

## ANAEROBIC INFECTIONS AND ENDOCRINOLOGY

**Amrutha Lakhotia,** Dept of Medicine, MVJ Medical College & Research Hospital, Hoskote. INDIA. <u>lakhotiaamrutha@gmail.com</u>

**R. Varadarajulu, MD, DNB,** Professor, Dept of Medicine, MVJ Medical College & Research Hospital, Hoskote. INDIA. <u>varadarajuludr@gmail.com</u>

KVS Hari Kumar, MD, DNB, Consultant Endocrinologist, MAGNA Clinics, Hyderabad, INDIA. hariendo@gmail.com

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#### ABSTRACT

Anaerobic bacteria are present as part of the normal microbial flora in the human body. These bacteria turn virulent whenever the host defense mechanisms are compromised. Diabetes and glucocorticoid abuse are the two common endocrine conditions that predisposes individuals to anaerobic infections. Anaerobic infections are common in tropical countries and can affect any tissue or gland resulting in severe organ dysfunction. Microbial endocrinology deals with the bidirectional interaction between the hormones and the microbes. The interaction is influenced by the virulence factors released from the microbes, inflammatory mediators, and the hormonal dysfunction. In this chapter, we shall discuss the various anaerobic bacterial infections relevant in endocrinology practices.

#### INTRODUCTION

The term "anaerobic" broadly denotes intolerance to oxygen. Anaerobic bacteria are the commonest bacteria in the bacterial flora present on the skin and mucous membranes (1). They are broadly divided into three types based on their relation to oxygen and growth potential as shown in figure 1.



#### Figure 1. Types of anaerobic bacteria

Virtually all anaerobic infections are derived from the normal bacterial flora of the body. The virulence characteristics of the organisms are kept in check by the defense mechanisms and a breach in the same may lead to infection. The risk of anaerobic infection is determined by the balance between the inoculum, virulence characteristics, and the host defenses. Previously, anaerobic infections were considered to be less prevalent due to the lack of identification techniques and the fastidious nature of the bacteria (2). Increased awareness, antibiotic misuse resulting in changing microbiome, ease of culture and diagnostic techniques helped in demonstrating that anaerobic infections also are frequent in clinical practice. Microbial endocrinology is a term coined in 1992, to describe the bi-directional interplay between microbes and endocrine hormones (3). Endocrine glands are located deep in the human body with the exception of the thyroid gland. Most of the endocrine glands have a thick capsule protecting them from the contagious spread of infection. The endocrine glandular tissue is highly vascular, thereby not conducive for the growth of anaerobic bacteria. However, anaerobes can overcome the host defenses resulting in infection and breaks in the anatomic barrier can occur due to surgery, trauma, or the disease process itself from within. The predisposing factors for anaerobic infections include diabetes, immunosuppression, malignancy, neutropenia, and decreased redox potential in the tissues.

## INTERPLAY BETWEEN ANAEROBIC BACTERIA AND HORMONES

The taxonomy of anaerobes has changed recently due to improvement in diagnostic techniques. the The development of advanced culture methods. next generation sequencing technology, and metagenomics has improved the understanding of anaerobic bacteria (4). Previously, the antibiotic susceptibility pattern of most of the anaerobes was not clear due to the difficulties in culture methods. Advanced diagnostic techniques like DNA hybridization, mass spectrometry, multiplex PCR, and oligonucleotide array technologies helped in improving the classification as well as the understanding of antibiotic susceptibility patterns of these bacteria. A simple taxonomical classification of anaerobic bacteria useful in clinical practice is shown in figure 2.



Figure 2. Types of anaerobic bacteria

#### **Estrogen and Vaginal Flora**

The healthy vaginal flora consists of Lactobacillus species and estrogen plays an important role in maintaining this flora (5). Estrogen increases vaginal epithelial activity resulting in a thickened layer of epithelium with glycogen deposition. The Lactobacilli breaks the glycogen into lactic acid and hydrogen peroxide locally, resulting in the vaginal pH being maintained in acidic range (< 4.5) to prevent the growth of anaerobic bacteria. Bacterial vaginosis is a common infection in women due to a shift of the vaginal microbiome from Lactobacillus flora to a mixture of facultative and obligatory anaerobic bacteria. The typical microorganisms include Gardnerella vaginalis, Mycoplasma hominis, and Atopobium vaginae. Postmenopausal females have a higher risk of bacterial vaginosis due to the precipitous decline in the concentration of estradiol. Evidence shows that topical estrogen therapy in these women normalize the vaginal flora and reduce the risk of anaerobic infections (6).

#### **Adrenal Hormone and Anaerobes**

Exposure to any form of stress elevates sympathetic nervous system activity and releases adrenaline and noradrenaline from the adrenal medulla. Prolonged stress induces a shift in immunity from Th1 linked cellular immunity to Th2 linked humoral immunity. In addition to many host tissues, microbes also respond to the catecholamines and increase their virulent characteristics (7). The hormonal communication between bacteria and humans involves the presence of interkingdom signaling receptors. Bacterial cell membrane bound histidine kinases (QseC and QseE) act as adrenergic sensors to detect the local hormone concentrations. QseC also modulate the expression of many genes that increase the virulence and inflammation. This is one of the mechanisms that interlink the immune-endocrine interactive pathway mediated by stress hormones.

Stress induced alterations in the anaerobes of the gingival flora led to the observation that noradrenaline and adrenaline act as environmental cues for bacteria (8). The spectrum of biological effects of the stress hormones on gingival flora could range from halitosis to atherosclerotic plaque rupture leading to acute coronary syndrome. These hormones affect the growth of Fusobacterium, Propionibacterium, and Prevotella and the hormonal effects are mostly species or strain specific. The biological adverse effects are mediated by changes in biofilms, bacterial adaptation techniques, bacterial adherence, and release of the cytotoxic enzymes.

#### DIABETES AND ANAEROBIC INFECTIONS

Diabetes mellitus (DM) is the most common metabolic and endocrine disorder that predisposes an individual to the development of infections. The defective immune responses seen in patients with DM could exacerbate the risk of anaerobic infections. Though many superficial and deep infections are common in patients with DM, few amongst them are unique in their description. The unique anaerobic infections seen in patients with DM include emphysematous cholecystitis and emphysematous pyelonephritis. Malignant otitis externa is also unique to DM but is mostly polymicrobial in origin.

## **Diabetic Foot Disease**

Diabetic foot disease is the commonest cause of lower limb amputation in clinical practice. The lifetime risk for a diabetic foot disease is about 25% in certain patients with diabetes. The infections are usually polymicrobial in nature and lead to considerable morbidity and occasional mortality. Anaerobic infections are more common in wounds that are deep seated and are often resistant to the antibiotics and conservative measures (9). Peptostreptococcus and Bacteroides species are the two common anaerobic bacteria of the diabetic foot. Anaerobic bacteria could be either primary or secondary colonizers in the etiology of diabetic foot ulcers. The ischemic and necrotic wounds have a higher rate of anaerobic infection due to the associated low blood supply and low redox potential that facilitate the growth of these bacteria. There is an ethnic variation in the bacterial etiology of diabetic foot infections. Anaerobic osteomyelitis is typically seen associated with diabetic foot ulcers and presents with a chronic non-healing ulcer of the leg. Early surgical debridement, antibiotic therapy with a spectrum against anaerobes, foot revascularization along with proper foot care are the guiding principles in the management of diabetic foot disease.

## Fournier's Gangrene

Fournier's gangrene (FG), first described in 1883, is a rare necrotizing infection of the perineal and genital skin due to both aerobic and anaerobic organisms (10). There is a male preponderance and the disease is mostly described in middle age and elderly patients. The predisposing factors FG include for diabetes mellitus. immunosuppression, and alcoholism. Recently SGLT2 inhibitors have been linked with an increased risk of FG. The condition leads to microthrombi of the small subcutaneous vessels leading to local necrosis and gangrene which is a fertile nidus for anaerobic bacteria to spread rapidly in the subcutaneous tissues. Initially, the patient presents with cellulitis of the scrotal skin and progression of symptoms may lead to severe sepsis and death. The reported mortality rates with FG are about 25 -30% and the management includes extensive surgical debridement along with broad spectrum antibiotics and hemodynamic supportive measures.

## **Necrotizing Fasciitis**

Necrotizing fasciitis (NF) is a life-threatening soft tissue infection that causes local tissue destruction, necrosis, and severe sepsis (11). FG is also a form of NF restricted to the genital area. NF is divided into four types based on the etiological organisms. Type 1 NF is polymicrobial in origin including anaerobes, whereas, type 2 NF is due to either

Streptococcus or Staphylococcus. Type 3 and 4 are less common and are due to Vibrio species and fungi respectively. The predisposing factors include DM, malignancy, immunosuppression, alcohol abuse, and systemic chronic debilitating disease. Initial presentation mimics that of cellulitis and early clues to the NF are pain and systemic features out of proportion to the local swelling and the presence of hemorrhagic bullae. Patients with diabetes and NF tend to have polymicrobial infections, severe renal impairment, delayed diagnosis. and multiple co-morbid ailments in comparison to NF patients without diabetes (12). Management principles are similar to FG and include surgical debridement, broad spectrum antibiotics, and supportive measures.

#### Periodontitis

Infection of the tissues surrounding the teeth are known as periodontitis and is usually caused by the anaerobic gramnegative bacteria. This is more common in patients with type 2 DM and this complication is often known as the "Sixth" complication of diabetes. The links between diabetes and periodontitis are mediated by oxidative stress, advanced glycation end products leading to immune dysfunction, inflammatory marker release, and increased tissue destruction (13). Periodontitis also exacerbates insulin resistance due to the release of cytokines and chemokines. DM is characterized by periapical bone destruction, poor wound healing, and also has a direct effect on the dental pulp integrity. Periodontitis is an independent marker of mortality in patients with T2DM and it is essential to treat these two conditions simultaneously for better outcomes.

## **ORGAN SPECIFIC ANAEROBIC INFECTIONS**

Endocrine glands are usually resistant to localized infections due to their location, high vascularity, and in some glands the presence of a protective capsule preventing the local spread of infection. However, these natural barriers are broken in certain conditions leading to the development of infections.

## Thyroid Gland

The thyroid gland is resistant to bacterial infection due to the high iodine content, blood supply, and thick capsule. Acute suppurative thyroiditis (AST) is a complication due to the anaerobic bacterial infection of the thyroid gland (14). Porphyromonas, Propionibacterium and Streptococcus are the common bacteria that have been reported to lead to AST. Many of these bacteria live as commensals in the gingival epithelium. These patients usually present with a tender neck mass and systemic features of inflammation, similar to the presentation of subacute thyroiditis (SAT). It is essential to differentiate between AST and SAT, as glucocorticoids worsen the former and are indicated in the later condition. The majority of the AST patients are euthyroid, whereas, the SAT presents with features of thyrotoxicosis. AST is seen involving the left side of thyroid gland, whereas, SAT involves both sides similarly. Ultrasonography and aspiration cytology aid in the confirmation of the diagnosis. Therapy consists of appropriate antimicrobial drugs and surgical drainage of an abscess if present.

## **Pituitary Gland**

The intrasellar location and the high rate of blood flow per gram makes the pituitary gland resistant to the development of local infections. However, a few case reports have described anaerobic abscesses in the sella that could be due to blood stream infection (15). The patients present with features of a pituitary mass including local compression and hormonal dysfunction. Surgical drainage of the abscess along with prolonged antianaerobic therapy is essential for recovery. There may be residual hormonal dysfunction in patients necessitating long-term hormonal replacement.

## Adrenal Gland

Adrenal gland infections are very rare in clinical practice and are usually predisposed by the presence of a blood collection in the gland. The presenting features include fever with chills, abdominal pain, and occasionally features of adrenal deficiency. The infection is mostly due to the aerobic bacilli, but polymicrobial infections are not uncommon. Recent reports suggest the beneficial role of metagenomic next generation sequencing (mNGS) that helps in the early identification of the anaerobic infection (16). mNGS technology helps in identification of multiple anaerobic bacteria simultaneously and the results are available in less than 48 hr, unlike conventional culture which takes more than a week. Management is similar to any other organ involvement with pus drainage and prolonged antibiotics.

#### INFERTILITY AND ANAEROBIC INFECTIONS

Infertility affects about 10 - 15% of couples and infections constitute one of the major contributory factors for infertility (17). Female and male factors account for about 40% of etiologies exclusively, whereas, both partners along with an idiopathic etiology account for the remaining 20%. Anaerobic infections constitute one of the common infectious causes of infertility, albeit, predominantly in females.

#### **Female Infertility**

Pelvic inflammatory disease (PID) is the commonest cause leading to female infertility due to tubal adhesions, mucosal damage, and tubal occlusion. PID is caused by multiple organisms which include Chlamydia, Neisseria, and anaerobes. Bacterial vaginosis is a major contributory factor in the pathogenesis of PID as evidenced by the identification of the similar microbial flora (18). Bacteria ascend the genital tract via the endocervical and endometrial epithelia including the lymphatics. Lower abdominal pain and vaginal discharge are the two common symptoms of PID. Early identification of PID, prompt antibiotic therapy, and surgical drainage of the pus result in the cure without residual tubal complications. Patients with recurrent abortions have also been shown to have vaginal colonization with Gardnerella vaginalis and facultative anaerobes (18). This indicates an association between the altered vaginal microflora, local and systemic inflammation, change in the immune mediators. impaired implantation, chemokines and cytokines, placentation, and blood vessel transformation culminating into the recurrent abortions.

## Male Infertility

Anaerobic infections affect semen quality and the total sperm concentration leading to male infertility. The semen samples from sub-fertile men are characterized by the presence of a large number of pus cells and multiple bacteria (19). Anaerobic bacteria affect the ability of the sperm to penetrate the cervical mucosa by the release of microbial toxins. Anaerobic infections are not routinely identified with the standard methods of culture and should be ruled out in all patients with unexplained oligoasthenospermia along with the presence of pus cells in the semen. Positive microbial cultures, however do not convey the exact location of the infection as the semen consists of secretions from the multiple glands including the prostate. A classic four specimen technique could be helpful in the localization of the infection and these patients require long term antibiotic therapy.

#### **GUT ANAEROBES AND METABOLIC DISORDERS**

Gut microbes are essential for the host immune system and help in digestion and maintenance of local tissue integrity. The intestinal bacteria mediate their beneficial effects by breaking dietary constituents into various short chain fatty acids which act as beneficial signals in metabolism and immunomodulation (21). Though it's very difficult to characterize the entire gut microbiome, parameters such as alpha species diversity, ratio between the beneficial (Akkermansia, Bifidobacterium, Lactobacillus etc.) and the harmful (Enterococcus, Bacteroides, Lachnospiraceae etc.) bacteria are used in laboratory evaluation. Recent reports have emerged that the gut microbiome plays important role in the an etiopathogenesis of metabolic disorders including type 2 DM and obesity.

Diet and environmental factors play an important role in shaping the gut microbiome. The diversity in the gut microbiota could also be a contributory factor in the prevalence of the metabolic disorders between different ethnic populations (22). Increasing use of the antibiotics, environmental pollution, and consumption of refined products have led to alterations in the microbial flora with a shift from a healthy flora to an unhealthy one. Proinflammatory molecules secreted from intestinal bacteria translocate to the blood stream triggering metabolic endotoxemia, which is described as the leaky gut syndrome. The gut-blood barrier is often broken with the colonization of the anaerobic bacteria in the gut replacing the normal flora.

The microflora in individuals is a key determinant in directing the response to antibiotics and probiotics. The fecal samples of Japanese patients with T2DM showed lower bacterial counts of obligatory anaerobes and higher content of facultative anaerobes in comparison to the control population. There is also a higher percentage of

gut bacteria in the circulation, thereby confirming the leaky-gut hypothesis (23). Apart from metabolic disorders, the gut dysbiosis has not been shown to affect other endocrine disorders.

# ENDOCRINE ISSUES WITH THE ANTIMICROBIALS USED AGAINST ANAEROBES

Antimicrobials are the cornerstone of therapy against the anaerobic infections. In a few cases, the antibiotic therapy is supplemented with the surgical drainage of the pus. The therapy is often prolonged due to the slow growth rate of the anaerobes, polymicrobial nature of the infection, and the development of antibiotic resistance (24). The commonly used antimicrobials against anaerobic infections include metronidazole, carbapenems, quinolones, betalactams, chloramphenicol, tigecycline, and clindamycin. Many of these drugs have no significant endocrine sideeffects except for the dysglycemia with the use of quinolones. Other endocrine effects due to the protracted use of these drugs are summarized in the table 1.

Table 1. Endocrine Side-Effects of Antimicrobials used Against Anaerobic Infection	
Drug	Endocrine side-effects
Metronidazole	Altered gut microbiome
	Anterior pituitary inhibition
Quinolones	Dysglycemia,
	Reduced absorption of levothyroxine
	Seizures in thyrotoxicosis patients
Beta-lactams	Fractures
Tigecycline	Hypoglycemia
Chloramphenicol	Inhibition of thyroid hormones production
Clindamycin &	Nil
Carbapenems	

#### CONCLUSION

Anaerobic infections are common in clinical practice and diabetes is the most common endocrine condition predisposing for these infections. Anaerobic organisms have hormonal interactions with gonadal and adrenal hormones and the field of microbial endocrinology is expanding rapidly. Organ specific anaerobic infections may lead to endocrine dysfunction in the form of infertility,

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glandular abscess, and hypofunction of the involved endocrine axis. A high index of clinical suspicion is essential to identify anaerobic infections especially in the tropical countries. The principles of management are prolonged antibiotic therapy along with drainage of the pus. Systemic supportive therapy and extensive debridement is essential in life threatening anaerobic infections like necrotizing fasciitis.

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