PATH 417

# CASE 4: One Too Many Hamburgers

## Body Systems Questions

Lindsay Richter

# The Case:

10-year-old Ronnie McDonald has developed abdominal cramps, bloody diarrhea and a low grade fever. His parents take him to see the family doctor.

The doctor asks about what Ronnie may have eaten in the past week and his parents recall that last weekend at a neighbor's barbecue they were concerned that the hamburgers may not have been cooked thoroughly and Ronnie had eaten two burgers.

The doctor performs a physical examination noting no rebound tenderness just some mild periumbilical tenderness. He asks the parents to collect a stool sample for the Microbiology Laboratory and to take Ronnie to the local lab for some routine bloodwork.

*Objective characteristics usually detected by a healthcare professional*

## Signs:

- Mild periumbilical tenderness
- Low grade fever
- No rebound tenderness

*Characteristics experienced by the patient, which may be subjective*

## Symptoms:

- Abdominal cramps
- Bloody diarrhea
- Low grade fever

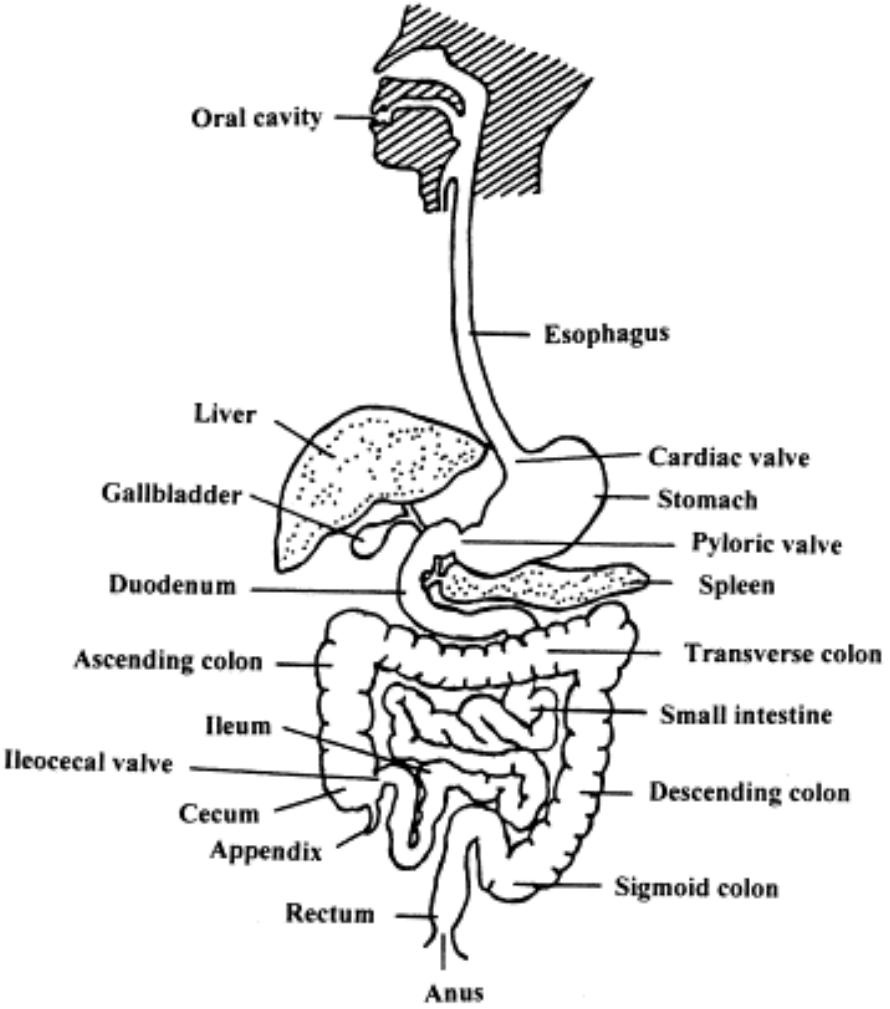
History: possibility of eating undercooked red meat + signs and symptoms

# Gastrointestinal Infection

*Other signs and symptoms typical of this infection but not mentioned – vomiting, headache, nausea, fatigue, watery diarrhea, dehydration, loss of appetite*

# Affected Body System:

# Gastrointestinal System




*Consists of:*

*1) the gastrointestinal tract (GI tract)*

*2) the accessory exocrine glands*

Gastrointestinal Tract:

- Mouth
- Esophagus
- Stomach
- Small intestine
- Large intestine

Major Accessory Exocrine Glands:

- Salivary gland
- Liver
- Gallbladder
- Pancreas

*Main functions:*

*- Assimilation of nutrients and excretion of waste products via the biliary system*

*The GI tract follows a structure of a muscular tube surrounded by a mucous membrane.*
*Four main layers:*

## 1) Mucosa

1. Epithelium
2. Lamina propria
   - loose supporting tissue
   - plasma cells and lymphocytes dispersed throughout
3. Muscularis mucosae
   - several layers of smooth muscle fibers

*Four types of mucosa:*

1) Squamous mucosa
2) Gastric type secretory mucosa
3) Intestinal type absorptive mucosa
4) Colorectal type

## 2) Submucosa

- collagenous connective tissue supporting mucosa
- has blood vessels. nerves, lymphatics

## 3) Muscularis propria

- smooth muscle with circular + longitudinal layers
- peristalsis

## 4) Adventitia

- loose supporting tissue
- blood vessels, nerves, adipose tissue

## Mouth, Salivary Glands:

main functions (mouth) – to chew (form bolus) + to taste

- mastication: reduces the particle size of food + increases its exposure to saliva
- saliva: secreted from several salivary glands + mixes to produce a composite juice (mildly alkaline)

main functions (saliva) – lubrication (moisten + dissolve chemicals within food), protection (neutralize bacterial acids, reduce bacterial growth via lysozymes, lactoferrin and IgA binding protein), digestion (α-amylase + lingual lipase)

## Stomach:

main functions – triturating + mixing the food bolus with pepsin + acid

- gastric acid: sterilizes the upper gut
- proximal stomach: storage function
- distal stomach: phasic contractions to propel solid food against pylorus
- also secretes intrinsic factor: vitamin B12 absorption

five anatomic areas – cardia (secrete mucus, bicarbonate to protect surface), fundus + body (secretory region – produce acid + pepsin), pyloric antrum (mixes gastric contents), pyloric sphincter (empties into small intestine)

## Large Intestine:

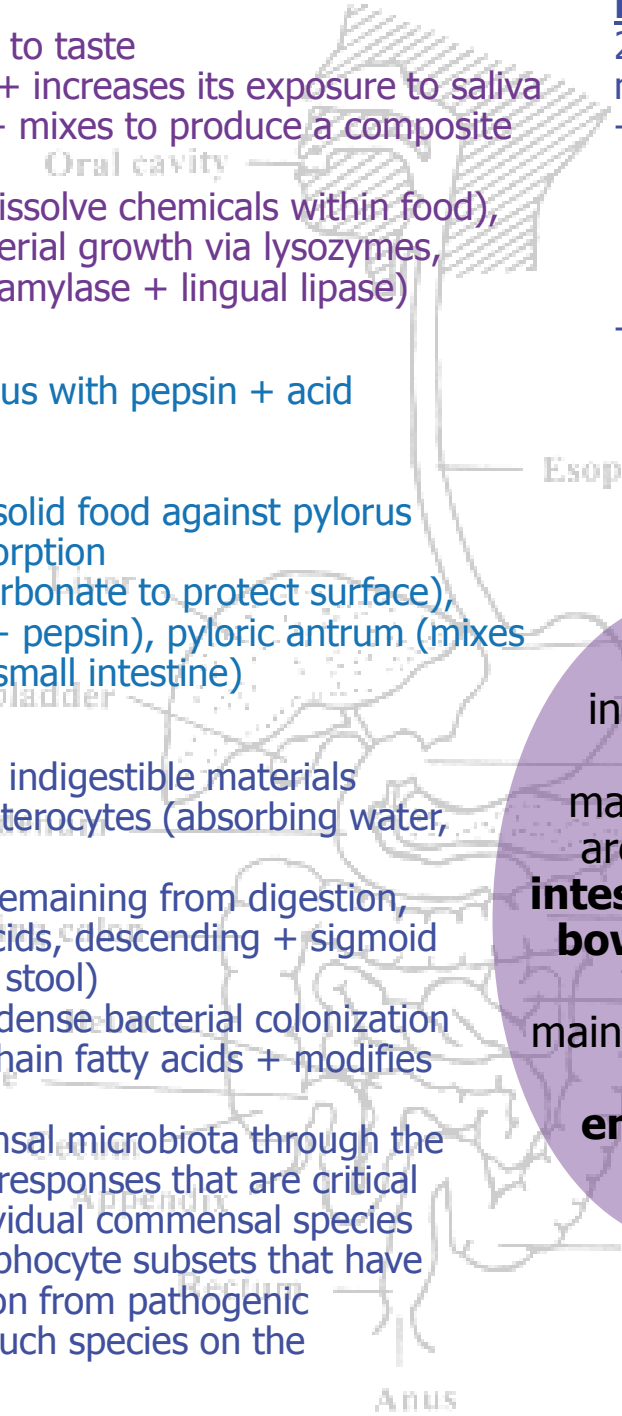
main functions – reservoir for storage of wastes + indigestible materials

-> cellular components: goblet cells (mucus) + enterocytes (absorbing water, salts and vitamins)

-> regions: ascending + transverse (absorb fluid remaining from digestion, salvage dietary by-products ie. short-chain fatty acids, descending + sigmoid (peristaltic contractions and mass actions to expel stool)

colonic mucosa: dehydrates stool; colonic lumen: dense bacterial colonization that ferments undigested carbohydrates + short-chain fatty acids + modifies some luminal solutes, e.g. bile acids and bilirubin.

-> bacteria + immune system: sensing of commensal microbiota through the TLR-MyD88 signaling pathway can trigger several responses that are critical for maintaining host-microbial homeostasis + individual commensal species can influence the makeup of lamina propria T lymphocyte subsets that have distinct effector functions -> also provide protection from pathogenic bacterial species by inhibiting the colonization of such species on the intestinal epithelium




in the case,

main affected area: **lower intestine/lower bowel region**

main affected cell type: **enterocyte**

## Esophagus:

25cm muscular tube lined with moist stratified epithelium

main functions – to move food + liquid to the stomach

- three functional zones: 1. upper (6-8cm), closely related to the pharyngeal musculature + consists of striated muscle; 2. middle (12-14cm), consists of smooth muscle; 3. lower (3-4cm), consists of smooth muscle + corresponds with lower esophageal sphincter
- swallowing induces primary peristalsis (wave) then secondary

## Small Intestine (+ pancreas, liver, gall bladder):

- first 12 in. = duodenum: critical regulator of digestion + absorption; triturated food mixes with pancreatic juice (enzymes for carb, protein, fat digestion + bicarbonate for pH) + bile (secreted by liver, stored in gallbladder, used in lipid digestion) in the duodenum; chemo- + mechanosensitive nerve endings monitor contents + coordinate GI functions
  - jejunum: site of absorption of nutrients; surface folds, tall villi, microvilli -> increase surface area
  - ileum: less actively engaged in nutrient absorption except specific solutes ie. conjugated bile acids + absorption of vitamin B12

->also helps with waste elimination (bile contents + motor function to deliver to colon)

->important function: water absorption (90%)

-> cellular components: enterocytes (main absorptive cell), goblets (mucin production), paneth (lysozyme secretion, phagocytosis), G (gastrin secretion), I (cholecystokinin secretion) K (motilin secretion) and S cells (secretin secretion)

# *E. coli* infection:

# Disruptions to GI Tract Functions

- Enterohaemorrhagic *E.coli* (*E.coli* O157:H7) -> most likely causative agent (associated with bloody diarrhea 85% of the time); highly virulent with a low infectious dose (fewer than 10-100 CFU)

**Survival in the Stomach**

-> requires acid resistance: possesses 3 overlapping systems

1. requires the alternative sigma factor RpoS + glucose repression
2. requires arginine addition during exposure to acidic environments (adiA+ cysB)
3. requires glutamate for protection in low pH environments (gadA or gadB, + gadC

- other proteins: RNA polymerase-associated SspA, chaperone HdeA and DNA-binding protein Dps

**In the Small Intestine (SI)**

-> *E. coli* can adhere to the epithelial wall + release toxins that may affect the enterocytes

- rapid propulsion of the SI contents -> adherence disrupted -> entry into the large intestine

**In the Large Intestine (LI)**

-> less rapid movement - allowing for *E. coli* to colonize

**Colonization**

- *E. coli* releases relatively large amounts of Shiga toxins -> two types: Shiga toxin 1 (Stx1) + Shiga toxin 2 (Stx2); same functions but are antigenically different
  - composed of two subunits: A (action) + B (adherence - binds to Gb3 receptors on epithelial cells)
  - A subunit: internalized via endocytosis + cleaved into 2 components (A1 [cleaves adenine from the 28S rRNA subunit -> disable protein synthesis -> cell death] + A2)

- **destruction of colonic endothelial cells** -> results in blood escaping through the basolateral membrane of the colonic endothelial cells and into the lumen -> bloody diarrhea
- **Shiga toxins** -> initiate an extreme inflammatory response -> further tissue damage to host endothelial cells
- **Shiga toxins** -> increasing intracellular cGMP levels -> decrease in intestinal fluid uptake + net secretion of fluid -> diarrhea
- **inflammatory immune response** requires recruitment of cells of the innate immune system -> large quantities of blood transported to infection site -> blood leaking into the lumen of the colon -> bloody diarrhea
- **destruction of endothelial cells** -> reduces # of enterocytes (reabsorption of water) -> diarrhea

# *C. jejuni* infection:

# Disruptions to GI Tract Functions

- *C. jejuni* -> food-borne enteric pathogen -> causes gastroenteritis, leading to diarrhea, abdominal pain, fever, nausea, + vomiting (after an incubation period of about 24-72 hours)
-> primarily colonize the small and large intestine -> cause significant hemorrhagic inflammation and enteritis in humans
- in the large intestine -> ulceration and colorectal inflammation

**Bacterial Adhesion + Invasion**

- Occurs in intestinal epithelium
- Bacterial factors to initiate the inflammatory processes + diarrhea:
  - **capsular polysaccharides** (CPS): allow *C. jejuni* to survive + persist; structural variability, similarity to host antigens, + resistance to phagocytosis and complement-mediated killing
  - **flagellum**: enables the bacteria to overcome peristalsis + enter the mucus layer; also capable of undergoing N and O-linked post translational glycosylation pathways to alter flagellum gene expression -> adapt to the host's immune response

**Mucosal Damage + Inflammatory Lesions**

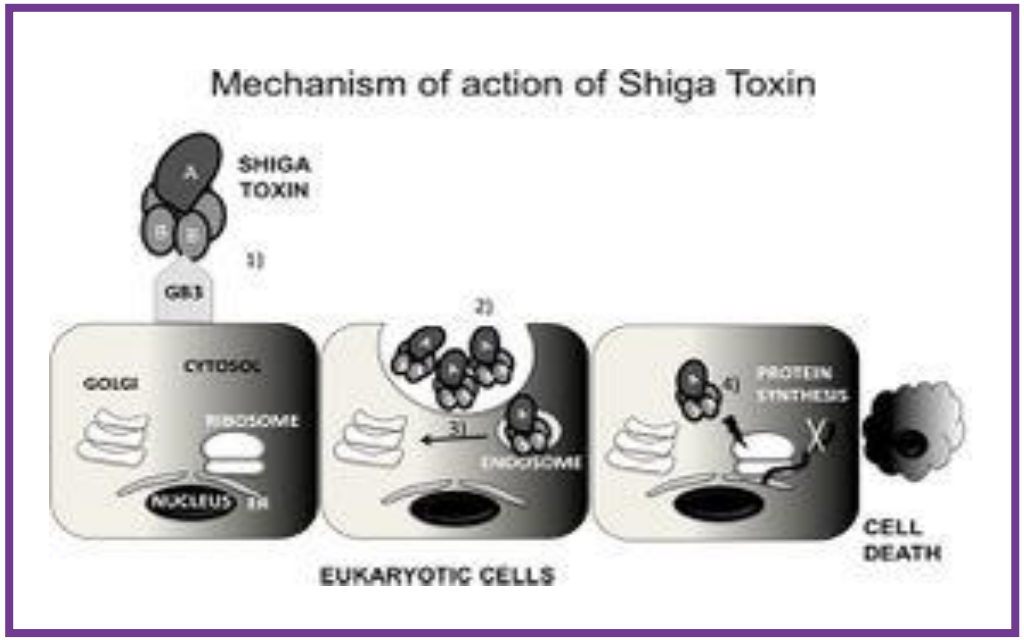
- Bacterial factors:
  - **Enterotoxin production:** observed in some isolates of *C. jejuni* -> cytolethal distending toxin (CDT) -> cause eukaryotic cells to arrest in the cell cycle's G2/M phase -> inhibits mitosis -> ultimately resulting in cell death
    - CDT consists of three membrane-associated protein subunits -> required for inducing the pro-inflammatory host response (release of interleukin-8 + other cytokines that cause fever, tissue damage + diarrhea in the host)

# *E. coli* infection:

# Secondary Sites of Infection

**Hemolytic-uremic Syndrome (HUS)**

- *E. coli* does not directly colonize the kidneys BUT if **Shiga Toxin** enters the bloodstream -> can affect kidney function => causing hemolytic-uremic syndrome (HUS)
- inflamed colon -> permit the transmural absorption of Shiga Toxin + LPS into bloodstream -> travel to the kidney -> toxin can bind endothelial cells of small blood vessels -> cause cell death
- red blood cells: pass by this damaged area -> become distorted + lyse -> hemolytic anemia
- fibrin and platelets: adhere to the damaged endothelial surface -> cause thrombocytopenia
- renal tissue necrosis -> renal failure -> death if left untreated

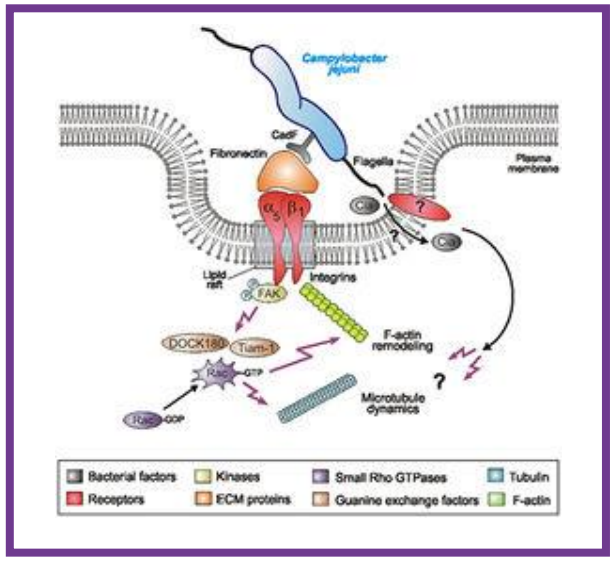



**Thrombotic Thrombocytopenic Purpura (TTP)**

- another possible complication -> shares the same characteristics as HUS with the added symptoms of fever and neurologic symptoms
- endothelial cells: secrete ADAMTS13 (a protease that degrades ultralarge von Willebrand factor multimers) -> if endothelial cells are damaged by Shiga Toxin -> proportion of multimers remain anchored to endothelial cells -> attract platelet formation + intravascular platelet-fibrin thrombi -> causes the above-mentioned symptoms

# *C. jejuni* infection:

# Secondary Sites of Infection




*C. jejuni* adheres to host cells via the fibronectin-binding protein CadF which acts as a bridge engaging the integrin β1 receptor

**Locally**

- *C. jejuni* can spread within the GI tract -> cause cholecystitis, pancreatitis + peritonitis
- can invade the epithelium or live within the mucus layer
- Bacterial factors:
    - Flagella: motility + adherence
    - Surface proteins: affinity for several components
        -> CadF binds to fibronectin
        -> JlpA (adhesin) binds to Human epithialial type 2 (HEp-2) cells
    - Endotoxic Lipid A component of LOS: epithelial cells -> secrete IL-8 -> inflammatory response

**In the Bloodstream**

- *C. jejuni* can access the bloodstream -> cross epithelial cells + spread to other areas of the body [rare (<1%)]
- Bacteremia of *C. jejeni* infections -> cause meningitis, endocarditis, septic arthritis, osteomyelitis + neonatal sepsis
- vulnerability to complement-mediated lysis -> difficult to survive in the bloodstream

**Post-infectious Autoimmune Disease**

- serious post-infectious autoimmune disease: Guillain-Barre syndrome (GBS)
    - causes muscle weakness -> autoimmune response to the peripheral nervous system
    - lead to life-threatening situations (if the muscles used for breathing are compromised)

- molecular mimicry between bacterial lipooligosaccharide + human GM1 ganglioside -> host develops anti-GM1 antibodies -> destruction of the myelin sheath + axons -> impairs nerve function + signal transduction

# Routine Bloodwork:

# 1. Complete Blood Count (CBC)

- provides information on blood cell production, function, + the immune system by looking at the red + white blood cell numbers, cell dimensions, + hemoglobin weight
- results can be indicative of blood + bone marrow disorders, infection + inflammation
- blood is drawn from the patient + analyzed

| Test Parameter | Normal Range | Description |
|---|---|---|
| Red blood cell count (RBC count) | 4.0 to 6.2 million/µL | • Number of erythrocytes per cubic centimeter of blood • Elevated levels can be a sign of dehydration, as plasma volume will decrease • Decreased levels are associated with anemia |
| Hematocrit (Hct) | Women 35-47% Men 39-50% | • Percentage of RBC volume to total blood volume |
| Hemoglobin (Hgb) | Women 12-16g/dL Men 14-18g/dL | • Number of hemoglobin molecules measured in grams per deciliter • Hemoglobin functions to transport CO2 and O2 |
| *RBC indices* | | |
| Mean corpuscular volume | 82 to 93 µm3 | • Indicates the size of the RBC by size or volume |
| Mean corpuscular Hgb | 26 to 34 pg | • A measure of the average weight of Hgb in a RBC |
| Mean corpuscular Hgb concentration | 31% to 38% | • Average concentration of Hgb in the RBC |
| Red blood cell distribution width (RDW) | 11.5-14.5% | • Measures variation in RBC size/volume, and results are usually compared with MCV • Can help to determine if anemia is present if RDW and MCV are high |
| Platelet count | 150,000 to 400,000 µL | • Increases in platelet count (thrombocytosis) • Not an indicator of how platelets function |
| White blood cell count (WBC) | 4,500 to 11,000/µL | • Determines number of WBC's (leukocytes) a total number and percentage • Trauma, burns, infections trigger inflammation, which increases the amount of leukocytes circulating in the blood • Elevated results (>11,000µL) is referred to as leukocytosis • Can indicate issues such as infection, burns, radiation exposure, lymphoma, anxiety • Decreased counts (<4,500µL) is referred to as leukopenia • Can indicate disorders affecting production of WBCs or WBC destruction stemming from viral infections |

# Routine Bloodwork:

# 2. Basic Metabolic Panel (BMP)

- evaluates the patient's metabolism through some of the key compounds + electrolytes in the body
- results can provide information on kidney function, liver function + acid/base balance

| Test Parameter | Normal Range | Description |
|---|---|---|
| Blood glucose | 70-100mg/dL (3.9-5.5 mmol/L) | • Measures amount of glucose in the blood • Elevated results may be indicative of pancreatitis, hyperthyroidism, glucagonoma • Decreased levels indicate hypothyroidism, too much diabetes medication |
| Blood urea nitrogen | 7-20mg/dL | • Measures amount of blood nitrogen in the blood • Provides an indicator of kidney and liver function • When protein is broken down, the liver produces urea and the kidney filters it out into urine • High values may indicate kidney failure, GI bleeding, excessive protein levels in the GI tract • Lower values may indicate liver failure |
| Creatinine | 0.8-1.4mg/dL | • Measures levels of creatinine, which is a produce of muscle metabolism • Used to evaluate kidney function as the kidney filters out creatinine from the body • High values can be indicative of kidney failure • Low values can be indicative of muscular dystrophy |
| *Electrolytes* | | |
| Sodium | 136-144 mEq/L | • High levels (hypernatremia) can be indicative of diarrhea as there is less fluid reabsorption in the body • Low levels (hyponatremia) can also be due to diarrhea or overhydration |
| Potassium | 3.7-5.2mEq/L | • Kidney failure can prevent clearing of K+, resulting in higher levels • Low values can indicate chronic diarrhea and vomiting |
| Chloride | 101-111mmol/L | • Increased levels (hyperchloremia) can be signs of kidney failure or dehydration • Hypochloremia can be sign of congestive heart failure and prolonged vomiting |
| Carbon dioxide | 20-29 mmol/L | • Most of the CO2 in the body is in the form of HCO3-, so this test is a measure of blood bicarbonate level • Increased levels can indicate impaired lung function or breathing disorders • Decreased levels can indicate kidney disease or chronic diarrhea |

# Routine Bloodwork:

# 3. C-reactive Protein (CRP)

- indicator for inflammation

| Test Parameter | Normal Range | Description |
|---|---|---|
| C-reactive protein | Low: <1.0mg/L<br>Average: 1.0-3.0mg/L<br>High: >3.0mg/L | • IL-6, IL-1β, and tumor necrosis factor-α (TNF-α) stimulate production of CRP from the liver during inflammation<br>• Can be used to detect inflammation during an infection<br>•Higher levels can indicate an infection or a heart attack |