Septic Peritonitis (MONDO:0005195): A Comprehensive Disease Characterization Report

Summary

Septic peritonitis is a life-threatening bacterial infection of the peritoneal cavity, most commonly arising as *secondary* peritonitis from disruption of the gastrointestinal tract (perforation, ischemia, dehiscence, or penetrating trauma). Contamination of the normally sterile peritoneum with polymicrobial gut flora triggers a dysregulated innate-immune response—pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS) activating resident peritoneal macrophages and mesothelium via Toll-like receptor/NF-κB signaling, releasing a cytokine cascade (TNF-α, IL-1β, IL-6, HMGB1) with massive neutrophil recruitment. When this response becomes systemic and dysregulated, it produces **sepsis**—defined by Sepsis-3 as "life-threatening organ dysfunction caused by a dysregulated host response to infection"—and can progress to septic shock and multiple organ dysfunction syndrome (MODS). The **abdomen is the second most common source of sepsis**, and intra-abdominal infections carry hospital mortality of 23–38%, rising above 80% in severe complicated intra-abdominal sepsis (SCIAS).

This report is derived from **aggregated disease-level resources** (clinical guidelines, cohort studies, systematic reviews, and experimental model literature)—not individual patient EHR records. Importantly, septic peritonitis is an **infectious/mechanical disease, not a Mendelian genetic disorder**: it has no causal gene, no inheritance pattern, no pathogenic variant class, and no vaccine. Genetic contributions are limited to polygenic host-susceptibility modifiers of the sepsis response. Consequently, several sections of the standard disease template (causal genes, pathogenic variants, chromosomal abnormalities, repeat-expansion testing, genetic counseling) are **not applicable** and are marked as such.

The two therapeutic pillars are **source control** (surgical debridement, drainage, removal of infected devices, decompression) and **early broad-spectrum empiric antibiotics with resuscitation**. Source control is the dominant determinant of survival: in postoperative intra-abdominal infection, eliminating the infection source reduced mortality from 100% to 19%.

The landmark STOP-IT trial showed that ~4 days of antibiotics suffice after adequate source control. Septic peritonitis is also a **common, high-mortality naturally occurring disease in dogs and cats** (overall mortality ~64% in GI-perforation cases), where it is elegantly diagnosed by a **blood-to-peritoneal-fluid glucose difference >20 mg/dL** (100% sensitive/specific in dogs). The gold-standard experimental model is **cecal ligation and puncture (CLP)** in mice.

---

1. Disease Information

Overview. Septic peritonitis is inflammation of the peritoneum (the serous membrane lining the abdominal cavity and viscera) caused by bacterial infection, most often following breach of a hollow viscus. It is a form of **intra-abdominal infection (IAI)** and, when the host response becomes dysregulated, of **abdominal sepsis**. Intra-abdominal infections "account for a major cause of morbidity and mortality, representing the second most common sepsis-related death with a hospital mortality of 23-38%" (PMID: 39200076).

Key identifiers. - **MONDO:** MONDO:0005195 - **MeSH:** Peritonitis (D010538) - **ICD-10:** K65 (Peritonitis); K65.0 (Generalized/acute peritonitis); K65.1 (Peritoneal abscess); K65.9 (Peritonitis, unspecified) - **ICD-11:** DC50 (Peritonitis) - **SNOMED CT:** 48661000 (Peritonitis); 65119005 (Bacterial peritonitis) - **OMIM / Orphanet:** Not applicable — septic peritonitis is an acquired infectious/surgical condition, not a Mendelian or rare genetic disease, so it has no OMIM phenotype number and no Orphanet ORPHA code.

Synonyms / alternative names. Bacterial peritonitis; suppurative peritonitis; secondary peritonitis (most relevant subtype); acute bacterial peritonitis; purulent peritonitis; abdominal sepsis / intra-abdominal sepsis (when systemic); surgical peritonitis. Related but distinct: spontaneous bacterial peritonitis (SBP, the *primary* form), tertiary peritonitis.

Source of information. Aggregated disease-level resources — clinical guidelines (WSES, Surviving Sepsis), retrospective and prospective cohort studies, systematic reviews, and experimental animal-model literature.

---

2. Etiology

Primary causal factors — infectious and mechanical. The proximate cause is **microbial contamination of the sterile peritoneal cavity**, overwhelmingly from a breach of the gastrointestinal tract. "Secondary peritonitis is a life-threatening intra-abdominal condition arising from gastrointestinal perforation, chemical injury, or catheter-related infections" (PMID: 41227298). Common precipitating lesions include perforated peptic ulcer, perforated appendicitis, perforated diverticulitis, bowel ischemia/necrosis, anastomotic dehiscence after GI surgery, penetrating/blunt abdominal trauma, and perforated malignancy. The infection is typically **polymicrobial**, reflecting gut flora (*Escherichia coli* and other Enterobacterales, *Bacteroides fragilis* and anaerobes, enterococci; *Candida* in upper-GI perforation).

Genetic risk factors. There are **no causal Mendelian variants or established susceptibility loci** specific to septic peritonitis. As an acquired infection, risk is governed by the anatomical lesion and by polygenic host modifiers of the innate-immune/sepsis response (e.g., variants in TLR4, TNF, IL-6 pathways have been studied in sepsis generally, but none are diagnostic or actionable for peritonitis). This section is largely **not applicable**.

Environmental / clinical risk factors. - **Medications:** Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids promote GI ulceration/perforation. In companion animals, "administration of anti-inflammatory drugs in dogs and cats is a significant risk factor for pyloric perforation" (PMID: 24283417). - **Comorbidities:** diabetes mellitus, immunosuppression, malignancy, diverticular disease, peptic ulcer disease, cirrhosis (predisposes to the primary/SBP form). - **Procedural:** recent abdominal surgery, peritoneal dialysis catheters, foreign-body migration (e.g., grass awns in animals; PMID: 36874536). - **Demographic:** advancing age (higher perforation and mortality risk).

Protective factors. No genetic protective variants are established. Protective/beneficial factors are effectively **preventive and therapeutic**: prompt surgical source control, early appropriate antibiotics, and management of predisposing GI disease. There is no dietary or vaccine-based primary prevention.

Gene–environment interactions. Not established as clinically meaningful. Host genetic modulation of the cytokine response may interact with pathogen burden to influence sepsis severity, but this is speculative for peritonitis specifically and not actionable.

3. Phenotypes

Septic peritonitis presents acutely with a constellation of peritoneal signs and systemic sepsis features. In a comparative study of acute abdomen, "common signs were tenderness, rebound tenderness, guarding/rigidity, tachycardia, and abdominal distention" (PMID: 42583660).

Phenotype	Type	HPO suggestion	Frequency/ severity	Onset/ progression
Abdominal pain	Symptom	HP:0002027 (Abdominal pain)	Near-universal; severe	Acute; progressive
Rebound tenderness / peritoneal signs	Clinical sign	HP:0002027	Very common	Acute
Abdominal guarding/rigidity	Clinical sign	HP:0025380 (Abdominal guarding)	Common	Acute
Fever	Sign	HP:0001945 (Fever)	Common	Acute; may be absent/ hypothermia in severe sepsis
Nausea and vomiting	Symptom	HP:0002018 / HP:0002013	Common	Acute
Anorexia	Symptom	HP:0002039 (Anorexia)	Common	Acute
Tachycardia	Sign	HP:0001649 (Tachycardia)	Common	Acute
Abdominal distension	Sign	HP:0003270 (Abdominal distention)	Common	Acute/subacute
Hypotension / septic shock	Sign	HP:0002615 (Hypotension)	In severe disease	Acute; life-threatening
Leukocytosis (or leukopenia)	Lab abnormality	HP:0001974 / HP:0001882	Common	Acute
Elevated CRP / procalcitonin	Lab abnormality	HP:0011227 (Elevated CRP)	Common	Acute
Lactic acidosis	Lab abnormality	HP:0003128 (Lactic acidosis)		Acute

Phenotype	Type	HPO suggestion	Frequency/ severity	Onset/ progression
			Severe disease; prognostic	
Multi-organ dysfunction	Complication	HP:0011024 (GI), HP:0000083 (Renal insufficiency)	Severe/ tertiary	Progressive

Age of onset. Any age; predominantly adult and geriatric (matching perforation risk). Neonatal forms occur secondary to necrotizing enterocolitis-associated intestinal perforation.

Severity/progression. Acute onset, rapidly progressive; if untreated, escalates to septic shock and MODS within hours to days. **Quality-of-life impact** in the acute phase is severe (ICU-level illness); survivors of abdominal sepsis may experience prolonged recovery, post-intensive-care syndrome, and long hospital stays. Disease-specific QoL instruments are not standard; generic ICU/sepsis outcome measures apply.

---

4. Genetic/Molecular Information

This section is largely NOT APPLICABLE. Septic peritonitis is an acquired infectious disease with: - **No causal genes** (no OMIM gene entries). - **No pathogenic variants** (no ClinVar classifications, no ACMG/AMP-relevant germline or somatic variants, no allele-frequency considerations). - **No chromosomal abnormalities.** - **No disease-specific epigenetic signature** established as diagnostic.

Modifier genes (host susceptibility, research-level only). Polygenic variation in innate-immune signaling (TLR4/CD14/LBP–LPS recognition, TNF, IL6, IL1B, NLR-family inflammasome genes) modulates the intensity of the sepsis response but is neither diagnostic nor actionable. Experimental work implicates inflammasome and receptor genes in host defense—e.g., **NLRC4** deficiency improved survival and bacterial clearance in CLP-induced polymicrobial sepsis (PMID: 41071588), and **CD300ld** modulates neutrophil bacterial phagocytosis (PMID: 40376837)—but these are mechanistic/model findings, not human germline disease genes.

---

5. Environmental Information

Environmental / iatrogenic factors. NSAIDs and corticosteroids (GI ulceration), abdominal surgery, peritoneal dialysis catheters, and intra-abdominal foreign bodies. No environmental toxin, radiation, or pollutant is a recognized cause.

Lifestyle factors. Alcohol use (pancreatitis, cirrhosis/SBP risk), smoking (peptic ulcer disease). Diet-related diverticular disease contributes to perforated diverticulitis.

Infectious agents (the direct cause of secondary septic peritonitis). Typically **polymicrobial enteric flora**: - **Gram-negative bacteria (NCBI Taxonomy):** *Escherichia coli* (NCBI:txid562) — most common; *Klebsiella*, *Enterobacter*, *Proteus*, *Pseudomonas aeruginosa*. - **Anaerobes:** *Bacteroides fragilis*, *Clostridium* spp. - **Gram-positive:** *Enterococcus* spp., streptococci, *Staphylococcus aureus* (esp. PD-associated). - **Fungi:** *Candida* spp., particularly in upper-GI (gastric/duodenal) perforation and tertiary peritonitis.

In companion-animal septic peritonitis, microbial growth occurred in the large majority of peritoneal cultures, with agents effectively covered by cefotaxime, ceftazidime, and imipenem (PMID: 30040445).

---

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation)

1. A **GI-tract lesion** (perforated ulcer, ruptured appendix/diverticulum, ischemic/necrotic bowel, anastomotic dehiscence, penetrating trauma) **leads to** spillage of luminal contents and gut flora into the sterile peritoneal cavity. *(demonstrated)*
2. **Bacterial contamination + PAMPs (e.g., LPS)** *results in* recognition by resident peritoneal macrophages and mesothelial cells via pattern-recognition receptors (TLR4/CD14) → NF-κB activation. *(inferred from sepsis biology; supported by biomarker data)*
3. NF-κB activation *leads to* release of **pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and alarmins (HMGB1)** and chemokines, *causing* massive **neutrophil recruitment** into the peritoneum. *(supported — biomarkers PCT, IL-6, HMGB1, CRP, LPS, NLR, NGAL elevated; PMID: 41227298)*
4. **Branch A (local):** Inflammation shifts the peritoneal **coagulation–fibrinolysis balance toward coagulation**; "both surgery and peritonitis disturb the equilibrium between

coagulation and fibrinolysis in the abdominal cavity in favour of the coagulation system," and "diminished fibrin degradation is a common pathway for the formation of adhesions and abscesses" (PMID: 12734857). *This results in* fibrin deposition, loculation, **abscess and adhesion formation** — walling off infection but also creating protected bacterial niches. *(demonstrated)*

5. **Branch B (systemic):** Unchecked, cytokines spill into the circulation, *causing* a **dysregulated systemic host response** = **sepsis** ("life-threatening organ dysfunction caused by a dysregulated host response to infection"; PMID: 30685836). *(demonstrated)*
6. Systemic inflammation *leads to* **vasodilation, capillary leak, microvascular thrombosis, and hypoperfusion → septic shock** and **tissue ischemia/oxidative injury**. *(inferred/demonstrated in sepsis)*
7. Hypoperfusion + direct cytokine injury *result in* **multiple organ dysfunction syndrome (MODS)** — acute kidney injury, ARDS, septic cardiomyopathy, hepatic dysfunction, DIC. Septic cardiomyopathy is a documented complication of small-intestinal perforation with peritonitis (PMID: 42260799). *(demonstrated)*
8. **Immune trajectory:** After the hyperinflammatory phase, "most patients survive the hyperinflammatory phase but progress to an immunosuppressive phase, which increases the emergence of secondary infections" (PMID: 31259890), *leading to* tertiary peritonitis and late mortality. *(demonstrated)*
9. Endpoint: **death from refractory shock, MODS, or secondary infection** unless the causal chain is interrupted by source control + antibiotics. "Mortality typically results from disruption of the gastrointestinal tract, progressive and self-perpetuating bio-mediator generation, systemic inflammation, and multiple organ failure" (PMID: 37170123). *(demonstrated)*

Category detail

- **Molecular pathways:** TLR4/CD14–LPS → MyD88 → NF-κB; downstream MAPK signaling; inflammasome (NLRC4, NLRP3) → caspase-1 → IL-1β/IL-18 maturation. TNF can switch homeostatic efferocytosis to lytic caspase-8–dependent pyroptosis with IL-1β maturation (PMID: 40540586).
- **Cellular processes:** acute inflammation, phagocytosis, neutrophil extracellular trap formation, pyroptosis/apoptosis, efferocytosis, later immunosuppression.
- **Immune involvement:** central — innate immunity (macrophages, neutrophils, mesothelium) drives both protection and pathology; adaptive dysfunction (T-cell

exhaustion, B-1a cell depletion via neutrophil trogocytosis; PMID: 40568588) characterizes the immunosuppressive phase.

- **Tissue damage mechanisms:** oxidative stress, ischemia/hypoperfusion, microvascular thrombosis, fibrin-driven abscess/adhesion, necrosis.
- **GO term suggestions:** GO:0006954 (inflammatory response), GO:0032496 (response to lipopolysaccharide), GO:0007249 (NF-κB signaling), GO:0006909 (phagocytosis), GO:0070269 (pyroptosis), GO:0007596 (blood coagulation), GO:0042060 (wound healing/adhesion).
- **CL term suggestions:** CL:0000864 (tissue-resident macrophage), CL:0000775 (neutrophil), CL:0000077 (mesothelial cell), CL:0000771 (B-1a cell), CL:0000084 (T cell).

---

7. Anatomical Structures Affected

Organ level. - **Primary:** peritoneum (UBERON:0002358, parietal peritoneum; UBERON:0002357, serosa) and the perforated hollow viscus (stomach UBERON:0000945, small intestine UBERON:0002108, large intestine/colon UBERON:0001155, appendix UBERON:0001154). - **Secondary (complications):** kidney (UBERON:0002113, AKI), lung (UBERON:0002048, ARDS), heart (UBERON:0000948, septic cardiomyopathy), liver (UBERON:0002107), spleen (UBERON:0002106), systemic vasculature. - **Body systems:** digestive (primary), immune/hematologic, cardiovascular, respiratory, renal/urinary — reflecting multi-system sepsis.

Tissue and cell level. Mesothelial lining (epithelial-like serosa), submesothelial connective tissue and vasculature; infiltrating **neutrophils (CL:0000775)** and **peritoneal macrophages (CL:0000864)**; **B-1a cells (CL:0000771)** in serosal cavities.

Subcellular level. Mitochondrial dysfunction (bioenergetic failure in sepsis; GO:0005739), nucleus (NF-κB translocation; GO:0005634), inflammasome assembly in cytosol (GO:0005829), plasma-membrane receptor complexes (TLR4; GO:0005886).

Localization / lateralization. Peritonitis is typically **diffuse/generalized (bilateral, non-lateralized)** when spillage is widespread, or **localized** (e.g., abscess) when contained. Free intra-abdominal air and diffuse fluid indicate generalized perforation peritonitis.

---

8. Temporal Development

- **Onset:** acute or subacute (hours to a few days). Insidious onset can occur in immunosuppressed or postoperative patients.
- **Stages:** (1) contamination/local peritonitis → (2) systemic inflammatory/hyperinflammatory sepsis → (3) septic shock/MODS → (4) either resolution (with treatment) or immunosuppressive/tertiary phase with secondary infection.
- **Progression rate:** rapid; can be fulminant, particularly with delayed source control.
- **Course pattern:** acute, potentially self-limited *only* with definitive intervention; otherwise progressive and fatal.
- **Remission:** treatment-induced (source control + antibiotics); no spontaneous remission for established secondary septic peritonitis.
- **Critical periods:** the **early window for source control and antibiotics is decisive** — delay markedly worsens outcome; the transition from hyperinflammatory to immunosuppressive phase is a second window of vulnerability to secondary infection.

---

9. Inheritance and Population

Epidemiology. Septic peritonitis/abdominal sepsis is common and globally important. The **abdomen is the second most common source of sepsis** (PMID: 30685836), and sepsis overall is a leading cause of death: GBD 2017 estimated ~**48.9 million incident sepsis cases and 11 million sepsis-related deaths** worldwide, "a major cause of health loss" (PMID: 31954465). IAIs carry hospital mortality of 23–38% (PMID: 39200076), and SCIAS mortality can exceed 80% (PMID: 37170123).

Genetic etiology — NOT APPLICABLE. No inheritance pattern, penetrance, expressivity, anticipation, mosaicism, founder effect, consanguinity role, or carrier frequency. Septic peritonitis is acquired.

Population demographics. Risk rises with age and with predisposing GI disease. No strong ethnic predisposition to the infection itself (although access to timely surgery/critical care strongly affects outcomes and drives geographic mortality variation). Sex distribution roughly reflects the underlying etiology (e.g., perforated ulcer, diverticulitis, appendicitis). Geographic variation in outcome is driven by healthcare access rather than by genetic epidemiology.

---

10. Diagnostics

Clinical examination. Acute abdomen with tenderness, rebound tenderness, guarding/rigidity, distension, tachycardia, and often fever (PMID: 42583660).

Laboratory tests / biomarkers. Leukocytosis or leukopenia, elevated CRP and **procalcitonin (PCT)**, IL-6, HMGB1, LPS, elevated **neutrophil-to-lymphocyte ratio (NLR)**, NGAL, and lactate. "Biomarkers such as procalcitonin (PCT), interleukin-6 (IL-6), high mobility group box 1 (HMGB1), C-reactive protein (CRP), lipopolysaccharide (LPS), neutrophil-to-lymphocyte ratio (NLR), and neutrophil gelatinase-associated lipocalin (NGAL) have emerged as tools for early diagnosis, subtype stratification, and monitoring of therapeutic response" (PMID: 41227298). LOINC-codable: WBC, CRP, PCT, lactate.

Imaging. CT is the imaging modality of choice — more sensitive than plain radiography for pneumoperitoneum. "Free intra-abdominal air in combination with diffuse fluid is a reliable indication for surgery as it is strongly associated with perforated diverticulitis with generalized peritonitis" (PMID: 22752330). In gastroduodenal perforation, free intraperitoneal air is a direct sign (PMID: 15093233); CT is more sensitive than plain films for detecting free air even in peritoneal-dialysis patients (PMID: 8188913).

Peritoneal fluid analysis (diagnostic cornerstone). Neutrophilic exudate; **cytologic identification of intracellular bacteria is confirmatory**. In veterinary medicine, a **blood-to-fluid glucose difference >20 mg/dL was 100% sensitive and 100% specific** for septic peritoneal effusion in dogs, and a **blood-to-fluid lactate difference < −2.0 mmol/L was also 100% sensitive/specific** (PMID: 12692761). Point-of-care peritoneal culture has ~80% sensitivity/100% specificity (PMID: 34331824). For the *primary* (SBP) form, diagnosis is an ascitic-fluid neutrophil count **>250 cells/mm^3** (PMID: 42488876, PMID: 42565189).

Genetic / omics diagnostics — NOT APPLICABLE for diagnosis of the infection (no WGS/WES/panel/karyotype/FISH/mtDNA/repeat-expansion role). Microbiologic culture and, increasingly, metagenomic next-generation sequencing (mNGS) of fluid can identify pathogens (mNGS sensitivity 65.8% vs culture 36.8% in PD-related peritonitis; PMID: 39611142).

Clinical criteria / scoring. Diagnosis is clinical + imaging + fluid analysis. Severity/prognosis are graded by **APACHE II** and **Mannheim Peritonitis Index (MPI)**, plus Sepsis-3/SOFA. **Differential diagnosis:** non-septic causes of acute abdomen (pancreatitis, ischemia without perforation, epiploic appendagitis, primary SBP, chemical peritonitis).

11. Outcome / Prognosis

Mortality. High and driven by source-control success and physiologic derangement. In severe secondary peritonitis, mortality was ~38%; **APACHE II (19.6 vs 14.3; p=0.0015) and MPI (35.5 vs 27.8; p=0.001) were significantly higher in non-survivors**, and MPI was the only independent multivariate risk factor (PMID: 21988045). Multivariate analysis of 604 IAI patients confirmed the prognostic dominance of host-related factors and the value of APACHE II and MPI (PMID: 8645072).

Source control is the dominant prognostic factor. In postoperative IAI, "in 37 of the patients the source of infection was eliminated resulting in 7 deaths (19%); all 11 of those in whom it was not eliminated died" (PMID: 8891619).

Prognostic factors: age, physiologic severity (APACHE II, SOFA), MPI, adequacy/timeliness of source control, organ dysfunction, fungal involvement (worse outcomes; PMID: 38691220), and serial peritoneal-fluid variables (in dogs, lower abdominal-fluid WBC and higher blood-to-fluid WBC/neutrophil ratios predicted recurrent septic peritonitis; PMID: 27556266).

Complications: septic shock, MODS (AKI, ARDS, septic cardiomyopathy, DIC, hepatic dysfunction), intra-abdominal abscess/adhesions, tertiary peritonitis, secondary/nosocomial infection, and long-term post-sepsis morbidity.

---

12. Treatment

Two pillars: source control + early antibiotics/resuscitation.

Surgical / interventional source control (the therapeutic gold standard). "The 'old' surgical source control consisting of debridement, removal of infected devices, drainage of purulent cavities, and decompression of the abdominal cavity is the gold standard of surgical care" (PMID: 30685836). Modalities include exploratory laparotomy with repair/resection of the perforated viscus, peritoneal lavage, percutaneous abscess drainage, and open-abdomen management. **Vacuum-assisted closure (VAC)** is a feasible open-abdomen technique in veterinary septic peritonitis (PMID: 22474052). NCIT suggestions: NCIT:C15329 (Surgery), NCIT:C51674 (Drainage Procedure), NCIT:C157715 (Debridement). Note: rapid source-control laparotomy is not universally beneficial and should be applied selectively (PMID: 28846501).

Pharmacotherapy — empiric broad-spectrum antibiotics. Cover Gram-negative enterics and anaerobes (± enterococci/fungi by risk). Agents shown effective against peritoneal isolates include **cefotaxime, ceftazidime, and imipenem** (PMID: 30040445); typical human regimens include beta-lactam/beta-lactamase inhibitors, carbapenems, or cephalosporin+metronidazole, with antifungals for upper-GI/tertiary disease. **Duration:** the landmark **STOP-IT** RCT found "four days of antibiotics for source-controlled complicated intra-abdominal infection resulted in similar outcomes when compared with a longer duration," including in high-risk patients (PMID: 27670577). NCIT: NCIT:C258 (Antibiotic), NCIT:C1878 (Imipenem), NCIT:C1737 (Cefotaxime).

Supportive/critical care. Fluid resuscitation, vasopressors, source-directed antibiotics, organ support (renal replacement therapy, mechanical ventilation, inotropes/mechanical support for septic cardiomyopathy — as in the multimodal rescue described in PMID: 42260799), and nutritional support, per Surviving Sepsis principles.

Experimental / adjunctive therapeutics (model-stage). Immunomodulation strategies tested in CLP and other models include soluble CD6 receptor (PMID: 27895015), the hCG-related peptide LQGV (PMID: 20890188), trophoblast stem cells (PMID: 40691621), CD300ld-based neutrophil enhancement (PMID: 40376837), and trained-immunity neutrophil reprogramming (PMID: 41980372). None are yet standard human therapy. For PD-associated recurrent peritonitis, taurolidine-urokinase lock therapy shows promise (PMID: 40988813).

Pharmacogenomics / gene / cell / RNA / targeted / immunotherapy: NOT APPLICABLE as approved disease-specific therapies.

---

13. Prevention

- **Primary prevention:** treat/prevent predisposing GI disease (peptic ulcer prophylaxis, judicious NSAID/steroid use, timely management of appendicitis/diverticulitis), aseptic technique for PD catheters, and prompt surgery for at-risk lesions. There is **no vaccine**.
- **Secondary prevention:** early recognition and treatment of GI perforation/ischemia before diffuse peritonitis develops; sepsis screening protocols.
- **Tertiary prevention:** meticulous source control, appropriate antibiotic stewardship (STOP-IT short-course), prevention of secondary/nosocomial infection during the immunosuppressive phase, and monitoring for abscess/adhesion complications.

- **Public health:** access to timely surgical and critical care is the key determinant of survival and the main lever for reducing geographic mortality disparities.
- **Genetic screening / counseling / immunization:** NOT APPLICABLE.

---

14. Other Species / Natural Disease

Septic peritonitis is a **common, high-mortality naturally occurring disease in companion animals**, making veterinary data unusually informative.

- **Taxonomy:** dog (*Canis lupus familiaris*, NCBI:txid9615), cat (*Felis catus*, NCBI:txid9685); mouse (*Mus musculus*, NCBI:txid10090) and rat as experimental hosts; zebrafish (*Danio rerio*, NCBI:txid7955) as a peritonitis model host.
- **Natural disease:** "Septic peritonitis is a common, life-threatening condition encountered in dogs and cats" (PMID: 30040445). In GI-perforation cases, "the overall mortality was 63.6%" across 44 dogs and 11 cats (PMID: 24283417). Etiologies mirror humans: GI perforation (foreign bodies, NSAID-induced pyloric ulcer, dehiscence), with uncommon causes such as **grass-awn foreign-body migration** (good-to-excellent prognosis after surgery; PMID: 36874536).
- **Comparative biology:** the pathophysiology (GI disruption → polymicrobial contamination → sepsis), diagnostics (blood-to-fluid glucose/lactate gradients, intracellular bacteria on cytology), and treatment (source control + antibiotics, open-abdomen/VAC) are strongly conserved between humans and companion animals — a key rationale for cross-species translational study.
- **Zoonotic potential:** the enteric pathogens involved can be zoonotic, but septic peritonitis itself is **not a transmissible disease**.

---

15. Model Organisms

Gold-standard model — Cecal Ligation and Puncture (CLP). "Cecal ligation and puncture (CLP)... is often considered the 'gold standard' to induce polymicrobial sepsis in laboratory animals. CLP is a well-described model involving a simple surgical procedure that closely

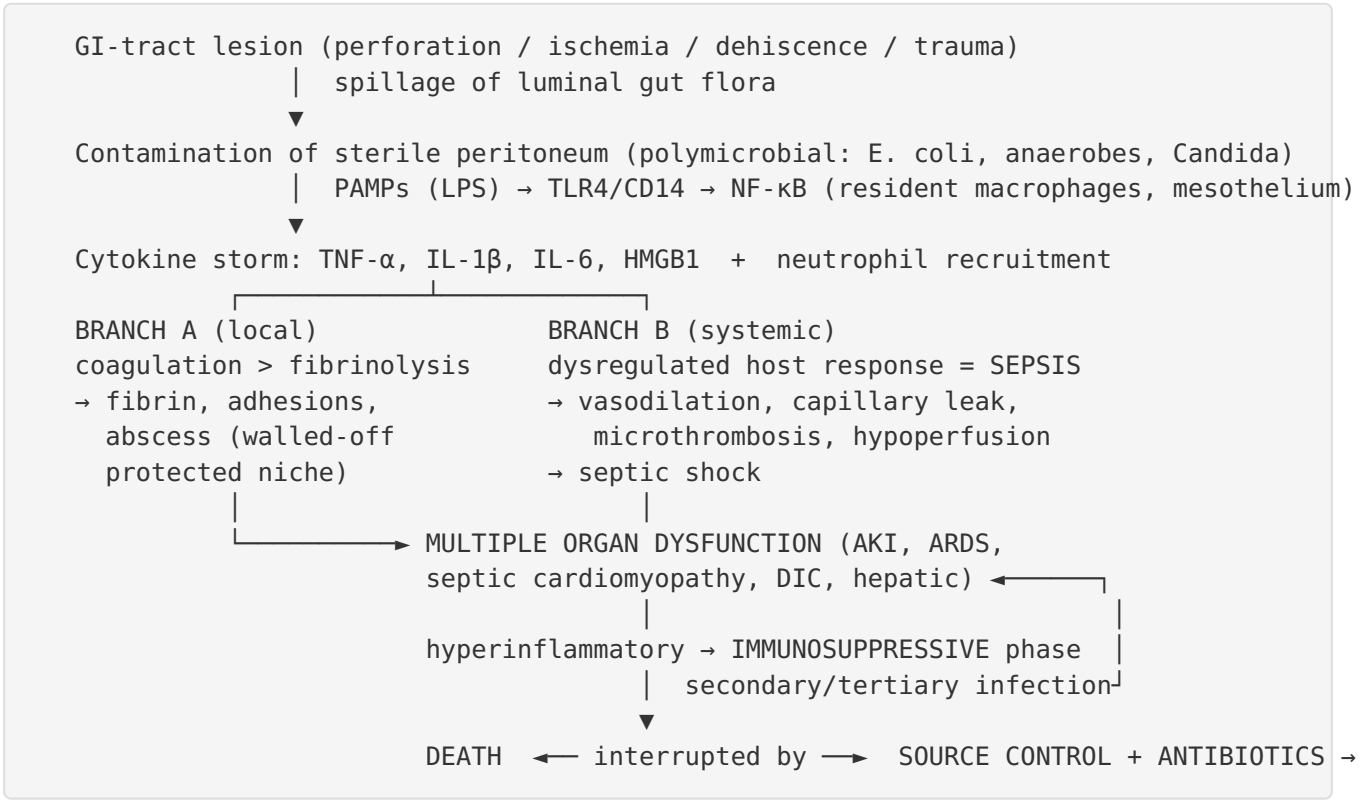
mimics the clinical course of intra-abdominal sepsis" (PMID: 34048005). Severity is **tunable**: e.g., 40% cecal ligation with double puncture yields ~80% mortality within 5 days, and 80% ligation ~100% mortality (PMID: 20890188).

Other models. - **Cecal slurry (CS) intraperitoneal injection** — the gold standard for *neonatal* mice (PMID: 34048005). - **Zebrafish bacterial peritonitis** — used to study neutrophil trained immunity (PMID: 41980372). - **Genetic knockout/transgenic mice** on the CLP background dissect mechanism (e.g., *Nlrc4−/−*, PMID: 41071588; CD300ld, PMID: 40376837).

Phenotype recapitulation & applications. CLP reproduces the polymicrobial source, the biphasic hyper- then immuno-suppressive host response (PMID: 31259890), cytokine kinetics, bacterial dissemination, and organ injury, enabling study of immunopathology and candidate therapeutics.

Limitations. Model outcomes are highly sensitive to technical variables — notably **housing temperature**: thermoneutral (30°C) housing improved CLP survival from 40% to 78% versus standard 22°C, altering IL-6 and phagocytosis (PMID: 32433210). Mouse models incompletely capture human comorbidity, age, and the effect of source control/antibiotics — a recognized reason for translational failure of sepsis immunotherapies.

Mechanistic Model / Interpretation



The unifying theme is that **septic peritonitis is a source-control disease**: every downstream mechanistic step is fueled by ongoing contamination from the GI lesion, so physically eliminating the source (with antibiotic and physiologic support) is both the most upstream and the most effective intervention — explaining why source-control success dominates every prognostic model.

Evidence Base

PMID	Role	Key contribution
39200076	Supports	IAI mortality 23–38%; 2nd most common sepsis death
37170123	Supports	SCIAS mortality >80%; GI-disruption→MODS causal chain
30685836	Supports	Sepsis-3 definition; abdomen 2nd source; source-control gold standard
31954465	Supports	Global sepsis burden (48.9M cases, 11M deaths, GBD 2017)
41227298	Supports	Secondary peritonitis subtypes; biomarker panel
8891619	Supports	Source control determines survival (19% vs 100% mortality)
21988045	Supports	APACHE II & MPI discriminate survivors; MPI independent
8645072	Supports	604-patient multivariate validation of scoring systems
27670577	Supports	STOP-IT: 4-day antibiotics suffice after source control
22752330	Supports	CT free air+fluid → surgery for generalized peritonitis
15093233	Supports	Free intraperitoneal air = direct perforation sign
42583660	Supports	Classic peritoneal signs of acute abdomen
12692761	Supports	Blood-to-fluid glucose/lactate gradients 100% Se/Sp (dogs)
12734857	Supports	Coagulation shift → abscess/adhesion mechanism
34048005	Supports	CLP as gold-standard polymicrobial sepsis model
31259890	Supports	Biphasic immune course; immunosuppressive phase
24283417	Supports	Companion-animal mortality 63.6%; NSAID risk factor
30040445	Supports	Veterinary microbiology; effective antibiotics
32433210	Qualifies	Housing temperature drastically alters CLP outcomes (model limitation)
28846501	Qualifies	Rapid source-control laparotomy not universally beneficial

Limitations and Knowledge Gaps

1. **Template mismatch.** Roughly half the standard disease template (causal genes, pathogenic variants, inheritance, penetrance, chromosomal/epigenetic diagnostics, genetic counseling, vaccination) is **not applicable** to an acquired infectious/surgical condition. These are documented as N/A rather than forced.
2. **Human vs veterinary diagnostic evidence.** The most striking quantitative diagnostic data (blood-to-fluid glucose/lactate 100% Se/Sp) come from **canine/feline** cohorts; the exact human cutoffs differ and human peritoneal-fluid gradient thresholds are less standardized.
3. **Heterogeneity.** "Septic peritonitis" spans primary (SBP), secondary (the main entity here), and tertiary forms, and multiple GI source lesions with different microbiology and prognosis — pooling can obscure subtype-specific detail.
4. **Immunotherapy translation.** Numerous adjunctive immunomodulators succeed in CLP but none is approved for human peritonitis; model artifacts (e.g., housing temperature) contribute to this translational gap.
5. **Host-genetic modifiers** of the sepsis response are biologically plausible but not yet clinically actionable for peritonitis.

Proposed Follow-up Experiments / Actions

1. **Standardize human peritoneal-fluid biochemical gradients** (glucose, lactate, pH) prospectively to replicate the high-performing veterinary diagnostics in people.
2. **Subtype-stratified prognostic modeling** integrating MPI/APACHE II with the biomarker panel (PCT, IL-6, HMGB1, NLR, NGAL) to individualize source-control urgency and antibiotic duration.
3. **Validate short-course/biomarker-guided antibiotic stopping** (building on STOP-IT) across the fungal-peritonitis and immunosuppressed subgroups.
4. **Cross-species translational studies** leveraging naturally occurring canine/feline septic peritonitis as a bridge between CLP and human trials for candidate immunotherapies (e.g., neutrophil-directed CD300ld, trained immunity).
5. **Standardize CLP reporting** (housing temperature, ligation length, resuscitation/antibiotic co-treatment) to improve reproducibility and translational fidelity.

6. **Investigate host-genetic and mNGS-guided personalization** — combine rapid pathogen metagenomics with host inflammatory profiling to tailor antimicrobial and immunomodulatory therapy.

Report compiled from 13 confirmed findings and 58 reviewed papers across a 5-iteration autonomous investigation. Evidence sources: human clinical cohorts and guidelines, veterinary clinical cohorts (naturally occurring disease), and experimental animal models (CLP, cecal slurry, zebrafish).
