total dose of CPP was 31mL/kg; median duration was 16 hours; mean rate of administration was 1.8mL/kg/hr
    - Mean Alb pre CPP was 1.5mg/dL and 2.1 mg/dL post – significant
  - May be viable option for treatment of hypoAlb, less expensive, don't need clotting factors

Treatment - Fluids

- Canine specific albumin (Craft JVECC 2012)
  - Transfusion of 5% CSA resulted in increase in Alb, COP, and Doppler BP 2 hours after and Alb increase persisted for 24 hours
  - Found to be safe with minimal adverse events
- Human albumin (Mazzaferro JVECC 2020)
  - Anaphylactoid and type III sensitivity documented in initial studies in healthy dogs (anti-human Alb Abs)
  - Mild reactions previously reported in critically ill dogs
  - CUVS case report – type III glomerulonephritis and AKI secondary to human serum Alb administration in 2 critically ill dogs (both septic peritonitis) → dogs presented with signs of serum sickness (fever, lethargy, lameness, angioedema, vomiting, urticaria, joint swelling, vomiting, hyporexia), progressed to oligoanuric AKI

Treatment - Antibiotics

- Empirical selection to start
  - Often polymicrobial - E coli, clostridium, enterococcus common
  - B-lactam + aminoglycoside or fluroquinolone; metro may be considered
    - Risk of AKI – aminoglycoside not ideal
    - Fluroquinolone – emerging resistance
    - Metro – does not greatly increase coverage beyond spectrum of B-lactams (added coverage for Bacteroides)
  - Humans – trending toward single agent therapy → third generation cephalosporin +/- metronidazole

Treatment - Antibiotics

- Appropriate antibiotic selection: at least 1 of the Abx included in the empirical antimicrobial treatment plan given within the first 24 hours of diagnosis is effective against the pathogen(s) isolated based on antimicrobial susceptibility testing
    - Dickinson JVECC 2014
        - Abdominal surgery and Abx in the 30 days prior to septic peritonitis were significantly associated with inappropriate Abx selection but did not affect survival
        - Clavamox > fluoroquinolone, cefuroxime most common
        - Multimodal empiric Abx was not associated with improved outcome nor increased likelihood of appropriate empirical Abx selection
        - Empiric Abx selection was considered appropriate (no resistance) in 52.6% of cases
        - Most common were Clavamox/Unasyn, cefuroxime, FQ (same for most common inappropriate Abx)
        - No difference in survival for dogs receiving appropriate empirical Abx (58.5%) or not (52.6%)
    - Scotti JVECC 2019
        - Cats treated with appropriate Abx 4.4x more likely to survive

Treatment - Antibiotics

- Antibiotic protocols (Abelson JVECC 2013)
  - Developed based on SSCG recommendations / survival benefit for early Abx administration
    - Kumar 2006 – each hour of delay of appropriate Abx increased mortality rate by 7.6%
    - Delay in Abx by 6 hours – 43% survival vs 79.9% survival if given within 1 hour
  - Development of an antibiotic protocol for ER doctors and readily available Abx helped shorten time to Abx administration in dogs with septic peritonitis
  - No difference in survival in the pre vs post protocol group (6 hr vs 1 hr)
  - Did not affect intra-op culture results

- How long to give – not really clear (Keir JVECC 2015)
  - Often discharged with 7-14 days of Abx for septic peritonitis
  - Human medicine shorter duration of Abx results in clinical outcome comparable to patients treated longer
  - Development of biomarkers may help guide length of treatment
    - CRP used to guide treatment of pneumonia (Viitanen JVIM 2017)

Table 1. Antibiotics and Dosages Recommended for Treating Dogs and Cats With Septic Peritonitis[4]

Drug	Dosage	Antimicrobial Coverage
Ampicillin	20–40 mg/kg IV q8h	G+: ++ G–: + Anaerobes: +
Cefaxolin	20 mg/kg IV q8h	G+: ++ G–: ± Anaerobes: +
Cefotaxime	20–80 mg/kg IV or IM q8h	G+: + G–: ++ Anaerobes: +
Ceftiofur	2.2–4.4 mg/kg SC q12h	G+: ++ G–: ++ Anaerobes: +
Enrofloxacin	5–20 mg/kg IV q24h	G+: ++ G–: ++
Amikacin	10–15 mg/kg IV q24h	G+: ++ G–: ++
Metronidazole	10 mg/kg IV q8h	Anaerobes: ++

G+ = gram positive, *G–* = gram negative.

Table 91-6 **Commonly Used Constant Rate Infusion Vasopressor Therapy**

Vasopressor	Dose rate
Norepinephrine	0.1-2 mcg/kg/min IV
Vasopressin	0.5-5 mU/kg/min IV
Dopamine	5-15 mcg/kg/min IV

Vasopressors

Beta blockers

- Early SIRS and sepsis – tachycardia due to hypovolemia, low systemic vascular resistance = appropriate increase in HR to maintain CO → overtime autonomic dysfunction, myocardial depression, vascular hypo reactivity may develop
- Persistent tachycardia despite treatment of hypovolemia, anemia, pain, agitation has been shown to increase risk of cardiac adverse events
  - Increased myocardial oxygen demand, decreased diastolic filling and coronary perfusion
- Esmolol has been shown to result in decreased morbidity and mortality in people with septic shock
- Beta blockade provides rate control and may have effects on lipid and glucose metabolism, glucose homeostasis, cytokine expression, myocardial function in SIRS/sepsis
- Santoro Beer JVECC 2019 – case report; used in 2 dogs with persistent tachyarrhythmias

Pain Management

- Pain management – multimodal
  - Pain can be severe – abdomen has a large number of sympathetic pain fibers
- Opioid + ketamine + lidocaine
  - Opioids can cause ileus, resp depression, urine retention
  - Combo therapy can reduce doses and thereby adverse effects
- Lidocaine – Bellini JAVMA 2016
  - Dogs getting lidocaine + opioids intra-op had improved short term survival (48 hours) than those with opioids only (2mg/kg bolus then 50 mcg/kg/min)
  - Lidocaine has analgesic, immunomodulatory/anti-inflammatory and anti-endotoxin effects
- Epidurals / epidural catheterization may be considered

Table 3. List of cut-off points with the sensitivity, specificity, and accuracy for hospital mortality at ICU admission

Parameters upon ICU admission	Cut-off points	Sensitivity	Specificity	Accuracy
$ScvO_2$ (%)	52	64.5%	100%	83.3%
Lactate	3.15	63.6%	84.2%	76.7%
(mmol/L)	3.50	54.5%	89.5%	76.7%
Base deficit	−9.5	100%	68.4%	80%
(mmol/L)	−14.5	72.7%	84.2%	80%
	−15.5	63.6%	89.5%	80%
	−16.5	54.5%	94.7%	80%

EGDT

- Conti-Patara JVECC 2012
- Goal directed therapy - clinical parameters, ScvO2, lactate, base deficit
  - Dog with severe sepsis / septic shock secondary to pyometra
- Admission ScvO2, lactate and BD were associated with non-survival
- ScvO2 and BD best discriminators of survival vs nonsurvival
  - Higher ScvO2 and lower BD – lower probability of death

HAT Therapy

- No studies sufficiently evaluating Vit C/ascorbic acid supplementation in critical illness; no harm in human medicine though unknown in veterinary (Gordon VCNA 2020)
- Thiamine – could not find any data
- Hydrocortisone – hypotension not responsive to fluids or vasopressors
  - Discussed in previous CIRCI BR

Source Control - Lavage

- Remove source / surgery
- Abdominal lavage with sterile saline
  - Remove all fluid - accumulation can impair opsonization and clearance
  - How much to lavage?
    - 200-300mL/kg (extrapolated from human literature)
- Marshall JVECC 2019 – culture pre/post lavage
  - 92.5% pre-lavage had positive culture growth, 87.5% had growth post lavage despite source control and sterile lavage
  - Resistance in 57.1% of organisms in pre-lavage and 67.5% in post lavage (MDR in 33% pre and 14.3% post) – E. coli, C. perfringens, E. faecalis, S. intermedius
    - May have been impacted by pre-operative abx use
  - Of the 40 dogs, 20 had new bacterial isolates identified post-lavage (contamination, effusion not evenly distributed, biofilm)

Source Control - Drains

- Open drainage
  - Used when unsatisfactory debridement occurs or significant effusate is anticipated; anaerobic infections
  - Closure 3-5 days later
  - Cons: massive fluid and protein loss, super infection, nosocomial infection, evisceration, bowel desiccation, labor intensive bandage changes, difficult to quantify fluid losses
- Vacuum assisted peritoneal drainage
  - Reduces amount of fluid lost and number of dressing changes
  - Nosocomial infections and hypoproteinemia are noted complications (Cioffi JVECC 2012)
- Jackson Pratt / closed suction drains
  - Dogs treated with closed suction drains had higher blood pressure than those with open drains (Mueller JAVMA 2001)
  - Pros: decreased risk for nosocomial infection, minimized risk of visceral herniation, reduced labor, can quantify output, no need for second surgery
  - Cons: fenestrated drain can be sealed by omentum, may only drain localized area of peritoneal cavity, frequent emptying needed, patient may still become hypoproteinemic and ascending infection can still occur

Post-op Care

- GI support
  - Anti-nausea/emetics
  - Prokinetics (metoclopramide, azithromycin, erythromycin, ranitidine)
  - PPIs – at risk of ulcers secondary to poor perfusion
- Nursing care
  - U-cath
  - Drain care
  - Recumbency care
  - PROM
  - Eye lubricant

Post-op Care - Nutrition

- Enteral preferred to parenteral
  - Helps restore proteins
  - Feeds enterocytes
  - Maintains tight junctions between epithelial cells
  - Stimulates blood flow
  - Releases endogenous trophic agents (cholecystokinin, gastrin, bile salts)
  - Reduces villous atrophy
  - Supports IgA producing lymphocytes in GALT
- Failure to meet nutritional demand → impaired wound healing and immune defenses
  - Better outcomes in dogs with parvo, pancreatitis if fed early
- G-tubes can be placed at time of surgery and facilitates earlier feeding; limited complications (Hansen JVECC 2019)

Post-op Care - Nutrition

- Early feeding within 24 hours after surgery (EN or PN) in dogs with septic peritonitis = earlier discharge by 1.6 days (Liu JVECC 2012)

- Smith JVECC 2019
  - Dogs that received PN only were less likely to survive and likely to be in hospital longer than dogs eating voluntarily (sicker population)
  - For each day without caloric intake in any form, LOH increased by 0.6 days (but not significant)
  - Patient's receiving PN +/- tube feeding had higher percentage of RER earlier in the course of nutritional support than those eating voluntarily but LOH and survival were not improved

- Lipids are preferred calorie source in sepsis but provision of ILE is controversial → when lipids exceed clearance capacity of lipoprotein lipase they accumulate in the reticuloendothelial system → suppress macrophage and immune function

Recurrent Secondary Septic Peritonitis

- Risk factors:
  - Preoperative hypoalbuminemia (Barfield JVECC 2016)
    - Survival in recurrent SSP was 49%
  - Preoperative septic peritonitis was more likely to result in intestinal R&A dehiscence
    - (11.4% of cases, 6.6% w/o PSP, 21.1% w/ PSP) (Davis Vet Surg 2017)
  - Indication for R&A did not influence the risk of dehiscence (Davis Vet Surg 2017)
  - Stapled anastomoses are less likely to dehisce in dogs with preoperative septic peritonitis (stapled 9.7%, hand-sewn 28.9%) (Davis Vet Surg 2017)

Recurrent Secondary Septic Peritonitis

- Fink JVECC 2020
  - Survival rate for first laparotomy was 78%
  - 15/149 dogs (10%) developed RSSP
    - Survival for RSSP was low – 8 euthanized, 3/7 re-Sx dogs survived (20%)
  - 93/149 (62.4%) had GI sepsis (36 were GIFB; 16 were linear)
  - Risk factors for RSSP
    - Significantly lower pre-op albumin (1.8mg/dL RSSP vs 2.2mg/dL noRSSP)
    - Significantly higher pre-op PCV (52% vs 45%)
    - Sepsis due to GIT (87%) – 4.4x more like to develop RSSP than dogs with sepsis of non GI origin
    - GI sepsis related to FB – 7.2x more likely to develop RSSP than GI sepsis due to other causes
      - Linear FB not more likely in this study
      - Mixed evidence for whether presence of GIFB caries a more favorable prognosis or not
        - GIFB can cause thrombosis and edema of the intestinal wall which may contribute to poor healing
        - Linear FB – micro perforations along mesenteric border can be missed
  - Median time to re-laparotomy was 3.1 days

Prognosis

- Depends on underlying cause
- Overall survival rate ranges 44-87.5% (dogs); cats up to 70% - most studies around 50%
  - Aseptic bile peritonitis survival rate 87-100%; septic bile peritonitis survival was 27-45%
  - Cats with uroperitoneum 62% survival rate
- Death usually due to refractory hypotension, DIC, MODS in immediate postoperative period
  - Survivors tend to have higher BP on presentation and intra/post-op; lesser vasopressors; higher Alb and pH; less prolonged aPTT
- Hypothermia and bradycardia in cats (though not noted in all studies), and inappropriate Abx and hyperglycemia associated with nonsurvival
- HypoiCa or failure to normalize iCa associated with mortality, longer hospitalization
- Lactate >4mmol/L on presentation, persistent post-op hyperlactatemia, decreased clearance/failure to normalize associated with nonsurvival

Prognosis

- Few differences overall in treatment of dogs with septic peritonitis from 1988-1993 to 1999-2003 (Bentley JVECC 2007)
  - Survival rate the same
  - More fluoroquinolones instead of aminoglycosides
  - Survivors had greater number of abx

Questions?