



AN OVERVIEW OF ANIMAL MODEL OF INFLAMMATORY BOWEL DISEASE

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Received 10th June 2022; Revised 15th July 2022; Accepted 29th Sept. 2022; Available online 1st May 2023

<https://doi.org/10.31032/IJBPAS/2023/12.5.7153>

ABSTRACT

Inflammatory Bowel Disease (IBD) is a general word that refers to a variety of disorders caused by chronic gastrointestinal inflammation. Ulcerative colitis and Crohn's disease are the two most serious inflammatory bowel diseases. In Crohn's disease, inflammation disturbs the whole digestive tract, while ulcerative colitis affects only the large intestine (also known as the colon). Both illnesses were caused by an impaired immune system response. Which have common symptoms and cause digestive problems and inflammation in the gastrointestinal tract. Although the basic etiology of IBD is unknown, there are several factors that may contribute to the pathogenesis of this disease, such as dysregulation of immune system or commensal bacteria, oxidative stress and inflammatory mediators. In order to understand these different etiological factors, a number of experimental models are available in the scientific research, including chemical-induced, spontaneous, genetically engineered and transgenic models. In recent decades, various IBD animal models have been produced. IBD animal models are important and invaluable instruments for studying the role of various factors in the pathogenesis of IBD and evaluating various therapeutic options. The current review focuses on the introduction of IBD and drug- induced IBD and the mechanisms that cause Croh's disease and ulcerative colitis, as well as the clinical situation.

Keywords: Inflammatory Bowel Disease, Pathophysiology, DSS

INTRODUCTION: -

Inflammatory bowel disease (IBD) is caused by a combination of genetic and environmental factors that influence immune responses. The two most common inflammatory bowel diseases are ulcerative colitis (UC) and Crohn's disease (CD). Crohn's disease and ulcerative colitis are both chronic inflammatory bowel diseases (IBD) that cause digestive problems and inflammation in the GI tract. It is mostly inflammation characteristic. Both children and adults suffer from both illnesses and men and women are affected similarly. Despite the similarities in the symptoms of these two conditions, there are some distinctions between CD and UC symptoms [1].

Crohn's disease is affects the mouth, anus, and all the layers of intestine. The mucosal layer of the colon is affected by ulcerative colitis. The rectum and intestine are also affected. Two English physicians, Wilks and Moxon, first identified colitis ulceration in 1875, differentiating this colitis from infectious disease diarrhoea. While it was not designated as a separate disease until 1875, an illness with related symptoms of ulcerative colitis is recorded both before and many years before the civil war [2].

Blood in the stool, extreme pain, and diarrhoea are all signs of ulcerative colitis,

while in severe cases of CD, there is often a risk of bleeding. Rectal bleeding is less common in CD, although rectal bleeding is more common in UC. More than half of people with CD have a deficiency in folate and vitamin D, while more than half of people with UC have an iron deficiency.

UC is more common than Crohn's disease around the world. Both diseases are more prevalent in the developed world, especially in North America and Western Europe, though their prevalence is growing in Asia. Overall, there are 1.2 to 20.3 cases per 100,000 people per year, with an incidence of 7.6 to 245 cases per 100,000 people per year [3].

Preclinical animal models of IBD are crucial for gaining a better understanding of the disease's pathogenesis. IBD is a chronic inflammatory disorder with two main classifications: Ulcerative Colitis (UC) and Crohn's Disease (CD). IBD is characterized by diarrhoea that is accompanied by blood, mucus, and pus in the stool. UC is characterized by inflammation of the colon mucosa, loss of mucus-forming goblet cells, crypt irregularity, and crypt abscesses, as well as neutrophils surrounding local blood vessels, plasma cell infiltration, and lymphoid aggregates in the lamina propria. Inflammatory lesions are most commonly found in the ileum and

colon in Crohn's disease. With extensive granuloma formations, these lesions are transmural [4].

Types of IBD: -

Crohn's Disease:-

From the mouth to the anus, Crohn's disease can affect any part of the GI tract. It usually disturbs the ileum, which connects the end of the small intestine to the beginning of the colon. Crohn's disease affects the entire thickness of the intestinal or bowel wall and is not restricted to a single area; there may be healthy parts of the intestine between diseased sections. Crohn's disease may look in "patches,"

disturbing some areas of the GI tract while leaving other sections fully untouched [5].

Ulcerative Colitis:-

Ulcerative colitis, like Crohn's disease, causes inflammation of the gastrointestinal tract. The large intestine (colon) and the rectum are the only areas of the body affected by UC. Only the innermost layer of the intestine's lining is affected by inflammation. It normally starts in the rectum and lower colon, but it can spread across the colon at any time. Multiple ulcers are caused by ulcerative colitis.

RISK FACTOR: -

The major risk factors for evolving UC and Crohn's disease Contain:

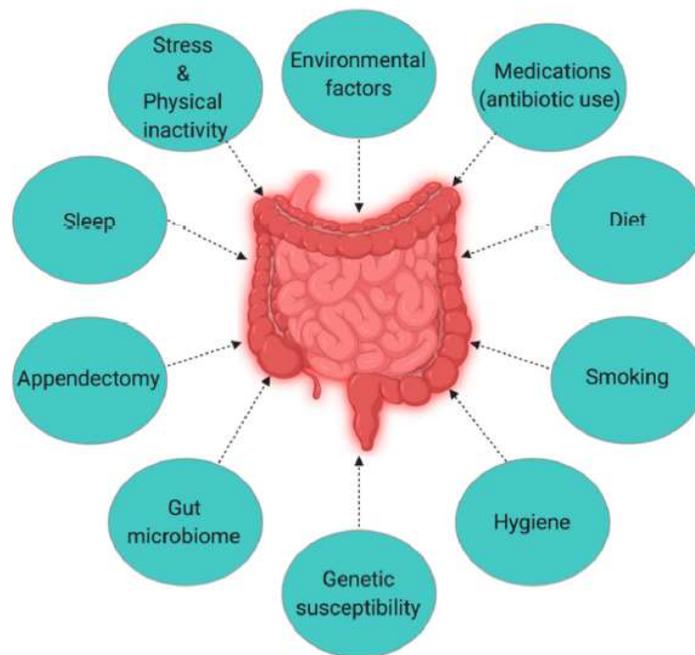


Figure 1: major risk factors of IBD

Symptoms of IBD:-

Table 1: Difference between Ulcerative colitis and Crohn's disease basis on symptoms

Symptoms	Ulcerative colitis	Crohn's disease
Diarrhea	Regular diarrhoea is very normal, but it might appear gradually and mildly or not at all	The occurrence of recurrent diarrhoea is fairly common.
Rectal bleeding	Stools nearly all contain blood. It may be easily observable or just visible under a microscope	Hemorrhage not as common as in UC, but can follow
Constipation	Constipation is a frequent sign of UC, although it is not as mutual as disease diarrhoea. It may happen during Nare - ups. As the symptom of an inflamed rectum stimulates a impulse reaction in colon, it allows the stools to be retained.	Constipation in Crohn's disease is usually a symptom of obstruction in the small intestine.
Abdominal Symptoms	Pain is a mild symptom that varies in severity. It may cause stomach cramps, a faint pain in the lower belly, or a pain along the top of the hipbone. Extreme pain can occur during flare-ups.	Recurrent bouts of discomfort in the lower right portion of the abdomen or above the pubis are the most frequent symptoms. Defecation is normally caused by defecation, which relieves it. Side effects such as bloating, fatigue, and vomiting are also likely. ^[11]
Fever	Extreme occurrences are possible.	The majority of the time, the rating is poor. Complications are indicated by a high fever and chills.
Loss of appetite, weight loss, and impaired growth in children	In mild or even relatively extreme UC, this is often not visible. Children and adolescents' development is sometimes hampered.	Typical. The average weight loss is ten to twenty percent of one's daily weight. Children and adolescents' development is commonly hampered.
Anal ulcers and fistulas	Nearly never a indication	Fistulas and sores nearby the anus may be quick signs Problems.

Treatment of IBD:-

The aim of therapy for inflammatory bowel disease is to reduce the inflammation that causes your signs and symptoms. In the best-case scenario, this could result in not just symptom relief but also long-term remission and reduced complications. Drug therapy or surgery was commonly used to treat IBD [6].

Aminosalicylates: These anti-inflammatory compounds include 5-aminosalicylic acid (5ASA). Other examples include sulfasalazine, balsalazide, mesalamine, and olsalazine. By inhibiting IL-1, TNF, and platelet activating factor, these drugs (given

orally or rectally) suppress antibody secretion (PAF). Inflammation of the intestine's wall may be reduced [7]. They were first created to treat colitis, with the aim of reducing symptoms and sustaining remission, but they may not be as effective in treating Crohn's disease.

Adverse effects: Headache, dizziness, epigastric pain, abdominal pain, nausea, vomiting, and diarrhea.

Corticosteroids:-

Drugs like prednisone, prednisolone, and budesonide inhibit the body's ability to initiate and maintain an inflammatory response. They have control over the

computer. In the short term, they're effective at controlling flare-ups.

Blocking phospholipase A2 in the arachidonic acid cascade changes the equilibrium between prostaglandins and leukotrienes, stimulates apoptosis in lymphocytes in the lamina propria, and suppresses cytokine transcription [8].

Side effects: bone loss, weight gain, infection, cataracts, skin breakability, sleep disturbance, and mood swings.

Antibiotics:-

People with Crohn's disease that affects the colon or the world around the anus can benefit from the antibiotics ciprofloxacin and metronidazole. When infections, such as abscesses, develop, they can be used. Antibiotics have no substantial clinical data to justify their use in the treatment of colitis [9].

Immune system suppressors:-

This medications increase the number of ways to inhibit the immune response that causes the body to release inflammation-inducing chemicals. These chemicals will harm the liner of the alimentary canal if they are released. Azathioprine (Azasan, Imuran), mercaptopurine (Purinethol, Purixan), and methotrexate (Trexall) are examples of immunosuppressive medications.

Other medications and supplements: Certain medications can help alleviate your sig

ns and symptoms in addition to controlling inflammation, please always see your physician before taking any over-the-counter medicines.

Your doctor may suggest one or more of the following treatments depending on the seriousness of your IBD.

Anti-diarrheal medications:-

Through bulking up the faeces, a fiber substitute like psyllium powder (Metamucil) or methylcellulose (Citrucel) will help alleviate mild to severe diarrhoea. Loperamide (Imodium A-D) can be useful for more acute diarrhoea. Vitamins and nutritional supplements: If you are not absorbing enough nutrients, your doctor can prescribe vitamins and nutritional supplements. Inflammation may be reduced by bowel rest in the short term.

Animal Models of IBD:-

Importance of Animal Model: -

Animal models are getting used to judge the standard and quantity of the immune reaction, to work out the simplest distribution and formulation path, and to work out infection and disease transmission safety. It aids researchers in gaining a deeper understanding of the processes underlying IBD [10] Several animal models are developed within the previous couple of decades to explain the dynamics of IBD pathogenesis, delineate

underlying molecular mechanisms, and assess possible human therapeutics. In IBD science, animal models are utilized in studies that fall under five categories: answering scientific concerns, evaluating preclinical effectiveness, evaluating pharmacokinetics, and evaluating pharmacodynamics (PK), safety testing, and biomarker studies. Furthermore, the animals are extremely useful for testing new therapeutic methods. Several experimental models of IBD, especially mice and rats, are established over time to conduct experimental studies. according to the shape of induction, animal models of intestinal inflammation are often divided into five classes:

1. **Inducible methods of IBD animal models**
2. **Genetic methods of IBD animal models**
3. **Antigen - specific forms of colitis**
4. **Microbiome-Induced Models**
5. **Adoptive transfer models**
6. **Spontaneous methods of IBD animal models**

Inducible methods of IBD animal models: -

Chemically Induced Models:-

In preclinical studies, chemically induced models are the foremost commonly used model type. The very fact that they

are relatively inexpensive and may be built quickly and simply are two of their main advantages. However, it's important to watch an equivalent procedure and pay careful attention to a spread of variables which will have a negative effect on the models' reproducibility across vivariums [11]. Chemical batch, strain, gender, animal source, chemical supplier, dosing amount, frequency, and length are all factors to think about. While several chemicals have the power to cause IBD in mice, the foremost commonly used models depend upon some chemicals are:

- **dextran sulfate sodium (DSS)**
- **trinitrobenzene sulfonic acid (TNBS)**
- **oxazolone**
- **Acetic acid-induced colitis**
- **Indomethacin induce**

DSS (Dextran Sulphate Sodium):-Since the condition caused is somewhat similar to the human disease, DSS technique has been used to induce colitis since 1985.

Mechanism: -

DSS (dextran sulphate sodium) disrupts the epithelial barrier, exposing the lamina propria to luminal contents and causing vascular and mucosal damage, leading to inflammatory pathways being activated.

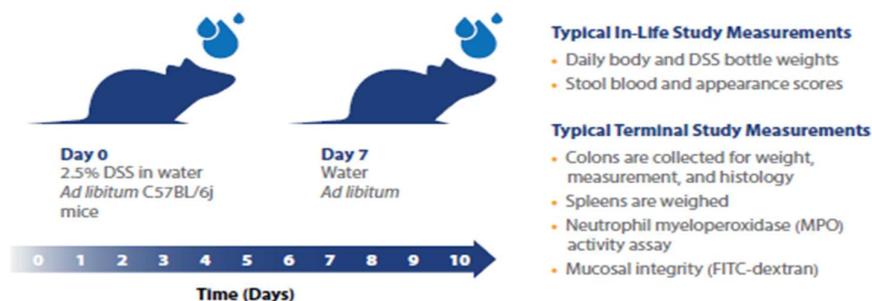


Figure 7: DSS Animal Model

Methodology: - The drug is dissolved in water for five to 7 days before administered to the animals. Symptoms of DSS-induced inflammation include bleeding, ulcers, and granulocyte infiltration, which are on the brink of diarrhoea. Within the chronic phase of swelling, which is analogous to colitis in persons, dysplasia is common [11].

The inflammatory immune reaction occurs as soon because the intestinal epithelium is disrupted, as antigens within the lumen inherit contact with protected cells within the mucosa and submucosa regions. Depending on the doses and drugs times, serious and long-lasting sorts of the disease could also be caused. DSS has also been wont to cause IBD in transgenic and immunodeficient animals, with the bulk of them being vulnerable to intestinal inflammation. Additionally, when this agent is present, the symptoms and pathology become more serious [12].

Limitations: Knowing and characterizing the inflammatory and immunological mechanisms involved in intestinal inflammation, and hence the pathogenesis of IBD, is insufficient.

Advantages: It includes methodologies that are thought to be simple to implement, as well as its own methodology. Because of its simplicity, it can be used in a variety of experimental protocols.

TBNS (Trinitrobenzene sulphonic acid):-

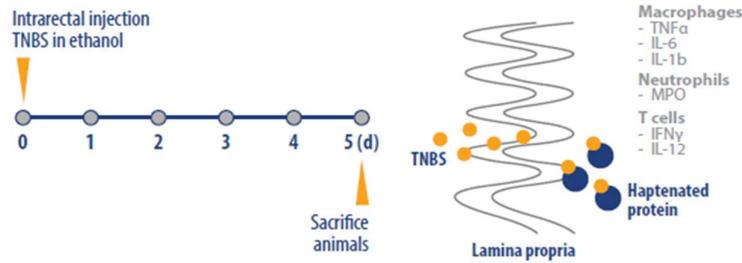


Figure 8: TBNS Animal Model

In hapten-induced inflammatory bowel disease, rectal administration of the TNBS compounds dinitrobenzene acid (DNBS) or oxazolone dissolved in plant material is possible.

The hapten chosen, as well as the animal's situation and the agent's route of administration, influence the type of response elicited (Th1/Th2) [13]. The agent (TNBS, DNBS, or oxazolone) is said to bind autologous macromolecules or microbiota byproducts, being immunogenic, and activating the interaction with specific antigens and cells in the system, while ethanol is used to weaken the interior organ mucosa membrane. In transgenic and immunodeficient species, as well as those susceptible to immune-mediated redness, IBD models elicited by hapten, similar to those elicited by DSS, can be used. With the TNBS-induced model, a single dose may be administered at the start of the study, resulting in acute inflammation and a Th1 response in 2–3 days [14].

Initial sensitization with TNBS could be performed by part treatment or through skin in the event of a prolonged hypersensitivity response to TNBS-haptenized colonic proteins, and another administration should be undertaken a half-dozen days later [15].

As TNBS is applied rectally with ethyl alcohol, microbiota proteins become haptenized, and T CD4+ cells emerge. The severity and hence the degree of inflammation is believed to be influenced by genetic factors in the animals, as well as the presence or absence of microorganisms that activate T cells [16].

T CD4+ cells are closely linked to Th1-mediated immune responses through the IL-12 cytokines, resulting in transmural inflammation close to CD. The IBD model induced by DNBS is similar to the one induced by TNBS since there is substantial tissue disruption and an acute inflammatory response [17].

Since CD exists, T CD4+ cells are also needed. 242 A Truthful Therapeutic Approach to Experimental Animal Models

of Human Diseases. Oxazolone is regularly assumed after presensitization of animal tissue (abdomen), which reasons improved Th2 cytokine manufacture and inflammation in the distal colon, like to colitis.

Oxazolone-Induced Model:-

The oxazolone-induced model primarily elicits a Th2-mediated immune response that finishes up in diffuse colonic inflammation and includes several options of human inflammatory bowel disease (UC), alongside similarities in immunopathogenesis.

Although oxazolone is additionally a haptenating agent like TNBS, the inflammation iatrogenic during this model is completely different from that caused by TNBS, and instead a bit likes UC in anatomy options and distribution [18].

Model Development

Oxazolone might be a classical haptenating agent, traditionally used to study delayed-type hypersensitivity reactions within the skin. Consequently, illness induction during this model generally involves 2 phases:

- ✚ A sensitization part
- ✚ An stimulation part

In the sensitization section, the abdominal fur is shaven and a solution of

oxazolone in 100% ethyl alcohol is applied to the skin. once five days, the animals area unit challenged with part administration of oxazolone in five hundredth ethyl alcohol, causing harm inflammatory bowel disease characterized by tissue ulceration, fast infiltration of lymphocytes and neutrophils into the plate propria of the colon, and submucosal swelling [19].

Colitis development is then monitored over an amount of 7-10 days, that typically includes daily weight measure and assessment of stool consistency and stool blood levels. not like TNBS-induced inflammatory bowel disease, the inflammatory response is characterized by elevated plate propria natural killer T cells and inflated production of IL-13, that's tons of an equivalent as human UC. Similar to the TNBS model, Intrarectal dosing of oxazolone in AN ethyl alcohol vehicle leads to background colon irritation, and mortality is typically ascertained throughout treatment.

Acetic acid-induced colitis:-

Another way to reason chemical injury to the membrane epithelium and activate a provisional composition that mimics UC is to administered diluted acid intrarectally. The primary study of this model was definite by MacPherson and Pfeiffer17, who instilled 10%50% acid into the rat

percentage for 10 seconds before flushing the lumen 3 times with saline. In these rats, histopathological selections involved ulceration of the distal colon and sepalcher differences, as well as diffuse redness in an acid dose-dependent manner.

The ulcerated and separated mucosa, with injury scattering to the L-P, continues to improve in mice within days and rats within weeks. Over the years, subsequent revisions and developments absorbed on variable the acid concentration and, as a outcome, the trace time. The most recent protocol is dead exploitation four-dimensional acid with 15 30 sec. of exposure the tissue injury considered at intervals the first twenty-four hours of acid induction isn't immunological in nature; later enemas of high concentration of acid into the lumen regularly bring perforations. As a result, any medicine that detects immune responses must be evaluated within 24 hours of induction.

Advantages: - acid acid-induced inflammatory bowel disease are its low value and thus the straightforward administration. There are outsized sorts of reports that describe compounds which will ameliorate acid acid-induced inflammatory bowel disease. These embody compounds close to target reactive necrophilous species like N-

acetyl aminoalkanoic acid, trimetazidine, vitamin E, and endocrine, suggesting that acid acid-induced inflammatory bowel disease is additionally an honest model to see the efficaciousness of medication that aim to interfere with reactive aerophilous species pathologic process.

Indomethacin induced:-

indomethacin (in one hundred percent alcohol so diluted with five saleratus or in alkyl cellulose) and administration within the daily die as a result of fasted rats grow attenuated lesions in a dose-dependent manner in rodents indomethacin (in one hundred percent alcohol so diluted with five saleratus or in alkyl cellulose) and administration within the regular die as a result of fasted rats develop attenuated lesions Initial tissue damage is mediated in part by the defensive prostaglandins PGE1, PGE2, and prostacyclin synthesis inhibition.

Advantage: -In acute or chronic stages, this paradigm has the advantage of being purely iatrogenic. It affects both small and large intestines and is said to cause more viscus lesions.

2. Genetic methods of IBD animal models:-

Genetically Engineered Mouse Models of IBD:-

- Alteration of cytokine function

- IL - 10 knock - out mouse
- IL - 2 knock - out mouse
- TNF ΔARE mice
- STAT - 4 transgenic mice
- Alteration of T - cell function
 - T - cell receptor a - knock - out mouse
 - T - cell receptor B - knock - out mouse
 - HLA - B27 transgenic rat

3. Antigen - specific sorts of colitis: -

The tumor redness evoked by intragroup injection of mycobacterial twine problem into mice or rats, the tumor redness evoked by intragroup injection of sublimate microorganism cell wall fragments (also called peptidoglycan - sugar advanced, PG - PS), and fixings - specific redness are the three CD animal models that make up this class. Though the PG - note model's duplicability can be a disadvantage, it offers a lot of intriguing possibilities. PG - note rats acquire pathology and illness as extra-intestinal signs, similar to CD rats, in addition to the quality anatomy seen in CD rats. But it's a fixings-specific redness

model that uses DO11 that's the most thrilling model in this class.

CONCLUSION: -

Preclinical research and drug discovery benefit greatly from the use of IBD mouse models. Although no single model is fully clinically applicable, various models are used to investigate various disease mechanisms. Researchers should choose the most suitable mouse model for each analysis by knowing the variations, benefits, and drawbacks of the various IBD models available.

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