Non-neoplastic salivary Gland diseases

- The more common are mumps) acute suppurative sialadenitis, Sjogren syndrome and drug-induced xerostomia.

**CONGENITAL SALIVARY GLAND DISEASE**

**Salivary gland agenesis**

- Extremely uncommon, M:F = 2:1
- There can be variation in the number of absent salivary glands and hence the degree of associated xerostomia, dysarthria and/or dysphagia varies accordingly. Lack of saliva predisposes to dental caries, gingival disease, candidosis and acute infective sialadenitis, although in children rampant dental caries may be the only initial sign of underlying salivary agenesis.
- Salivary gland aplasia may occur in isolation or be associated with other ectodermal defects, in particular lacrimal apparatus abnormalities.

**INFECTIONS OF THE SALIVARY GLAND**

- Viral and bacterial infections are the most common. (the salivary glands may be the site of asymptomatic viral infection ie HHV6, HHV8, Cytomegalovirus).
- Saliva can transmit HIV, HHV8, Hepatitis B, Hepatitis C
- Of note, xerostomia is more likely with viral (e.g. hepatitis C virus and HIV) than bacterial infection of the salivary glands.

![Table 147.2 Infections of the salivary glands](image)
Mumps (epidemic parotitis)

- Mumps is an acute generalized paramyxovirus infection of children and young adults.
- Mumps typically affects the major salivary glands

**TRANSMISSION:**

- Droplet route, incubation period is 14 to 18 days.

**SYMPTOMS:**

- Patients present with initial pyrexia, chills and facial pain.
- The parotids are typically bilaterally enlarged, although this may initially be unilateral.
- There is often swelling of the submandibular glands together with lymphadenopathy, giving rise to profound facial and neck swelling.
- Rarely, sublingual swelling may be so profound as to cause elevation of the tongue and dysphagia and dysarthria.
- The salivary swelling tends to diminish after approximately four to five days and may precede more complicated aspects of the illness.
- Orchitis may develop approximately four to five days after the onset of parotitis, typically only one testicle is affected.
- Orchitis tends to arise in post-pubertal boys (rarely progresses to complications)
- Mumps can give rise to a lymphocytic or viral meningitis. This again commences a few days after the development of parotitis, although can occur in the absence of salivary gland disease.
- Other neurological manifestations include retrobulbar neuritis and encephalitis.
- Deafness is possible, but rare. Pancreatic infection may give rise to mild upper abdominal pain, but acute and long-term complications are unusual.

**DIAGNOSIS:**

- Clinical
- Paramyxovirus specific IgA or IgG.
- Viral culture is possible, but generally unnecessary as serological methods are highly sensitive.

**TREATMENT:**

- There is no specific treatment for mumps, analgesia and appropriate fluid intake being the mainstays of therapy. It has been suggested that corticosteroids may be effective for severe parotitis
- Prevention ➔ MMR vaccine.

**HIV SALIVARY GLAND DISEASE**

- Salivary gland disease can arise in 4-8 percent of adults and children with HIV infection.
- HIV salivary gland disease is a distinct disorder characterized by recurrent and/or persistent major salivary gland enlargement (mainly b/l parotid) and xerostomia. M>F
GENETIC ASSOCIATION:

- HIV salivary gland disease may be associated with HLA-DR5, and is part of a more generalized disorder termed Diffuse Infiltrated Lymphocytosis Syndrome (DILS) characterized by CD8+ T-cell infiltration of the lungs, salivary glands and lacrimal glands.

CLINICAL FEATURES:

- The clinical picture mimics that of Sjogren syndrome
- Patients with HIV disease generally do not have anti-Ro or anti-La antibodies - but do have hypergammaglobulinaemia.
- The minor salivary gland histopathology is generally similar to that of Sjogren syndrome, being dominated by perivascular, periacinar and periductal lymphocytic infiltrates, however, the majority of the infiltrating T cells are CD8+
- Salivary gland diseases in HIV can include HIV salivary gland disease proper, Kaposi sarcoma, NHL, Lymphadenopathy, Acute suppurative sialadenitis.

DIAGNOSIS:

- Again like sjogrens
- FNAC to r/o Malignancy

TREATMENT:

- Clinical signs are usually non-progressive and hence therapy is only indicated if there is notable cosmetic deformity or xerostomia.
- Antiretroviral therapy (ART) may cause at least some short-term resolution of the swelling.
- External radiation (e.g. 8-10 Gy) can cause transient improvement, although higher doses (e.g. 24 Gy) can cause resolution of disease for at least 24 months without causing severe xerostomia.
- Xerostomia independent of salivary gland involvement may arise in HIV infection as a consequence of some nucleoside analogue HIV reverse transcriptase inhibitors or protease inhibitors.

HEPATITIS C VIRUS INFECTION:

- Unlike the other hepatotropic hepatitis viruses, hepatitis C virus (HCV) frequently gives rise to a wide spectrum of extrahepatic manifestations that include salivary gland disease.
- Hepatitis C virus-associated salivary gland disease arises in perhaps as many as 80 percent of infected patients.
- MC symptom = Xerostomia
- The histopathological features of HCV-associated sialadentitis are similar, but not identical to those of Sjogren syndrome. In particular, there is a pericapillary lymphocytic infiltrate within the salivary glands.
- HCV infection may occasionally give rise to non Hodgkin's lymphoma and salivary disease akin to that of Sjogren syndrome.
SUPPURATIVE SIALADENITIS (SUPPURATIVE PAROTITIS)

Clinical features

- Acute suppurative sialadenitis is an uncommon disorder characterized by painful swelling - usually of the parotid glands (suppurative parotitis), **purulent discharge from the duct** of the affected gland.
- There is associated **dysguesia** and **cervical lymphadenopathy**.
- When disease is severe, there may be accompanying **pyrexia**, malaise and a risk of abscess formation and **parapharyngeal space infection** - including Ludwigs angina.

AETIOLOGY:

- Prematurity may be risk factor
- Usually 3 to 6 year children affected.
- Immunodeficiency and concurrent illness may predispose to childhood suppurative parotitis.
- Premature child on prolonged orogastric tube feeding.
- In adults, **longstanding xerostomia** (e.g. Sjogren syndrome) and **radiotherapy induced xerostomia** are the most likely risk factors, although other predisposing factors may include poor oral hygiene, diabetes mellitus, HIV disease and the use of total parenteral nutrition. Ductal obstruction (e.g. sialolithiasis, malignancy or foreign bodies) and infection as a consequence of bacteraemia may also predispose to acute suppurative sialadenitis.
- Can also be acquired nosocomially
- Organisms : S.Aureus, Streptococcus Viridans, Klebsiella, Bacteroides, fusobacterium, peptostreptococcus. There have been rare reports of acute sialadenitis associated with primary Mycobacterium,tuberculosis.

DIAGNOSIS:

- The diagnosis of acute suppurative sialadenitis is usually straightforward - being based upon the history and clinical picture.
- The benefits of sialography for the diagnosis of acute suppurative sialadenitis remain unclear
- Sialography may reveal areas of ductal stricture and sialectasis, the latter being most likely with recurrent disease.
- USG or MRI if abscess suspected.

COMPLICATIONS:

- There is a risk of abscess formation as a consequence of duct ectasis.
- Parapharyngeal space infection and Ludwig's angina.

Therapy

- Effective hydration and antibiotics are the mainstays of therapy (anti-staphylococcal penicillins, cephalosporins or clindamycin, flurithromycin)
Surgical drainage should be considered if there is a lack of clinical improvement after three to five days of antibiotic therapy, any (unlikely) facial nerve involvement, any involvement of deep fascial spaces, or abscess formation within the parenchyma of the gland.

Superficial parotidectomy may be required if disease becomes recurrent or chronic.

**RECURRENT PAROTITIS OF CHILDHOOD (JUVENILE RECURRENT PAROTITIS)**

- Usually associated with non obstructive sialectasis of the parotid gland.
- 3-6 yrs Males but if adults affected it is usually females.
- Localized pain and swelling upto 14 days. Fever and overlying erythema are common. Occasionally white mucous can be expressed from the parotid duct.
- U/l more than B/l
- Attacks around 1 to 5 per year.
- 90 percent patients have resolution by puberty
- USG and Sialography reveal sialectasis
- Aetiology unclear
- No treatment , Analgesics, and disease resolves.

**CHRONIC SCLEROSING SIALADENITIS (KUTINER TUMOUR)**

- Submandibular gland mostly affected
- Long standing asymptomatic swelling.
- Sialolith induced salivary stasis proposed as etiology. May be asso with retroperitoneal fibrosis as etiology.
- Histopath shows lymphocytic infiltrate, lymphoid follicle formation and extensive fibrosis with cirrhosis.

**SIALOLITHIASIS**

- **DEFINITION AND ETIOLOGY** :
  - Formation of calculus within ductal system of gland (MC submandibular > Sublingual, F>M, Adults > Children)
  - It is suggested that sialoliths may be associated with diabetes mellitus, hypertension and/or chronic liver disease and possibly nephrolithiasis.
- **CLINICAL PICTURE** :
  - Sialolithiasis presents as pain and swelling, typically in the submandibular gland with gustation or eating. The swelling is diffuse, develops rapidly and is often associated with a burning-like local pain.
  - Swelling is generally non-tender and gradually resolves over a few hours.
  - Long standing it can lead to acute suppurative sialadenitis or chronic non specific sialadenitis.
- **PATHOGENESIS** :
  - The cause of sialolith formation remains unknown, although it is suggested that development reflects a defect of migration of autophagosomes through the ductal system, or the calcification of mucous plugs.
  - The calculi are composed of both organic and non-organic material, the central medulla being the more organic.
- Calcium phosphate is the predominant salt of the calculi laid down as concentric shells of about 10 µm thickness.
- Investigations
- Plain radiographs (30% sialoliths mainly of parotid gland are radiolucent.)
- Ultrasonic scanning can detect both radiopaque and radiolucent sialoliths
- Sialography may also be helpful, although technically difficult when examining the submandibular and sublingual glands.
- CT MRI may be done

**Treatment**

- When small and accessible, it may be possible to express a sialolith from the submandibular duct by manual palpation, and many sialoliths can also be simply removed surgically - if within the anterior segment of the submandibular duct. (risk of stricture formation)
- Surgical removal of an affected gland may often be the only effective treatment for calculi in the posterior aspect of the duct or within the gland.
- Electromagnetic, electrostatic or laser lithotripsy.
- Lithotripsy may be aided by fluoroscopically guided basket retrieval of fragments or possibly sialoendoscopy. Lithotripsy seems to be most effective when the calculi are less than 7 mm in diameter
- Sialoendoscopy with subsequent balloon dilation of stenotic ducts may also be possible.

**DRUG INDUCED SIALADENITIS:**

- Painless, usually bilateral, salivary gland enlargement may be an occasional side effect of phenylbutazone, clozapine, sulphadiazine, cytosine arabinoside or chlorhexidine.

![Drug Induced Sialadenitis Table]

- Naproxen therapy was thought to be allergic in origin.
Mild acute sialadenitis (sometimes termed 'iodide mumps') can arise in response to iodine-based contrast media (e.g. for angioplasty).
Radioactive iodine, used for the treatment of thyroid cancer, can cause transient sialadenitis, indeed sialadenitis is the most frequent non-thyroid complication of radioactive iodine therapy. This sialadenitis manifests itself as transient xerostomia and unilateral or bilateral salivary gland enlargement, the parotid being particularly affected. The clinical features develop within 24 hours of iodine therapy and resolve within a week.
The risk of radioactive iodine-induced sialadenitis can be reduced by the use of lemon confectionery the increased salivary flow increasing the speed of carriage of radioactive iodine through the glands and hence reducing the extent of glandular radiation exposure.
The drugs most commonly implicated in xerostomia are TCA, BZD, Atropinics, beta blockers and antihistamines, tramadol, omeprazole, anti-HIV protease inhibitors.
Hydralazine, busulphan can lead to primary Sjogren's syndrome.

**SIALOSIS**
Sialosis is an uncommon non-neoplastic and noninflammatory disorder giving rise to bilateral non-painful enlargement of the major salivary glands.
5th to 6th decade
F>M
**PATHOLOGY :**
Although the precise aetiology is unknown, the underlying pathogenesis is thought to reflect a neuropathy.
Alcoholics, Malnutrition, Hypothyroidism, DM, reaction to antihypertensive medication, puberty, menopause.
**HPE :**
Characterized by acinar cell hypertrophy, atrophy of striated ducts with oedema of the interstitial connective tissue.
Ultimately there is widespread fatty replacement of acini.
**TREATMENT :**
The treatment of sialosis is often difficult. Management is typically directed towards correcting any underlying systemic disorder.
Rarely, surgical reduction of the parotid glands may be required.

**BULIMIA NERVOSA (Binge Eating)**
The aetiology of increased salivary gland size in bulimia nervosa remains unclear
May be, binge eating may result in functional hypertrophy of the salivary glands, Alternatively. Mild damage due to passage of fluid into the gland, autonomic neuropathy, endocrine disease or past alcohol use have also been suggested.
Of note, the salivary gland enlargement may correlate with the frequency of bulimic symptoms and with levels of serum amylase.
There presently remains no specific management for a salivary gland enlargement associated with bulimia nervosa; however. cessation of vomiting is generally associated with resolution of the parotid swelling.
Local application of heat, salivary substitutes and the use of cholinergics (including pilocarpine) may result in reduction in the size of the parotid glands. Superficial parotidectomy may rarely be required.

**PNEUMOPAROTITIS (PNEUMOSIALADENITIS, WIND PAROTITIS)**

- Pneumoparotitis is characterized by the presence of air within the parotid gland due to the reflux of pressurized air from the mouth into the parotid duct.
- The swelling may be unilateral or bilateral, and tender or non-tender.
- There may be crepitus and frothy saliva and air bubbles may emanate from the parotid duct during massage of the gland.
- The swelling of the parotid gland resolves over minutes to hours, although occasionally may take several days to resolve.
- Rarely, air may escape from the parotid gland giving rise to subcutaneous emphysema of the face and neck, mediastinum and possible pneumothorax.
- Pneumoparotitis is most likely in people where raised intraoral pressure is common - for example, wind instrumentalists, balloon and glass blowers, dental procedures using air-powered equipment, cough associated with chronic obstructive airways disease, cystic fibrosis, whistling, nose blowing and the Valsalva manoeuvre.
- There is often no need for detailed investigation as the history is often suggestive of the cause. Sialography may demonstrate air bubbles within the ducts and may also show sial ectasis if repeated episodes.
- USG and CT can be done.
- **TREATMENT:**
  - The avoidance of increases in intraoral pressures generally results in complete resolution of signs
  - Radiotherapy induced xerostomia is always irreversible.
  - Oral and perhaps high-dose topical pilocarpine may reduce the frequency and severity of radiotherapy-induced xerostomia and associated symptoms.

**SJOGREN SYNDROME**

- Sjogren syndrome is the second most common autoimmune connective tissue disorder characterized by xerostomia and xerophthalmia due to profound lymphocytic infiltration into the salivary and lacrimal glands.
- Primary Sjogren's synd. ➔ Only symptoms of eye and mouth (Xerophthalmia & Xerostomia)
- Secondary Sjogren's synd. ➔ Eye, Mouth + asso connective tissue disorder like RA and SLE.
- Many asymptomatic persons have circulating antinuclear antibodies relevant to Sjogren syndrome, but these are generally present in low titre.
- The xerostomia of Sjogren syndrome can be profound, giving rise to dysarthria and dysphagia. The oral dryness leads to retention of food on the teeth, mucosa and gingiva and thus increases the frequency of caries (particularly cervical disease) and acute gingivitis.
- There is an increased liability to candidal infection
- The long-standing xerostomia of Sjogren syndrome increases the liability to acute suppurative parotitis
The poor salivary output can lead to dysgeusia and loss of taste - many affected people report that most foodstuffs taste 'cardboard-like'.

Affected patients may have intermittent swelling of the major salivary glands - notably the parotid glands, this often reflects non-specific inflammatory change within the glands.

Solitary enlargement of a salivary gland may reflect chronic sialadentitis, acute suppurative parotitis, and importantly, mucosa-associated lymphoid tissue (MALT) tumour.

There is an increased risk of lymphoma approx. 2-4 percent of patients with long-standing Sjogren syndrome developing one or more non-Hodgkin's lymphoma within a major salivary gland.

**AETIOLOGY**

- The aetiology of Sjogren syndrome remains unknown.
- A viral aetiology - human retrovirus 5 was proposed, but now seems unlikely.

**Investigation**

- Ocular - Schirmer's test, performed without anaesthesia <= +5 mm in five minutes)
- Rose bengal score or other ocular dye score >= 4
- A low resting salivary flow rate and stimulated flow rate are typical of Sjogren's syndrome, cut off values of 0.1 mL/min for resting whole saliva and 0.5 mL/min for stimulated saliva have been considered diagnostic of gland hypofunction.
- Parotid sialography showing presence of diffuse sialectasis.
- Mandell has noted that salivary function changes, in addition to a lowered secretion rate include:
  - raised sodium and chloride but lowered phosphate;
  - raised titres of immunoglobulin (Ig)A, IgG, lactoferrin and albumin;
  - raised β2 microglobulin;
  - raised kallikrein concentrations;
  - a 20-fold elevation in the concentration of phospholipids;
  - increased concentrations of inflammatory mediators.
- Autoantibodies: presence in the serum of the following autoantibodies:
  - Antibodies to Ro(SSA) or La(SSB) antigens,

**Treatment**

**LOCAL AGENTS**

- Salivary substitutes = transient action
- Sialogogues are more effective then salivary substitutes.
- Chewing gum may enhance salivary flow rates, but these actions are likely to be transient.
- **SYSTEMIC AGENTS** :
  - Pilocarpine
  - Systemic pilocarpine increased salivary flow within two to three hours of administration.
  - A dosage of 5 mg pilocarpine four times daily for at least 12 weeks is clinically beneficial.
  - Bethanicol, Bromohexine, IFN alpha, Hydrocholoroquine, Vitamin supplementation, Acupuncture, Evening primrose oil. Electric stimulation, Cevimeline.
MICULICZ SYNDROME

- Miculicz's disease is a disorder characterized by multiple lymphoepithelial lesions of the lacrimal and salivary glands. It is probably a variant of Sjogren syndrome.

EXCESS SALIVATION (SIALORRHOEA)

- Difficulty in salivary control than hypersalivation.
- **AETIOLOGY:**
  - CP (cerebral palsy), ALS (Amyotrophic lateral sclerosis), Traumatic brain injury, stroke and Parkinson's disease.
  - Persistent drooling leads to angular cheilitis, excoriation of the lower facial skin and wetting of clothes.
  - There are no specific investigations for sialorrhoea, often the cause being established from the clinical history
  - Young adults with likely long-term illness, such as cerebral palsy, may benefit from
  - Surgical relocation of the submandibular ducts together with removal of the sublingual glands. Likewise, the parotid ducts may be relocated to pass out in the tonsillar fossa.
  - Anticholinergic agents, such as transdermal scopolamine or benztropine, have been suggested to be of longterm benefit, but
  - More recently intraglandular injection of botulinum toxin.
  - Low dose radiotherapy (8-12.5 Gy)