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and How We Fight It pg. 65

Brain Organoids in Disease Modelling
and Drug Testing pg. 104

3D Bio-Printing in Airway
Reconstructive Surgery pg. 112

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THIS ISSUE



Dear Reader,

Welcome to the second edition of Edge of Medicine, the **student-led science journal** of the European University Cyprus. This publication is dedicated to presenting the **latest research findings** in the realm of **medical sciences**.

Our mission is to keep readers informed of the most **recent pioneering discoveries** and advancements across **various medical disciplines**. Join us on this journey of discovering ground breaking research.

In this issue you can explore articles within the **categories** of: **Surgery, Neurology, Cardiology, Infectious Diseases, Dermatology, Microbiology, Pulmonology, Pediatrics, Regenerative Medicine, Otolaryngology, and Gynecology**.

I'm excited to announce that the present issue contains four **original pieces of research** that are published in our journal for the first time. You can find them in pages 11, 34, 73, 86.

If you are interested in **joining us**, feel free to **email** us at edgeofmedicine.mag@gmail.com or through our **instagram** account @edgeofmedicine.mag.

Yours sincerely,

A handwritten signature in black ink, appearing to read "Rosa Tsucala".

Rosa Tsucala
Editor in Chief
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Chronic Pain after Inguinal Hernia Repair: Risks and Management

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INTRODUCTION

Inguinal hernia repair used to carry risks concerning hernia recurrence in older times.

Although nowadays this problem has effectively been addressed, a new matter seems to have arisen causing a constant headache for surgeons regarding its solution.

Chronic pain appearing after every hernia repair and especially after **inguinal hernia repair**, is a multivariable issue, where parameters such as risk factors, different surgical techniques and management options, need to be taken into careful consideration by surgeons prior to any intervention, for the sake of the patient's health and safety.

CHRONIC PAIN

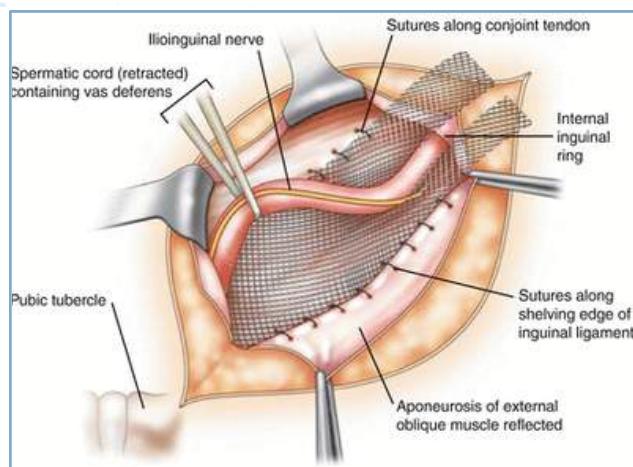
Chronic pain after inguinal hernia repair is a **common postoperative experience**. Studies suggest that anywhere from **11% to 54%** of people are affected to varying degrees, however most cases of chronic pain are mild or temporary and tend to resolve within a year after surgery. Although the definition of chronic pain tends to vary, according to latest literature studies, the physicians tend to reach a consensus stating that, pain persisting beyond the normal tissue healing time (assumed to be



be **3 months**), as defined by the **International Association for the Study of Pain**, with an extension past **6 months** (as the use of synthetic materials such as non-absorbable mesh has increased), is defined as chronic pain.

Chronic pain in the case of inguinal hernia repair can be a result of nerve injury, entrapment, or reaction to mesh, a medical device that is used to provide additional support to weakened or damaged tissue, and scar. **Proper nerve handling** at the time of initial hernia repair is crucial to decrease the incidence of chronic pain. If chronic pain exists post-operatively, the doctor may consult the patient to adopt either non-surgical or surgical methods for its management, according to **pain severity**. In cases of refractory pain, reoperation to address nerve entrapment or mesh-related complications is often needed and should be scheduled as soon as possible in order for the patient to have better chances to be relieved from the pain.

There are two different types of chronic pain a patient can experience: **nociceptive** and **neuropathic**. On the one hand, nociceptive pain (pain caused by the release of substances due to tissue damage or damage to organs) can occur mostly after **mesh malposition**, dislocation, or excessive inflammatory response of the immune system due to its recognition as foreign material. **Periostitis**, in case of mesh placement over the pubic tuber-cle, can also lead to such pain.



Nociceptive pain is usually continuous and **present at rest**. On the other hand, neuropathic pain (pain caused by damage to nerves) can be induced by partial or complete **nerve transection**, stretching, contusion, cautery damage or compression due to suture material or mesh. Neuropathic pain is described as an **activity induced**, sharp pain localized in proximity to the inguinal scar, with possible irradiating pain. Pain can also be triggered by physical examination.

The distribution of pain after an open inguinal hernia repair is the following; for the **iliohypogastric nerve**, the pain radiates to the midline above the pubis and laterally to the hip region. For the **ilioinguinal** and **genitofemoral nerves**, the pain radiates from the groin into the scrotum and penis or into the anterior part of the labia major and to the inside or the anterior surface of the thigh. Some patients reported pain at **unexpected locations**, even ones that bear no apparent relation to the innervation of the surgical field. For example, nine percent of patients have reported pain in the **lower abdomen**. These findings underline the importance of careful physical examination in diagnosing chronic post-surgical pain and its determination of nerve damage from surgery even when not suspected or identified.

PREDICTORS/RISKS

Previous studies including only patients who underwent open inguinal hernia repair have shown that the presence of **new recurrent hernias, early severe pain** after the index operation, and **young age** (<40 years) were predictors of longstanding inguinal pain. More recent studies comparing laparoscopic and open repairs have shown that chronic pain is statistically significantly more common after **open mesh repair** than laparoscopic TEP repair, while robotic surgeries had no statistically significant difference from laparoscopic surgeries. Younger age was associated with a greater incidence of chronic pain at follow up in our study, which

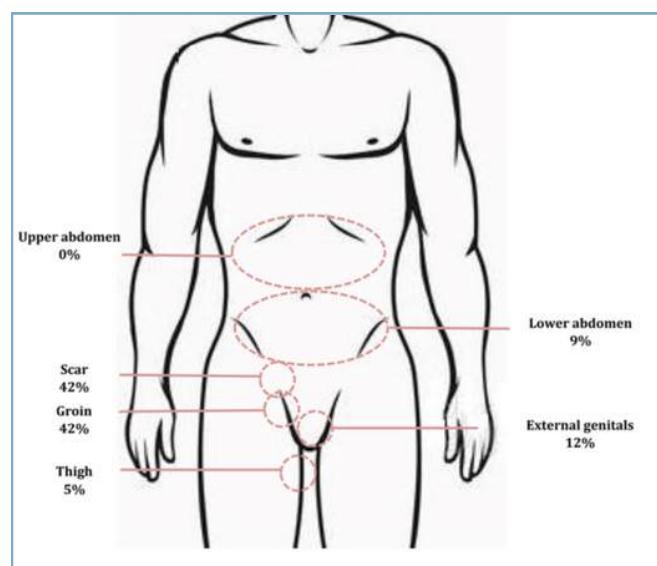
has been well-documented in the literature in patients undergoing both open and laparoscopic repair. This finding is consistent with studies that show that **female patients** are at **greater risk** of developing chronic pain after other types of operative procedures and this greater risk may be due to female patients having a greater **anxiety** regarding pain. Multiple studies have shown that preoperative pain is a risk factor for chronic pain. The fact that higher preoperative **VAS (Visual Analogue Scale)** pain scores were associated with chronic pain postoperatively is not surprising and may be an indicator that such a patient has a lower pain threshold or an **anatomic difference** predisposing to chronic pain. Finally, it was proven that use of a urinary catheter intraoperatively worked in favor of chronic pain. Studies addressing whether the use of mesh affects predisposition to chronic pain postoperatively or not, have revealed that the use of **multifilament polyester mesh** was a predictor of chronic pain, as it may cause a foreign body feeling compared with more lightweight mesh types.

MANAGEMENT

Each surgeon should bear in mind all of pre-operative, intra-operative and post-operative management of inguinal hernias and act accordingly in each case.

Preoperative pain prevention is an important step in **chronic pain therapy**, as preoperative pain is thought to be a negative prognostic factor for postoperative pain.

Randomized clinical trials concluded, cautiously, that **ketamine**, administered prior to surgery, may reduce the risk of chronic pain but that there is no evidence for recommending **gabapentinoids**, **pregabalin**, or other drugs for prevention of chronic postoperative pain. It is important to note that at this point, evidence is still not strong enough to systematically recommend **preoperative analgesics** for the prevention of chronic pain. Future studies might shed light on the matter and prove it beneficial, especially in patients at high risk of developing chronic pain.



During every inguinal hernia operation there is a risk of injuring the inguinal nerves during surgical manipulation. It is recommended, in the recently published **World Guidelines** for inguinal hernia repair, to identify the nerves but not to do a **planned resection**; however, if the nerves are in the way when placing the mesh, a "**pragmatic resection**" is recommended. If damaged nerves are found, the patient will suffer from chronic pain even after the

hernioplasty, and therefore it is recommended to consider a **simultaneous neurectomy**.

The proper management of post-operative inguinal hernia repair chronic pain initially involves physical examination in order to rule out any other possible cause of pain as well as declare any hernia repair associated pain. Afterwards, a scaled approach is recommended by first considering **non-surgical interventions** such as watchful waiting, pharmacological regimens that alleviate pain, injections and radiofrequency treatment, leaving surgery as the last resort. Surgery should include mesh removal and triple neurectomy following anterior approaches or mesh and tack removal following a posterior approach.

Watchful waiting is the first strategy implemented, as the pain might subside a few hours or days after the surgery. Basic analgesics can be used in the period of watchful waiting. If there are no improvements in the following months, a **systematic pharmacological intervention** should be approached, preferably in collaboration with **pain specialists**. Pharmacological regimens should be used as first-line treatment for chronic pain continuing **three to six months** after surgery. Some of the effective regimens include nonsteroidal anti-inflammatory drugs, gabapentinoids, tricyclic antidepressants, selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitors, and conventional analgesics.

Injections with local anesthetics have been tested and are used for both the relief of pain as well as for diagnostic purposes related to nerve damage identification. Authors recommend that this minimally invasive intervention must take place prior to explorative surgery with neurectomy, in order to control pain and enhance recovery. Injections with alcohol can be used for neurolysis. Although used conservatively, **radiofrequency ablation** constitutes a treatment method as well using heat to block the nerve (40°C), resulting in tissue damage. Lastly, an **implant device** can be used to stimulate nerves in order to provide pain relief for up to twelve months.

If all other interventions fail, the surgeon must consider **operating** on the patient. If the surgeon suspects that the mesh is the **source of the pain**, surgical removal of the mesh must be considered. However, the pain could be due to nerve damage, so simply removing the mesh may not reverse the neuropathic pain. Even if during the operation the nerves seem unaffected, there might still be ultrastructural damages to nerves that will cause pain irrespective of the mesh removal. Thus, it is recommended to perform triple neurectomy with mesh removal since it is nearly impossible to diagnose which nerves are involved in the pain. Neurectomy includes resection of the **genitofemoral**, the **iliohypogastric**, the **ilioinguinal**, or even the **lateral femoral cutaneous nerve** or a combination of these.

There is **no literature information** regarding whether selective or triple neurectomy is more beneficial for the patient. On the whole, when the nerves could be discriminated, the ilioinguinal nerve was the most frequently removed nerve, followed by the iliohypogastric nerve and the genitofemoral nerve. Replacement of the mesh should be performed in a future surgery, as a new mesh placement will make the evaluation of the outcome more challenging, especially when the pain is persistent.

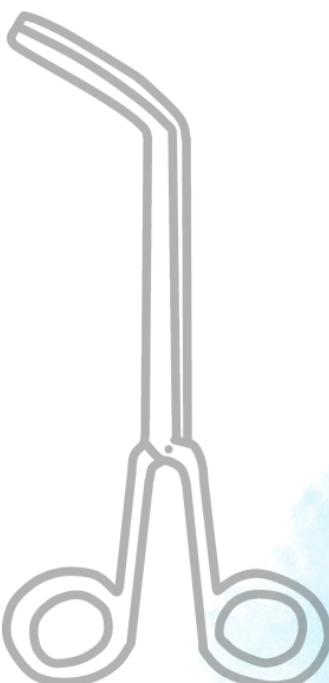
As in every surgery, **complications** can be present in this surgery as well, although limited. Hematoma formation, wound dehiscence, testicular atrophy, most probably due to ischemic orchiditis, and superficial surgical site infections were the most common complications. After mesh removal, the occurrence of a recurrent inguinal hernia can be expected as well.

CONCLUSION

Concluding this article, the cause of chronic pain after an inguinal hernia repair surgery, should be carefully examined and a discrimination should be made between nociceptive and neuropathic pain, whenever possible. The predictors and risks of chronic pain should be assessed thoroughly preoperatively and the surgeon should be aware of them in order to be able to estimate the surgical outcome and inform the patient about the postoperative recovery expectations. If postoperatively the patient presents with pain,

watchful waiting is initially suggested to evaluate whether the pain should be termed as "chronic pain" or if it subsides. In the case of chronic pain, there is a specific treatment plan with escalated non-operative therapies, with triple-neurectomy and mesh removal operation being the last treatment option, if all others fail. All in all, the cases of chronic pain require exceptional caution from the physicians' side, while the patients should be cooperative to achieve the best result for the sake of their health.

REFERENCES



Advanced Surgical Solutions for Multiple Hereditary Exostoses

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INTRODUCTION

Hereditary multiple exostoses, or HME in short, is a rare genetic disease that is exemplified by the growth of multiple osteochondromas near the growth plates of bones such as the ribs, pelvis, vertebrae, and especially long bones. Osteochondromas are benign bone tumors that grow outward from the cartilage-capped metaphysis of long bones. Initially, the osteochondromas are cartilaginous, however, over time they undertake endochondral ossification proximally and adjoin with neighboring osseous components. Osteochondromas form exclusively adjacent to growth plates, following strict pathogenic and topographical mechanisms. These tumors originate in the perichondrium via progenitor cells. HME presents with numerous clinical manifestations varying from restricted range of motion, limb deformity, chronic pain syndrome, and short stature. Individuals with HME are typically diagnosed at age of 3is rarely transformed into a malignant disease.



The risk of malignancy increases with age, although lifetime risk for malignancy remains low (2 – 5 %). Due to the considerable number of numerous are left in place. In turn, this causes life-long issues for the patient and increases the risk of malignant transformation. Currently, there is no non-invasive medical treatment to prevent or treat HME. At present, only surgery is used to remove symptomatic osteochondromas and correct physical complications.

PATOPHYSIOLOGY

Heterozygous loss-of-function mutations of EXT1 or EXT2 genes are the main cause of HME. These genes are responsible for encoding Golgi glycosyl-polymerases required for the synthesis of Heparin Sulfate (HS). HME patients exhibit a systemic decrease in roughly 50% of their HS levels, as both allele products of the EXT1 or EXT2 genes are required to function. Heparin Sulfate is a cell surface and matrix component proteoglycan that regulates a variety of physiological and

developmental processes. HS plays a role in regulating key signaling proteins in BMP (Bone morphogenic protein), FGF (fibroblast growth factor) and Hedgehog. The 50% systemic decrease in HS remains insufficient to trigger osteochondroma formation. Knudson's law of tumorigenicity states that the initiation of osteochondroma requires a more extreme decrease or complete loss in HS levels. This is accomplished by a "second hit" which consists of mutations in other genes, loss-of-heterozygosity, or aneuploidy. Studies have shown that the loss of both alleles of the EXT1 gene caused osteochondroma formation, whilst the loss of a single allele did not. Another experimental study compared the deletion of alleles of EXT1 in the perichondrium only to the growth plate and flanking perichondrium together. This study discovered that the deletion of EXT1 in the perichondrium alone is sufficient to stimulate osteochondroma formation.

NON-SURGICAL INTERVENTIONS:

There are currently no medical treatments for the prevention or treatment of osteochondromas. The mainstay of non-invasive treatment is observation as most osteochondromas are asymptomatic. As mentioned previously, osteochondromas originate in the perichondrium via progenitor cells. Thus, the onset of osteochondromas depends on the reprogramming of perichondrial cells from their normal phenotype to a chondrogenic cell lineage phenotype. This information is currently being used to develop treatment strategies that

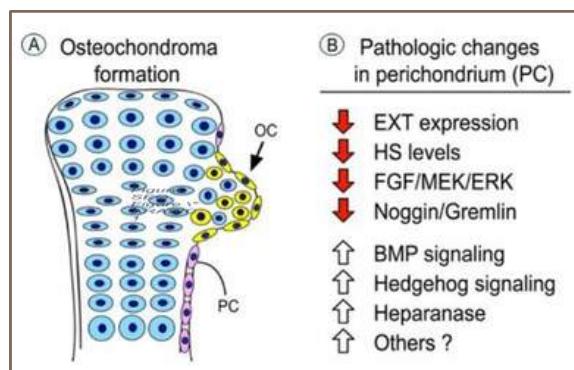


Figure 1

target signaling proteins found in the perichondrium. One significant mechanism that may play a role in reprogramming perichondrial cells from a mesenchymal to a chondrogenic lineage is the BMP signaling pathway, known for its strong chondrogenic capabilities. Studies demonstrated that canonical BMP signaling was inappropriately activated in the Ext1-null and HS-deficient perichondrium in HME mouse models (refer to Fig. 1), leading to the formation and growth of osteochondromas. These findings align with the understanding that HS and HS-rich proteoglycans typically restrain and modulate BMP signaling, allowing this pathway to become overly active during HS deficiency. This research has identified a specific therapeutic target, and Sinha et al. were the first to show that systemic oral administration of a BMP signaling antagonist effectively inhibited osteochondroma development in mouse models. Their data was confirmed by another group, which saw the treatment reduce osteochondroma size and volume by over 60% by 6 to 8 weeks. The drug used in the study was LDN-193189, an inhibitor of canonical BMP signaling.

SURGICAL INTERVENTIONS:

Surgical resection is the main course of treatment for osteochondromas that present symptoms. To stop recurrence, it is imperative to make sure that neither the cartilage cap nor the perichondrium are left in the resection bed. Ideally, the resection should be performed at the base of the stalk to remove the entire lesion along with its fibrous covering in one piece. When resecting a lesion from a patient with skeletal immaturity, it's critical to protect the growth plate. According to a limited research of young patients (average age 3.6 years) with digital osteochondromas, early surgical intervention is advised for lesions in the bone's non-epiphyseal metaphysis in order to preserve normal finger shape if recommended for laterally orientated tumors involving less than one third of the joint surface. Prior to undergoing surgical treatment, it is advisable to consider the likelihood of spontaneous regression of solitary osteochondromas in youngsters, since certain cases have been reported.

In rarer cases, more demanding surgical techniques may be required. This includes corrective procedures such as lengthening or corrective osteotomies. If the osteochondroma has caused a limb length discrepancy, treatment options involve lengthening the short limb with external fixation; Precice internal lengthening nail; and growth plate fusion (epiphysiodesis)

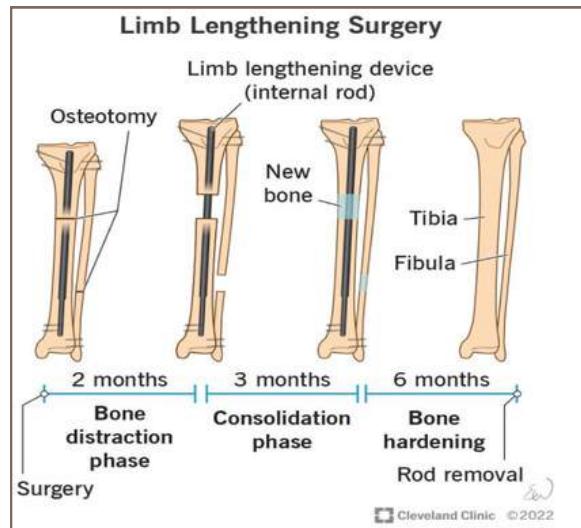


Figure 2

on the unaffected limb. Limb lengthening is a gradual process, typically taking several months. Limb lengthening involves an osteotomy followed by the insertion of an orthopedic lengthening device to the bone. Devices that remain on the outside of the body are known as external fixators, and devices inserted in the bone are internal devices, for example the Precice nail. After the surgical procedure, the bones are left to rest for up to a week. After this, the patient manually adjusts the orthopedic device, slowly pulling apart the two bone pieces. This process is known as the distraction phase.





As the two bone pieces are pulled apart, new bone forms between them, increasing the overall bone length. This new bone is known as regenerate bone. During the distraction phase, the patient adjusts the device, slowly pulling the bone apart roughly 1 mm per day. This phase lasts until the desired bone length is reached. Once the desired bone length is reached, an additional 2-3 months is required for the new bone to solidify. This is the consolidation phase. After this phase is complete and the bone has fully healed, the orthopedic device can then be removed.

CASE STUDY & CLINICAL OUTCOMES

A case report on PubMed from 2022 presents an otherwise healthy 13-year-old boy with many palpable and tender masses on his upper and lower extremities, along with right shoulder pain, of duration 2-3 months. Masses had been coming and slowly and progressively increasing in size and number during the past 10 years.

Past medical history revealed HME since the age of 6, and he had undergone surgery to remove osteochondromas from both scapulae.

Family history revealed that the boy's father, paternal grandmother, and paternal aunt were affected; about half of the family members were affected with HME. Genetic testing failed to show mutations in EXT1, EXT2, or EXT3 genes.



Figure 3

His physical examination and laboratory tests were unremarkable. There were, however, multiple osteochondromas at different sites in radiographic studies, specifically: distal radius and ulna; distal and proximal femurs, tibias and fibulas. Most of the osteochondromas showed ring and arc calcification in the right humeral metaphysis, suggesting possible malignant transformation.

An MRI with contrast showed a 6 cm mass with lobulated margins arising from the right humeral metaphysis. The mass was hyperintense to proton density fat-saturated images, hypointense to T1-weighted images, and had a cartilage cap measuring 2-3 mm in thickness that contained heterogeneous calcifications.

The boy underwent surgical excision of the right humeral mass. Though there were some complications during surgery, it was finally successful, and histological examination of the mass did not show any malignant tissue (Ha, 2022).

CONCLUSION

Heredity Multiple Exostoses (HME) is a genetic disorder of a very rare occurrence, and osteochondromas are the most common bone tumors occurring in both solitary as well as multiple forms of this tumor. MRI and CT are the main imaging techniques to visualize these tumors. Though there is an increased risk for malignant transformation in patients with HME, malignant change is relatively rare in benign osteochondromas. MRI is best suited for determining whether an osteochondroma is malignant, with cartilage cap thickness greater than or equal to 1.5 cm indicating the presence of malignant transformation. Also note that some patients with classic HME will test negative for EXT1, EXT2, and EXT3 mutations.

Surgical excision is the mainstay of treatment for symptomatic and large osteochondromas, and removal of the perichondrium significantly reduces the recurrence risk. The average number of surgeries required is about 2.5 for HME. Overall, surgical intervention brings down recurrence rates to about 0% to 15%.

Metastasis usually occurs in the lungs, and patients need to undergo MRI screening on an annual basis. The surgical treatment renders the person symptom-free, with low recurrence rates, few complications, and good follow-up to monitor malignancy.

REFERENCES



ACL RUPTURE: CONSERVATIVE VS. SURGICAL TREATMENT OPTIONS AND THEIR OUTCOMES

INTRODUCTION

The Anterior Cruciate Ligament (ACL) located in the knee is one of the most common ligaments in the body to be injured and commonly also involves trauma to the menisci, cartilage and/or other ligaments. (1) Due to its crucial role when it comes to stabilization of the knee joint, it is very important to identify and treat this trauma appropriately. In order to find the most suitable treatment option, many factors such as age, comorbidities and level of activity must be taken into account. (2) The biggest difference when it comes to treatment is decided between the conservative method or surgical method. The following article provides information on the choices and their outcomes.

ANATOMY AND PHYSIOLOGY OF THE ACL

With regards to treatment options, it is crucial to know the anatomy and physiology of the Anterior Cruciate Ligament (ACL). It is one of the strongest ligaments in the body; it protects the knee from anterior tibial translocation and rotatory force. The origin begins in the anterior intercondylar area of the tibia, then continues superoposteriorly and laterally to its insertion at the posteromedial side of the lateral femoral condyle.

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As it travels upwards it builds a cross with the posterior cruciate ligament hence the name cruciate. Both are contained within the joint's capsule. The ACL consists of two bundles, the antero-medial (AM) and the postero-lateral (PL) bundle which vary in their tension load according to the position of the knee. During flexion of the knee, mainly the AM bundle receives tension and during extension, mainly the PL bundle receives tension. Thus, the knee retains stability in regard to rotation and anterior translocation in every degree.(3)



Figure 1: Anatomy of the whole knee (11)



Figure 2: Anatomy of the double bundle formation; AM shown with solid line; PL shown with dashed line (18)

EPIDEMIOLOGY

With its annual incidence of 68.6 per 100.000 patient-years, ACL rupture is a major burden to individuals and society because the risk of sustaining an ACL rupture is high. (4) Especially females have been found to be at greater risk (1.4 - 9.5 times higher risk) compared to males resulting in a higher incidence in this gender group. These outcomes have been attributed to differences in intrinsic factors of the human body such as hormonal fluctuation, quadriceps dominance over hamstrings and greater pelvic width as well as extrinsic factors such as access to training facilities. (5)

MECHANISMS OF INJURY

Rupture of the ACL is most commonly found in young athletes due to traumas occurring during sports.

The mechanism of injury is generally divided in injuries sustained during an episode of contact and non-contact injuries. The latter (non-contact injuries) being way more common making up 70% of torn ACLs. During an injury contracted due to a contact, the lower leg is completely fixed while a torque with high force occurs whereas in non-contact injuries the force originates within the athlete itself including a quick change of direction and/or speed, jumping and pivoting. Thus athletes participating in specific sport activities such as soccer, skiing and basketball are predestined for such types of injuries. (6)

SYMPTOMS, DIAGNOSIS AND CLASSIFICATION OF INJURY

When sustaining an ACL rupture, patients often describe the feeling and/or sound of a pop. Additionally, they might feel pain and instability of the joint. During observation and examination depending on the degree of injury swelling due to effusion is found and even hemarthrosis in some cases, causing decreased range of motion in many patients. (6) These signs and symptoms often make physical examination difficult in the first few days. However, evaluation of the knee should be done as soon as possible.

Physical tests such as the Lachman test and the anterior drawer test, that are considered very accurate can aid in diagnosing a ruptured ACL.

During the Lachman test, which is the most sensitive test the patient is in supine position and the knee is flexed to 30 degrees. The examiner then pulls the tibia forward while fixating the femur. The test is considered positive when the tibia translocates anteriorly in relation to the femur.

Whereas during the anterior drawer test the patient's knee is flexed to 90 degrees while supine with the foot planted to the surface. The examiner attempts to move the proximal tibia forward after gripping it and placing the thumbs on the joint line. The test is considered positive when the tibia translocates anteriorly in relation to the femur.

In order to confirm the diagnosis in clinical practice an MRI is necessary during which the discontinuity or absence of the fibers or edema can be visible. Additionally, it is helpful to identify further injury coexisting with an ACL tear. (7)



Figure 3: T2 MRI sequence showing an ACL tear (14)

Based on the findings, the American Academy of Orthopedic Surgeons has classified the injury into Grade I, II or III. The definitions of each is listed in the table below. (8)

American Academy of Orthopaedic Surgeons ACL injury grading

ACL: Anterior Cruciate Ligament

Ref no- [3]

Grade 1 The ligament is stretched slightly, but the stability of the knee joint is not affected.

Grade 2 A stretch of the ligament to the point that it becomes loose, and this is also referred to as a partial tear.

Grade 3 The ligament is completely torn into two pieces, and the knee joint is no longer stable. This is the most common type of ACL injury.

Figure 4:
American Academy of Orthopedic Surgeons ACL injury grading (8)

CONSERVATIVE TREATMENT OPTIONS

Conservative treatment options when it comes to a torn ACL are quite limited, yet can be effective in certain patients. Especially during the first hours to days of injury every patient should have an adequate pain management plan that includes painkillers such as NSAIDs as well as topically cooling the knee. Additionally, they should rest and elevate the affected leg. In order to stabilize the knee during the day and night, braces can and should be worn performing certain activities in order to prevent further injuries due to the unstable knee. However, braces have shown not to be effective in improving the function. The most important form of conservative treatment is physical therapy. Treatment plans include re-establishing the full range of motion and then proceeding to strengthen the muscle groups around the knee to gain stability and attempt to replace the ACL. These muscles include the quadriceps, hamstrings, hip abductors, and core muscles. (7) Electrical stimulation can help in restoring and improving neuromuscular responses. (9) The decision for treating the patient conservatively is based on factors such as age, demand for physical activity and comorbidities. Patients that suffered a partial tear only have an indication for non-surgical treatment. This option is most often not suitable for people involved in high demand activities required during their profession as well as patients and athletes performing sports that are straining the knee, including certain movements such as pivoting and quick directional changes. These patients often require more permanent solutions that can only be solved by surgery. (6, 7)

SURGICAL TREATMENT OPTIONS

Surgical ACL reconstruction (ACLR) includes various possible techniques, and many factors influence the outcome. The procedure usually includes a graft that is inserted at the original location of the ligament through bone tunnels created into the femur and tibia to fixate the graft. The surgery is done arthroscopically thus being minimally invasive. Over the years, many reconstructive techniques have been developed to insert these grafts provided with different advantages and disadvantages shown in the table below.

A summary of the surgical techniques		
Surgical techniques	Pros	Cons
ACL reconstruction		
TT	–	Non-anatomic femoral tunnel position (34,35)
Transportal	Femoral tunnel position more anatomical than TT (36) Better rotatory stability of the knee than TT (10,36-39)	Still high graft failure rate and osteo-arthritis changes (23-26) The injury of the infrapatellar branch of the saphenous nerve injury (37)
All-inside	Capable of preserving the epiphysis (40) Less invasive technique (41)	A long learning curve (41) Technically difficult (41)
Over-the-top	Capable of preserving the epiphysis (42) Good knee stability in revision and skeletally immature cases (42,44,45)	non-anatomic reconstruction (43) High graft failure rate in younger patients (42,45,46)
Double-bundle	Better knee stability than single-bundle (11,47,48) Similar or better clinical outcomes compared to single-bundle (50-55) More anatomical reconstruction (57,58)	Long learning curve (49) High costs (56) Tunnel coalition (59-63)

Figure 5: A summary of surgical techniques of ACL reconstruction; TT: transtibial (17)

Different factors for example choosing the correct graft, correct positioning the tunnels and timing of the procedure determine the outcome of the surgery.

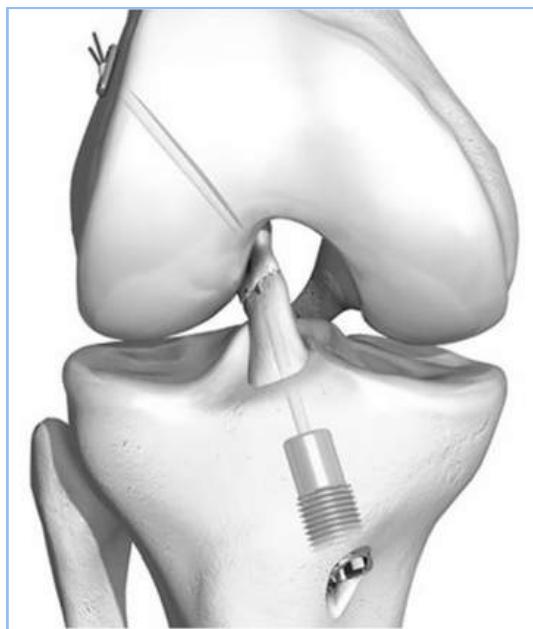


Figure 6: Visualization of an ACL reconstruction (19)

The graft can either be an allograft or an autograft meaning, either given by a donor or resected from the patient's own body with the latter (autografts) being more common due to lower risks of rejection. The graft is usually a tendon taken from a muscle in the leg. Various muscles have shown to provide for good grafts depending on several factors. One of the most commonly used muscles are the hamstrings, more specifically the semitendinosus with or without the gracilis muscle. The advantages of these is the low donor site morbidity and fast physical recovery time.

Unfortunately, this graft type is not as strong as others and has been shown to correlate with higher re-rupture incidences. It is not suitable for athletes as well as patients that have an additional rupture of the medial collateral ligament (MCL) since the removal of the tendon (travels along the medial side of the knee) would destabilize the knee medially even further. Another autologous graft type is the bone patellar tendon bone (BPTB). It used to be the gold standard because of its great strength (~160-170% stronger than native ACL) leading to lower retear rates, and good results in stabilizing the knee. However, many studies have found that it is often associated with anterior knee pain, kneeling pain as well as an increased risk of patellar fracture patellar tendon tear. Using the quadriceps tendon as a graft is also an option. Its advantage is a reduced rate of anterior knee pain while having a nearly as good strength as the BPTB graft. Compared to the hamstring graft studies, they have shown less flexor deficit but higher extension deficits that may persist in a form of weakness up to several years after the surgery. It also showed a lower re-rupture risk. (7, 10, 11, 12) Picking the right timing for performing the surgery plays an important role. Yet, the optimal timing has not been clearly defined but studies have shown that neither performing it within the first days nor after one year, provides optimal results.

The risks of undergoing the procedure within the first week has been associated with an increased risk of arthrofibrosis. Early reconstruction has also been linked to a decreased quadriceps strength. On the contrary delaying surgery for too long increases the risk for additional meniscal injury and chondral injuries. Despite these factors early surgery is limited by factors such as perioperative swelling, edema, hyperthermia, and ROM. Nevertheless, taking all these factors into account, no surgical technique nor timing is fully effective if there is no physical therapy prior and afterwards to reduce edema and swelling, restore the range of motion and support muscle strengthening and stabilization. (1, 17)

OUTCOMES

The outcomes of both conservative and surgical treatment have been very similar. Only in one point there seems to be a superiority of performing surgery. Studies have shown that surgery is superior when it comes to knee joint stability. (13) This is the reason why many patients, who have initially opted for a conservative strategy then decide to proceed with ACLR due to the remaining instability which potentiates further injuries due to falls. Especially when it comes to returning to pre-injury sporting level, non-operated people often don't achieve their prior results and have to reduce their activity level or even have to avoid certain activities.

This means that active patients that wish to return to their jumping, cutting and pivoting sports should undergo reconstruction of their ACL. But with surgery, many patients are able to return to their normal activities (80%), especially among professional athletes the majority (83%) return to their prior capacities. Whereas in the non-operated only 19% manage to do so. In order to achieve superior surgical outcomes the surgical technique needs to be optimal, meaning that the surgeon needs to perform the right drill-tunnel placement, appropriate graft selection and secure graft anchoring. (12) Additionally, patients with accompanying injuries to the menisci or collateral ligaments should be advised for surgery due to their even greater instability. (14) Some studies suggest that surgery provides a higher long-term quality of life. Despite what was thought for many years, recent data has shown that there is no definite increased risk for developing osteoarthritis if opting for conservative treatment. What also needs to be considered is the fact that after undergoing surgery a longer recovery period of at least 4-6 weeks is needed before being able to return to normal activity. Compared to conservative treatment where only 1-2 weeks is needed, depending on the individual's pain. This is an important factor that needs to be evaluated in regard to the person's profession and day to day life. (8)

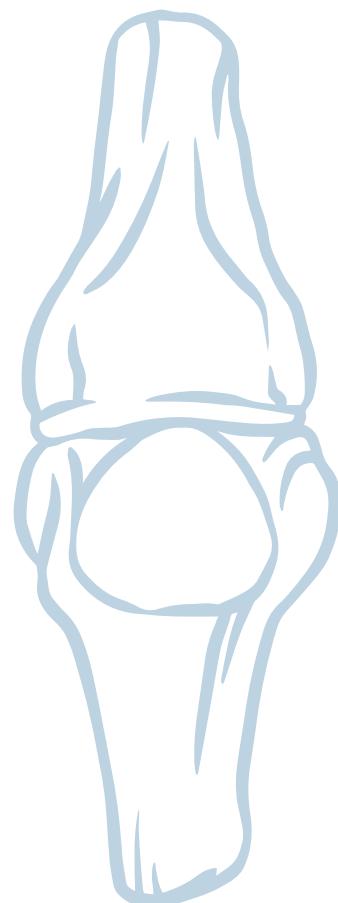
Surgical interventions are also related to higher costs which is another factor. All in all it must be said that the outcomes are very dependent on the level and quality of physical therapy. The chances are high that patients return back to their pre-injury state with minimal to none disabilities left with both options showing that conservative treatment with rehabilitation is a realistic alternative. (4, 13, 15, 16)

CONCLUSION

An ACL tear is a great burden in society, as it is one of the most common ligament injuries especially among female athletes. Despite its frequency, research is not unanimous about the best treatment because no definite superiority for either treatment option has been clearly identified yet. It greatly varies from situation to situation and depends on various factors (age, level and type of physical activity, exertional force on knee during day to day life and level of instability) which determines the options the patient should be advised with according to individualized treatment plan. In the end, it is always a patient's decision.

For certain circumstances there have been clear guidelines on performing surgery such as in athletes or when there are additional injuries to the knee such as a MCL tear and/or meniscal lesion.

For patients with only a partial tear the research recommends on proceeding with conservative treatment since surgery has no benefits in these cases. However more long-term studies are needed to clearly distinguish whether conservative or surgical treatment is the optimal.



REFERENCES





WRITERS

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Recent Advances in Diagnosis and Treatment of Alzheimer's Disease

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ABSTRACT

Dementia, impacting memory and cognitive functions, is predominantly caused by Alzheimer's Disease (AD), which accounts for 60% to 80% of cases in the elderly. AD is marked by neuronal atrophy, amyloid-beta plaques, and neurofibrillary tangles. Genetic factors like mutations in APP and ApoE* ϵ 4 contribute to its development. Recent advances in biomarker research and imaging techniques have enhanced early diagnosis. Emerging treatments, including monoclonal antibodies such as Donanemab, Aducanumab, and Lecanemab, show promise in slowing disease progression. This article reviews the pathophysiology, diagnostic advancements, and novel treatments for AD.

INTRODUCTION

Dementia is an umbrella term with a group of symptoms affecting memory, thought processes, and social interactions to a sufficient extent to interfere with daily life. It is accompanied by cognitive changes such as memory loss, confusion, getting lost, inattention, diminished problem-solving ability, impaired reasoning, loss of organisational skills, and loss of coordination.

Psychological changes also are seen, such as depression, anxiety, agitation, anger, inappropriate behaviours, and personality changes. [1]

Alzheimer's Disease (AD) is the most common cause of progressive neurodegenerative dementia [2] and accounts for 60% to 80% of cases in the elderly. As the global population ages, the prevalence of AD is expected to increase dramatically, posing significant challenges for healthcare systems, caregivers, and patients. The earliest signs are an impairment of recent memory function and attention, followed by failure of language skills, visual-spatial orientation, abstract thinking, and judgement. Alterations of personality inevitably accompany these defects.[3]

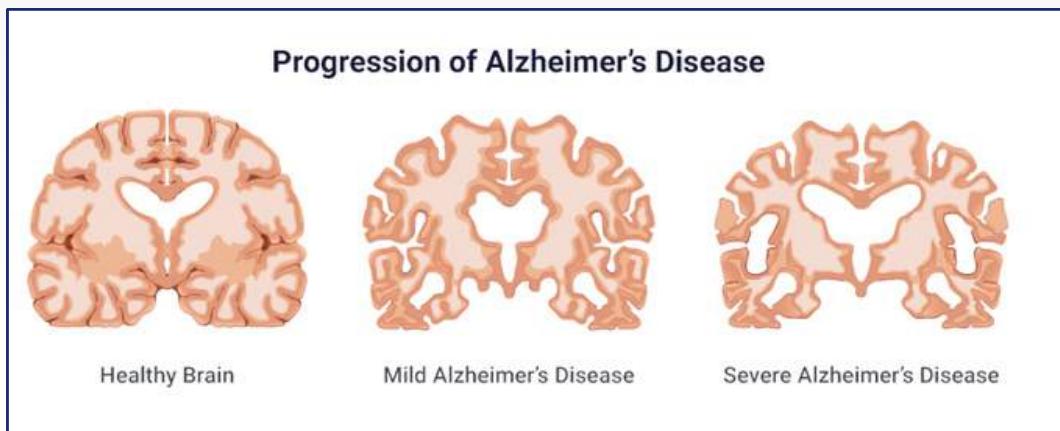
AD is characterised by extensive neuronal atrophy, especially in the cerebral cortex and hippocampus, due to a dramatic loss of acetylcholine (ACh).



The disease involves accumulation of amyloid-beta ($A\beta$) plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein in the brain, leading to a neuronal loss in the basal nucleus and nearby cholinergic cell groups.

[4] **[Fig. 1]**

*Fig. 1:
Coronal
sections of
the brain
depicting
the
progression
of the
disease [5]*



Recent years have seen significant progress in the diagnosis and treatment of AD. Advances in biomarker research and imaging techniques have enhanced early detection, while new therapeutic approaches, such as monoclonal antibodies targeting amyloid-beta, offer promising avenues for treatment.

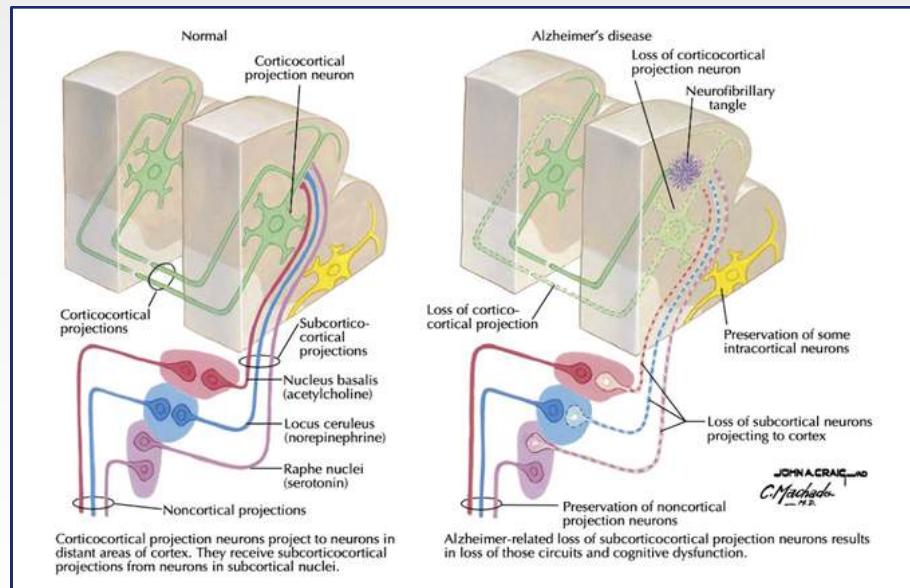
PATOPHYSIOLOGY

A healthy adult brain has billions of neurons, each with long, branching extensions. These extensions enable individual neurons to form connections with other neurons. At such connections, called synapses, information flows in tiny bursts of chemicals that are released by one neuron and taken up by another neuron.

The brain contains trillions of synapses, allowing signals to travel rapidly through the brain. These signals create the cellular basis of memories, thoughts, sensations, emotions, movements and skills. [6]

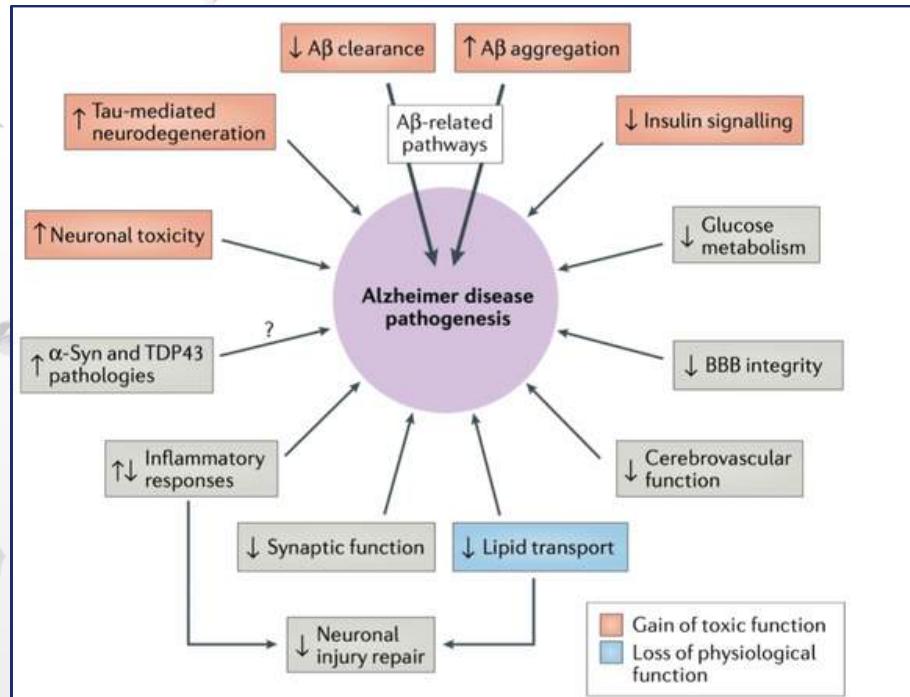
AD is characterised by accumulation of $A\beta$ plaques **outside** of neurons, and accumulation of neurofibrillary tangles composed of hyperphosphorylated tau protein **inside** of neurons, resulting in widespread neuronal loss. Together, they interfere between neuron-to-neuron communication at synapses and block the transportation of nutrients and other molecules essential for the normal function and survival of neurons. Their presence triggers an immune response, activating microglia and astrocytes, the primary immune cells of the brain, and releasing pro inflammatory cytokines, causing chronic neuroinflammation. This chronic neuroinflammation further exacerbates neuronal injury and contributes to the progression of AD.[6] **[Fig. 2]**

Fig. 2: Selective loss of cortico-cortical and subcortico-cortical projections [1]



Genetic predisposition also plays a pivotal factor in AD. When scientists started investigating mutant genes responsible for familial AD, they first looked at mutations of the gene encoding amyloid precursor protein (APP).^[3] Apolipoprotein-E ε4 (ApoE*ε4) has the best established association with the most notable genetic risk factor. It is associated with exacerbation of intraneuronal accumulation of Aβ, plaque deposition in the brain parenchyma and formation of neurotoxic Aβ oligomers [Fig. 3].^[7] Other genes involved include Presenilin-1 (PSEN1) and Presenilin-2 (PSEN2). Mutations of these two genes modify processing of APP and result in increased amounts of a particularly toxic form of Aβ peptide, Aβ42.^[3]

Fig. 3: Effects of APOE-ε4 on AD pathogenesis pathways [7]



ADVANCES IN DIAGNOSIS

Historically, the diagnosis of AD relied heavily on clinical evaluations and basic imaging techniques, such as MRI and CT scans. These methods were commonly used to visualise brain atrophy, particularly in the hippocampus. While useful, they lacked the specificity to identify the molecular changes characteristic of AD.

A very recent large-scale prospective cohort study, named COAST, showed that preclinical AD has been characterised by the presence of normal cognitive function and abnormal levels of cerebrospinal fluid (CSF) and blood biomarkers. CSF and blood samples, along with neuroimaging and neuropsychological examinations were being collected every 2-3 years, for a maximum followup time of 20 years.[8]

Neuropathologic abnormalities and changes in biomarker levels can begin **15 to 20 years before** clinical manifestations of AD! These CSF biomarkers include changes in levels of A β 42/40, tau protein[14] and phosphorylated tau181, and neurofilament light chain (*NfL*). These are indicators of preclinical AD and become abnormal sequentially, rather than simultaneously. The longitudinal study, based on comparative tests, demonstrated that **A β 42** levels start to decline approximately **18 years** before diagnosis, followed by *increases* in **NfL**, **p-tau** and **total tau** levels, which begin to change around **10 years** before diagnosis of AD.[8] **[Fig. 4]** **[Fig. 5]**

Recent advances have also allowed for the development of blood tests, such as those detecting plasma p-tau217, offering a less invasive and more accessible diagnostic tool. Comparative studies of plasma assays have demonstrated their high sensitivity and specificity for AD. One study compared two plasma p-tau217 assays, showing strong diagnostic performance and consistency with tau Positron Emission Tomography (tau-PET) imaging results.[9] tau-PET was highlighted as "*the best currently available neuroimaging marker*" in a very recent study showing the best performance as a stand-alone marker to predict progression to dementia[13]. **[Fig. 6]**

ADVANCES IN TREATMENT

The treatment landscape for AD is rapidly evolving, with significant progress in developing Disease-Modifying Therapies (DMTs). The current picture of available treatments for AD is limited, with many therapies and medications focusing solely on supportive care of patients and improving symptoms, rather than battling the disease.

There are at least three Cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and a N-methyl-d-aspartate (NMDA) antagonist (memantine) that do not affect the underlying brain changes that cause symptoms, nor do they alter the course of the disease. They improve symptoms by increasing the amount of neurotransmitters in the brain.

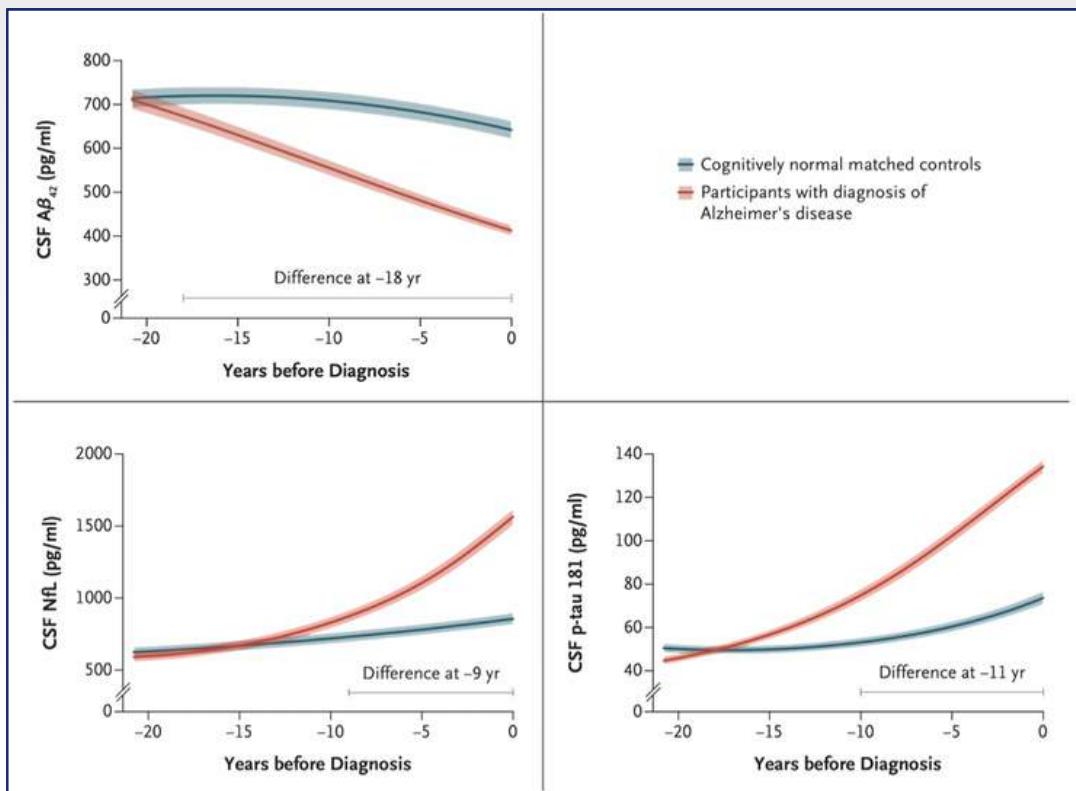


Fig. 4: Trajectory of Biomarkers before Diagnosis of Alzheimer's Disease [8]

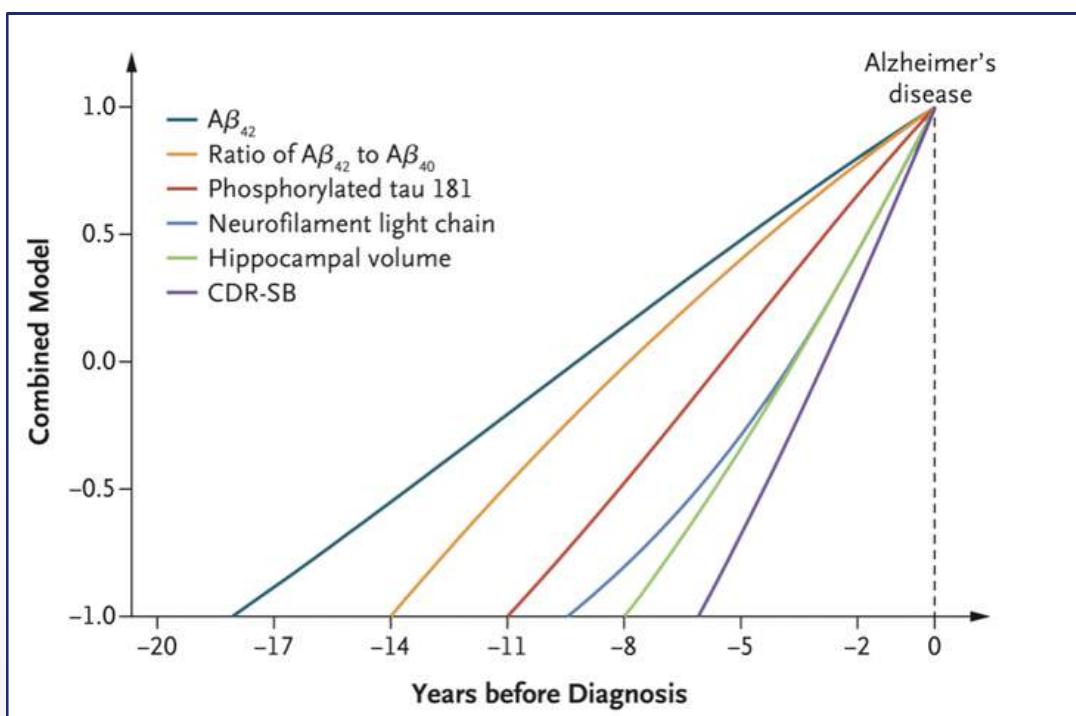


Fig. 5: Evolution of Biomarkers before Diagnosis of Alzheimer's Disease [8]

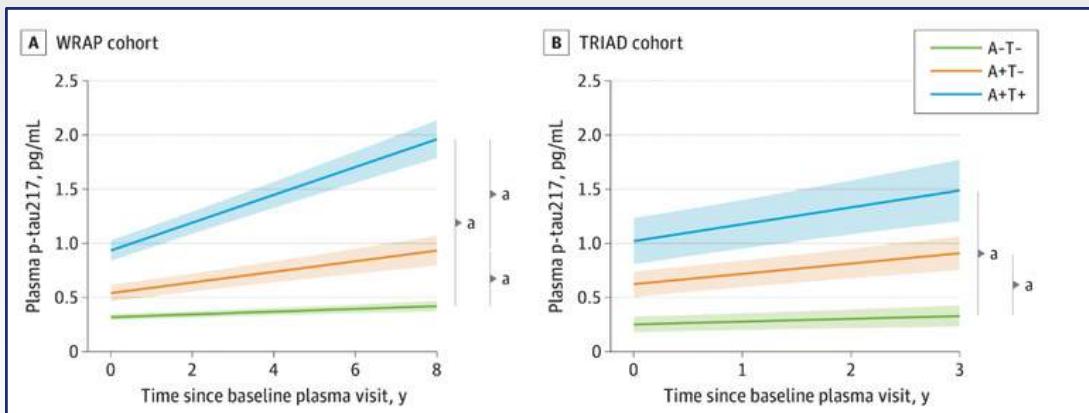


Fig. 6: Longitudinal Trajectories of Plasma Phosphorylated Tau 217 (p-Tau217) Values According to Amyloid β (A) and Tau (T) Status [9]

One of the most promising developments in AD treatment is the use of monoclonal antibodies targeting A β , namely **Donanemab**, **Aducanumab** and **Lecanemab**. These DMTs aim to reduce the accumulation of amyloid plaques in the brain.[10]

Aducanumab was one of the first monoclonal antibodies approved by the FDA for AD treatment. It works by binding to amyloid plaques and facilitating their clearance from the brain. Clinical trials have shown that aducanumab can reduce amyloid levels, although its efficacy in improving cognitive outcomes has been a subject of debate.[10]

Lecanemab is a recombinant humanised immunoglobulin gamma 1 (IgG1) anti-amyloid monoclonal antibody that binds to amyloid oligomers, protofibrils, and insoluble fibrils. It targets soluble A β aggregates, preventing them from forming plaques. It has shown promise in clinical trials by slowing cognitive decline in patients with early AD.[11]

Very recently, the FDA approved Donanemab for early Alzheimer's treatment. It is an IgG1 monoclonal antibody directed against insoluble, modified, N-terminal truncated form of A β present only in brain amyloid plaques. Targeting this modified form of A β , it allows it to remove amyloid plaques. A unique feature of donanemab is its finite dosing regimen, where treatment can be discontinued once amyloid plaques are no longer detectable, potentially leading to cost savings and higher patient preference. Among participants with early symptomatic Alzheimer disease and amyloid and tau pathology, donanemab significantly slowed clinical progression at 76 weeks[12] **[Fig. 7]**

CONCLUSION

Alzheimer's Disease poses significant challenges due to its complex nature and growing prevalence. Advances in biomarker research and imaging have improved early detection. New treatments, particularly monoclonal antibodies targeting amyloid-beta, offer hope in slowing disease progression. Ongoing research is essential to refine these therapies and explore new prevention and treatment strategies, aiming for better patient outcomes and effective management of AD.

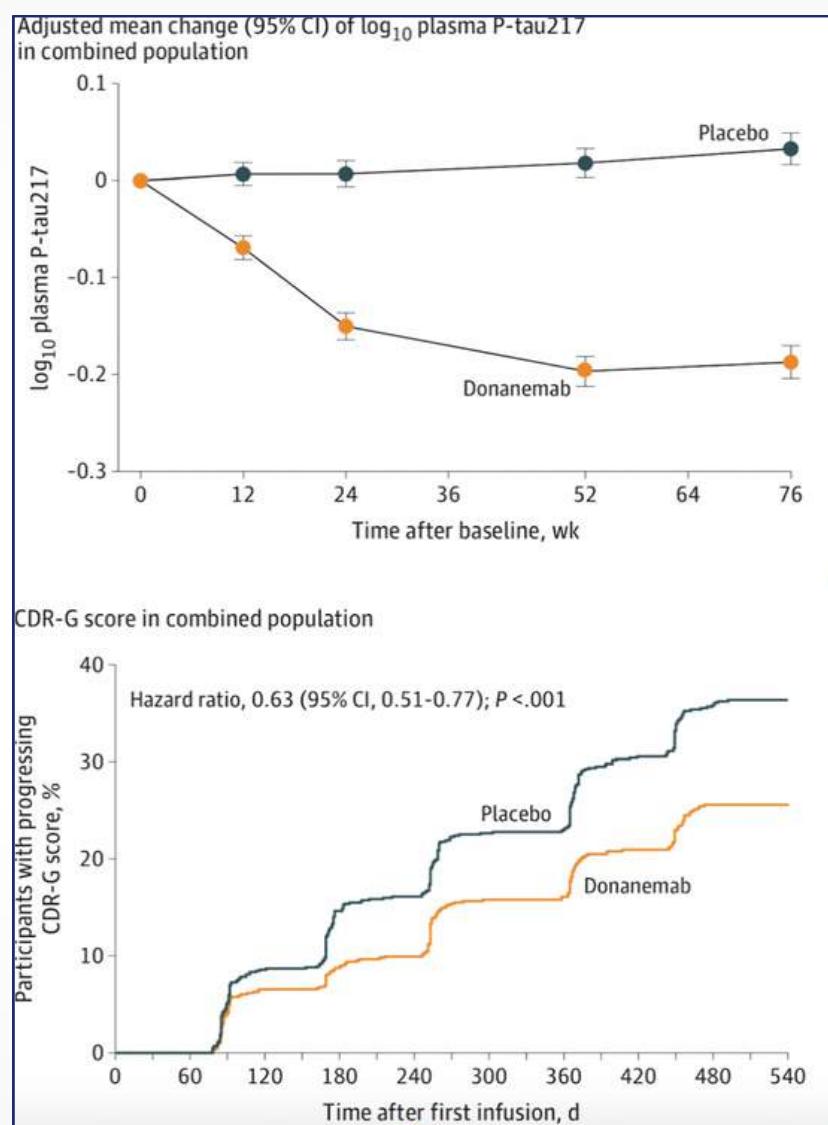


Fig. 7: Adjusted mean change (95% CI) of \log_{10} plasma P-tau217 (up) and CDR-G (Clinical Dementia Rating) score (down) [12]

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Leukodystrophies : **ACUTE DISSEMINATED ENCEPHALOMYELITIS**

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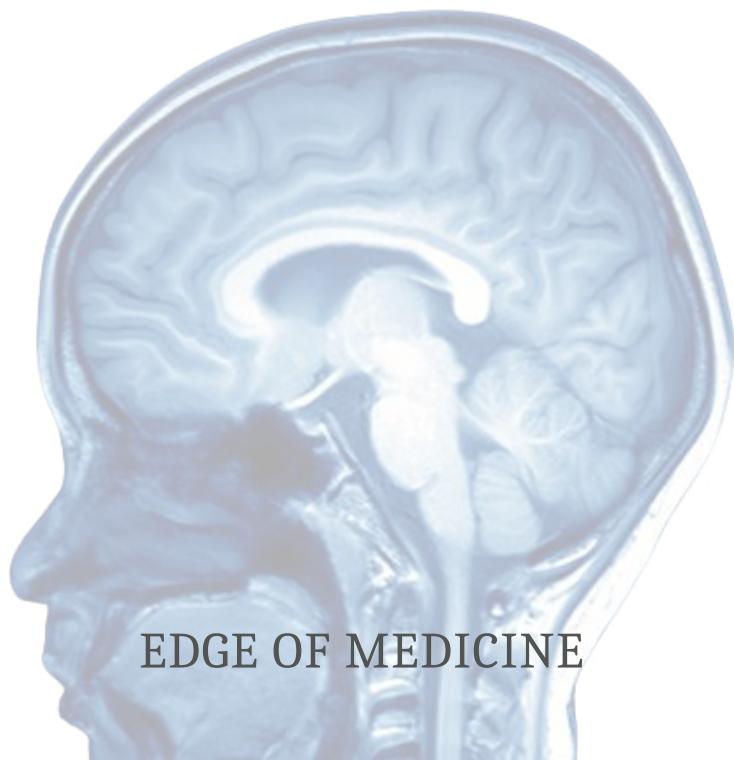
ABSTRACT

Leukodystrophy denotes a classification of rare, neurological disorders. It refers to genetic diseases that mainly affect the white matter of the central nervous system. To date, over 50 distinct leukodystrophies have been identified, including Acute disseminated encephalomyelitis (ADEM). ADEM is an uncommon, demyelinating condition of the central nervous system, marked by extensive inflammation and damage to the myelin sheath in the brain and spinal cord. It is usually triggered by a preceding viral or bacterial infection, and, though less frequently, can also follow vaccination. The pathogenesis of ADEM is still not fully understood, though prevailing theories propose that it involves a complex interaction of immune system dysfunction and autoimmune responses. ADEM can cause substantial neurological deficits and, in rare cases, may be life-threatening, emphasizing the necessity for immediate diagnosis and treatment.

INTRODUCTION

A leukodystrophy is a type of rare neurological disorder that affects the white matter of the brain and spinal cord. One of the rarest forms of leukodystrophy is Acute disseminated encephalomyelitis (ADEM), also known as post-infectious encephalomyelitis.

More specifically, ADEM delineates a swiftly progressing autoimmune disorder. This condition is marked by the demyelination (the term demyelination describes the damage caused to the myelin sheath, a protective cover that surrounds nerve fibers) of the brain and spinal cord, precipitated by an inflammatory response following a prior infection or immunization. The disease exhibits significant clinical heterogeneity with a wide range of clinical manifestations, from generalized central nervous system involvement and symptoms of encephalopathy with seizures to milder syndromes such as optic neuritis or myelitis.



The course of the disease is typically monophasic. However, there has been controversy regarding the existence of relapsing and multiphasic forms of the disease, due to the views that raise differential diagnostic challenges in distinguishing it from multiple sclerosis.

PATOPHYSIOLOGY

The precise mechanism underlying ADEM remains unknown; however, it is hypothesized to be linked to an atypical immune response triggered by an infection. An initial illness or infection is observed in 70-80% of ADEM patients. Other infections associated with the onset of ADEM include influenza, measles, mumps, rubella, varicella-zoster, Epstein-Barr virus, cytomegalovirus, and herpes simplex virus. Less frequently, ADEM may develop post-vaccination, although this occurrence has become exceedingly rare, accounting for less than 5% of all ADEM cases. These case reports do not necessarily establish a causal relationship between ADEM and vaccination.

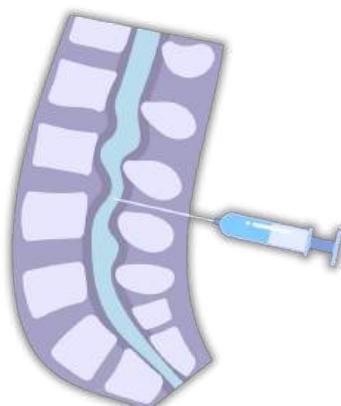
Recent studies suggest that a cell-mediated response or antibodies produced in response to an environmental trigger may cross-react with myelin autoantigens, including myelin oligodendrocyte glycoprotein (MOG). Antibodies to the MOG protein, which are more frequently observed in children, have been associated with a spectrum of inflammatory demyelinating conditions, characteristically seen in ADEM.

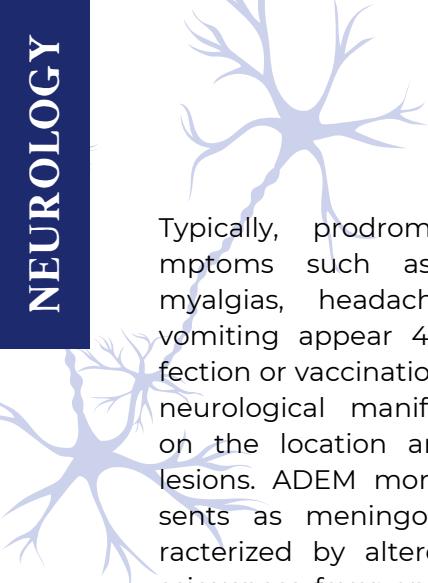
An alternative hypothesis posits that acute disseminated encephalomyelitis may result from increased vascular permeability and congestion in the central nervous system, induced by inflammation and circulating immune complexes following vaccination or infection.

It is believed that mononuclear infiltration of the central nervous system vasculature leads to perivascular edema and, in some cases, hemorrhage, which subsequently causes damage to adjacent neuronal cells, including demyelination.

CLINICAL FEATURES

Acute disseminated encephalomyelitis is generally a monophasic disorder that can occur at any age, though it is more common in children due to their higher frequency of immunization and exposure to antigens. It is important to note that both sexes are affected with equal frequency. Furthermore, the severity and progression of ADEM symptoms are subject to variation among individuals and may be contingent upon the age of onset and the location of brain lesions. While some individuals may experience a mild, limited form of the disorder, others may develop more severe symptoms. Life-threatening complications, such as respiratory failure, may occur in the most severe cases. Typically, prodromal systemic symptoms such as fever, malaise, myalgias, headache, nausea, and vomiting appear 4-21 days after infection or vaccination. The subsequent neurological manifestations depend on the location and extent of the lesions.





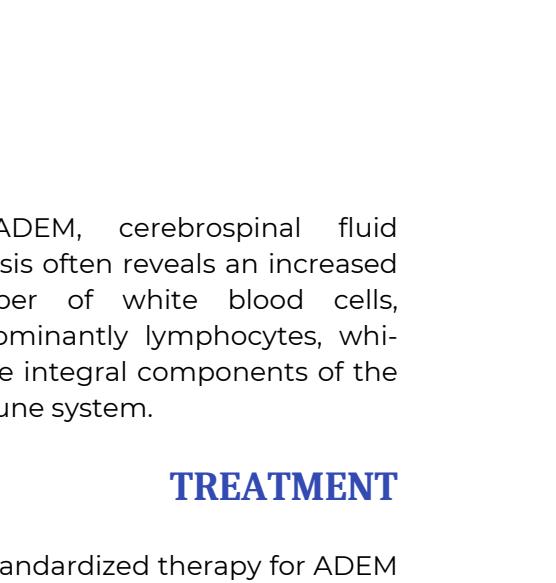
Typically, prodromal systemic symptoms such as fever, malaise, myalgias, headache, nausea, and vomiting appear 4-21 days after infection or vaccination. The subsequent neurological manifestations depend on the location and extent of the lesions. ADEM more commonly presents as meningoencephalitis, characterized by altered levels of consciousness, fever, and seizures.

Adults with post-infectious encephalomyelitis may exhibit peripheral nerve damage (neuropathy), experiencing symptoms such as weakness, pain, numbness, or a burning or tingling sensation in the extremities, which typically indicates a worse prognosis.

DIAGNOSIS

Diagnosing acute disseminated encephalomyelitis poses challenges due to its symptom overlap with other neurological disorders, such as multiple sclerosis. More specifically, diagnosis entails a comprehensive assessment, including clinical evaluation, brain and spine imaging via MRI or CT scans, and analysis of cerebrospinal fluid obtained through a lumbar puncture (A lumbar puncture involves inserting a needle into the lower back, specifically between the vertebrae of the spine).

More specifically, MRI findings in ADEM may demonstrate a single lesion—either large or small, confluent, or solitary—or multiple lesions dispersed throughout both the white matter and grey matter of the brain. The most characteristic presentation of ADEM on MRI is the presence of multiple, widespread, asymmetric lesions distributed bilaterally throughout the brain.



In ADEM, cerebrospinal fluid analysis often reveals an increased number of white blood cells, predominantly lymphocytes, which are integral components of the immune system.

TREATMENT

No standardized therapy for ADEM has been established. Most treatments employed for ADEM aim to mitigate the body's immune response to the antigenic stimulus elicited by the preceding infection or vaccination. Such therapies include corticosteroids, immunoglobulin (IVIg) therapy or plasmapheresis.

High doses of corticosteroids are the primary treatment for ADEM and are generally effective. Consequently, the therapeutic regimen entails the intravenous administration of high doses of methylprednisolone (1000 mg daily) or dexamethasone (1 mg/kg daily) over a period of 3-10 days, contingent upon the patient's response. In most cases, this approach results in a satisfactory outcome, with significant clinical improvement observed in approximately two-thirds of patients.

Patients who either do not respond to or exhibit intolerance to corticosteroid therapy may be treated with intravenous immunoglobulin (IVIg) for ADEM. For ADEM patients who have not responded to other treatment options, plasmapheresis has also been employed as a therapeutic option.

CONCLUSION

In conclusion, Acute Disseminated Encephalomyelitis (ADEM) is a rare, rapidly progressing autoimmune disorder characterized by widespread demyelination of the central nervous system, often precipitated by an infection or vaccination. The pathophysiological mechanisms of ADEM are not fully understood but are believed to involve an atypical immune response that leads to inflammation and subsequent myelin damage. Diagnostic challenges arise due to symptom overlap with multiple sclerosis. Although no standard therapy has been established for ADEM, current therapeutic approaches primarily focus on mitigating the immune responses. Despite the progress in understanding and treating ADEM, further research is essential to refine diagnostic criteria and therapeutic strategies, ultimately improving patient outcomes and advancing the field's knowledge of this complex disorder.

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From Puberty to Menopause: The role of hormonal shifts in migraine dynamics

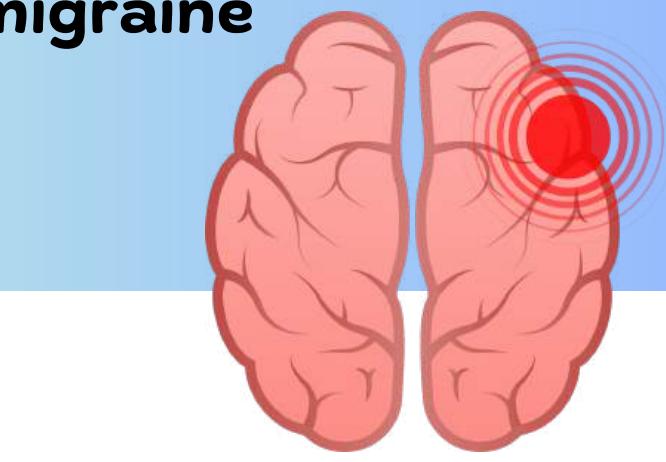
WRITTEN BY SAMA ABU HELOU
EDITED BY ELENI TZANETOU
DESIGNED BY APHRODITE P. PASCOE

ABSTRACT

Influenced by numerous factors, including hormonal fluctuations, migraines compose a debilitating and complex neurological disorder. In this article, we explore the role of key female hormones in the pathophysiology of migraines in women. To provide effective management and treatment strategies and techniques, a better understanding is necessary, especially for women experiencing hormonal changes in different life stages.

Introduction: The Link Between Hormone Fluctuations and Migraines

Throbbing and pulsating pain, usually occurring on one side of the head, is known as a migraine. The pain is triggered by the activation of the nerve fibers present within the brain blood vessels, passing through the three protective layers of the brain and the spinal cord, the meninges. The debilitating condition disproportionately affects women more than men due to the significant hormonal impact caused mostly by estrogen, progesterone, along with regulatory hormones such as Luteinizing hormone(LH) and Follicular Stimulating Hormone (FSH).



and androgens like testosterone, influence the frequency, severity, and onset of migraines.

Hormonal Influence on Migraines

A primary hormone having an essential role in the pathogenesis of migraine, is estrogen. The natural fluctuations of female sex hormones during menstrual cycles, pregnancy, menopause, or even the use of hormonal contraceptives and hormone replacement therapy (HRT) seem to have a greater influence on the occurrence of migraine episodes in comparison to the total or absolute levels of the hormone.

Hormonal Fluctuations and Their Impact on Migraines

Estrogen: Estrogen levels fluctuate throughout the menstrual cycle, pregnancy, and menopause, significantly impacting migraine incidence and severity. During the menstrual cycle, estrogen peaks during ovulation and drops sharply before menstruation, often triggering menstrual migraines.

Pregnancy, characterized by high and stable estrogen levels, is associated with a reduction in migraine frequency, whereas the transition to menopause, with fluctuating and declining estrogen levels, can increase migraine severity. These natural fluctuations appear to play a role in the pathophysiology of migraines in various ways:

1. Vascular Changes:

Estrogen fluctuations affect both vasoconstriction and vasodilation. In turn, the blood flow within the brain is affected, contributing to the onset of migraine. The drop in estrogen just before menstruation can lead to vasodilation, activating nerve fibers, and causing migraine pain.

2. Neurotransmitter Modulation:

The activity of other neurotransmitters, including serotonin, is also affected by the fluctuations of estrogen. Serotonin is involved in the regulation of both mood and pain, the fluctuating levels of it and its receptor activity have been evident to potentially trigger migraines.

3. Inflammatory Pathways:

Estrogen also affects inflammatory pathways. Changes in estrogen levels can influence the release of inflammatory mediators that are involved in migraine attacks, exacerbating the condition during periods of hormonal fluctuation.

Progesterone: Progesterone also plays a crucial role in migraine regulation. Its levels rise post-ovulation and peak during the luteal phase. A drop in both estrogen and progesterone before menstruation is a common trigger for menstrual migraines. Elevated progesterone levels during pregnancy correlate with reduced migraine frequency, whereas postpartum drops can trigger migraines. Mechanisms in which progesterone can lead to a higher susceptibility of migraines include:

1. GABA Receptor Modulation:

Progesterone enhances the activity of GABA-A receptors, increasing inhibitory neurotransmission. This modulation can reduce neuronal excitability, which may help alleviate migraine symptoms.

2. Neuroinflammation:

Progesterone has anti-inflammatory effects, reducing the production of inflammatory cytokines. This action helps lower neuroinflammation, a component of migraine attacks.

3. Vascular Effects:

Progesterone promotes vasodilation, counteracting abnormal blood vessel constriction and dilation seen in migraines. This vasodilatory effect may help reduce migraine severity.

4. Neurotransmitter Modulation:

Progesterone affects serotonin receptor activity, influencing migraine susceptibility. Its impact on serotonin pathways may explain the relationship between hormonal fluctuations and migraines.

5. Hormonal Interplay:

Progesterone levels fluctuate during the menstrual cycle, with a drop before menstruation often triggering migraines. This hormonal shift affects migraine onset and severity by altering estrogen and progesterone balance.

6. Impact on Cortisol Levels:

Progesterone influences cortisol secretion and the HPA axis, affecting stress response and pain perception. This interaction may contribute to migraine frequency and intensity.

Luteinizing Hormone and Follicular Stimulating Hormone: LH and FSH regulate the production of estrogen and progesterone. FSH stimulates the growth of ovarian follicles and estrogen production, while LH triggers ovulation and progesterone production. These hormones indirectly affect migraines by modulating estrogen and progesterone levels. Fluctuations in LH and FSH, such as those seen in PCOS or during perimenopause, can exacerbate migraines.

Testosterone: LH and FSH regulate the production of estrogen and progesterone. FSH stimulates the growth of ovarian follicles and estrogen production, while LH triggers ovulation and progesterone production. These hormones indirectly affect migraines by modulating estrogen and progesterone levels. Fluctuations in LH and FSH, such as those seen in PCOS or during peri-menopause, can exacerbate migraines.

PCOS and Migraines

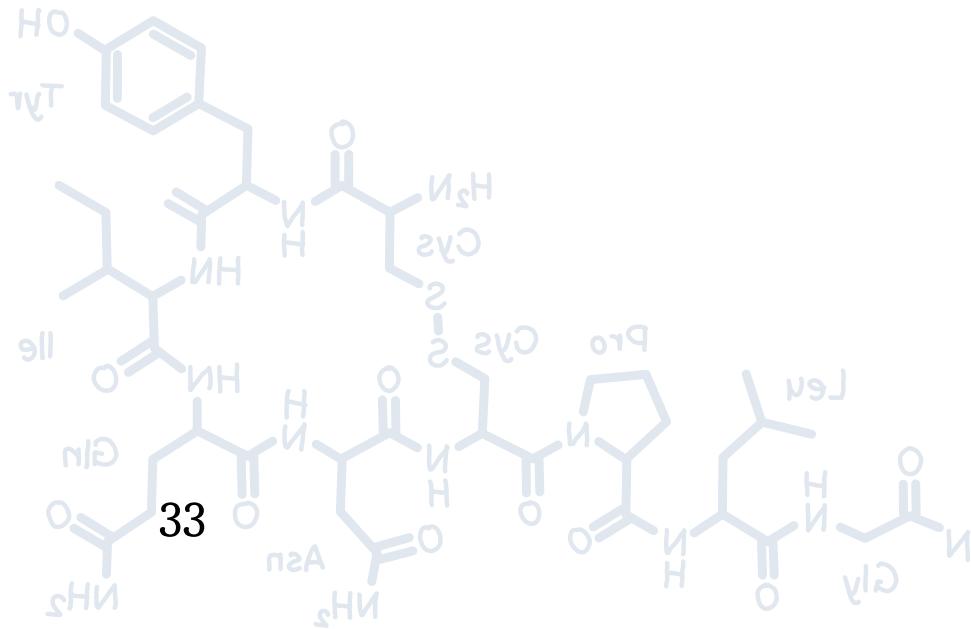
Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age, characterized by hyperandrogenism, chronic anovulation, and polycystic ovaries. Women with PCOS often exhibit elevated levels of LH and testosterone and altered, usually lower, FSH levels, leading to an imbalance in estrogen and progesterone. This hormonal dysregulation is associated with an increased prevalence of migraines. The hyperandrogenic state in PCOS can exacerbate migraine frequency and severity through its effects on serotonin modulation and vascular function. Additionally, insulin resistance, commonly seen in PCOS, may contribute to the inflammatory pathways involved in migraine pathophysiology. Managing PCOS symptoms and hormonal imbalances is crucial for mitigating migraine occurrences in affected women.



CONCLUSION

Understanding the hormonal influences on migraines provides crucial insights into the condition's complexity, particularly for women. The interplay of estrogen, progesterone, LH, FSH, and testosterone significantly impacts migraine patterns, highlighting the need for personalized treatment strategies. As research progresses, we can develop more effective approaches to managing migraines, ultimately improving the quality of life for those affected by these debilitating headaches. By focusing on the hormonal aspects of migraine, we pave the way for targeted therapies that address the specific needs of women experiencing hormonal changes.

REFERENCES



Stroke and Implicit and Explicit Costs: A Narrative Review

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ABSTRACT

Stroke exerts a massive impact globally on the patient's physical and mental health and the caregivers, as well as it tears through the socioeconomic fabric of the countries. Many resources are being pumped into public education related to stroke diagnosis, prevention, and risk factors. Despite this, many health organizations still estimate a growth in the incidence of strokes, with a simultaneous growth in capital costs associated with research, patient care, and rehabilitation.

Although strokes top the list of many epidemiological groupings such as cause of death worldwide, there isn't a lot of collective data for all the countries that shows either the mortality, incidence, prevalence and survival rates for stroke. Therefore, data about these rates that are available are ones that are going to be used in order to estimate the liability that a stroke holds on patients, government and caregivers in a random region or country.

INTRODUCTION

Stroke remains one of the most common conditions treated in hospitals, despite the wealth of clinical information available to the public and healthcare professionals alike. Indeed, in the United States, it is estimated that stroke accounts for '1 in every 19 deaths' (CDC). The burden of stroke is multifaceted and can be seen in terms of physical challenges, the burden on health services for patients and governments alike, and, importantly, in psychological terms for patients, their relatives, and carers.

Stroke has two different types which will be discussed later in this article: Ischemic and haemorrhagic and each of these two types is subdivided into two subtypes, each of them with a different cause for their prognosis.

As already mentioned, stroke does not only have a cost on the physical attributes of the patient but also plays a huge impact on the patient's mental health. Some articles have shown that stroke is one of the leading causes for patients to either develop dementia and depression (**Johnson, Onuma, Owolabi and Sachdev, 2021**).

Indeed, caregivers and guardians of stroke survivors must be vigilant as the 23% recurrent stroke looms. More importantly, this presents for many a continuous burden on family caregivers, who have to act in a very responsive and timely manner using the 'F.A.S.T' protocol, should a second stroke arise (**3 Ways to Avoid a Second Stroke, 2021**).

Lastly, the economic impact of stroke on a country's economy is huge. In 2017, the Stroke Alliance for Europe (SAFE) estimated that 60 billion euros were spent on stroke care across Europe, covering health services, social and informal care, and productivity losses. SAFE, however, projects that by the end of 2024, the costs could shoot up to 86 billion euros if healthcare services do not make the prevention and treatment of stroke, including rehabilitation for the psychological disturbances that many patients experience, a priority (**The Economic Impact of Stroke - SAFE, 2020**). Question: What are the actual direct and indirect costs of stroke to patients, caregivers, and the broader economy?

METHODS (SEARCH STRATEGY)

To reach accurate results in this review, various information and facts were gathered from several articles, websites, and documents.

In addition, to have accurate results, the facts must be up to date and that's why the resources used were all between the time frame of (2015-2021).

The keywords in this review are Stroke, Costs, Ischemic, Haemorrhagic and Brain Injury

The main resources were used from articles published on "PubMed" and "Google Scholar". In addition, to websites, documents and books found through "Google".

The English language was the one used to retrieve the information from the resources. These resources also included studies with numerical statistics which were conducted either by two methods (Cohort/Control).

BODY DISEASE PRESENTATION

Stroke is the sudden death of neurons, or brain cells, due to failure in the supply of oxygen to the brain (**Learn the signs of a stroke and what you can do to prevent one., 2021**).

Stroke signs and symptoms are obvious and can be detected easily, however when they're observed the patient, or the guardian must act F.A.S.T. F.A.S.T is an acronym that is used to identify a patient going through a stroke. The "F" refers to "Face Drooping", where one side of the face is drooping, which can be observed when asking the patient to smile. The "A" refers to "Arm Weakness", where one arm goes down and this is observed when asking the patient to elevate both arms. The "S" refers to "Speech Difficulty", where the sentences coming out of the patient are garbled.

The “T” refers to “Time to call 911”, where when all the above signs are present this is the major step to be taken (**Five Fast Facts about Stroke, 2021**).

However, there's a lot more signs/symptoms associated with stroke. Such as: The vision in one eye or even both decreases or becomes blurry, losing balances which might lead to falling without a reason, the patient is going to go through a serious headache, in addition to speech difficulty the patient will have a harsh time understanding other people (**Signs of stroke — Stroke Foundation - Australia, 2021**).

DIAGNOSIS

When a stroke occurs, its manifestations usually come at once, and medical personnel must confirm the presence of the stroke and its type. Despite all the education of the public, stroke is still misdiagnosed as another neurological condition.

Therefore, the first thing to be done is to order any imaging test, which varies from a Carotid Ultrasound, Cerebral Angiogram, Magnetic Resonance Imaging (MRI), Echocardiogram and Computerized tomography scan (CT).

First, Carotid Ultrasound is performed, which is considered the gold standard for the detection of plaque formation in the carotid arteries—the main source of blood to the brain—

which are potentially impeding blood flow (**Stroke - Diagnosis and treatment - Mayo Clinic, 2021**).

Secondly, in few scenarios, doctors can also make use of a Cerebral Angiogram to diagnose the condition. The test makes it possible to image the neck and brain arteries in a patient by injecting contrast dye that illuminates the vessels for imaging (**Stroke - Diagnosis and treatment - Mayo Clinic, 2021**).

Thirdly, is the MRI where a thorough image of the brain is generated using magnets and radio waves. This type of imaging can be used to detect if there's damage in the brain that might have been caused by either haemorrhagic or ischemic stroke (**Stroke - Diagnosis and treatment - Mayo Clinic, 2021**).

Fourthly, is the Echocardiogram, from its name (Echo" cardio" gram) meaning this type of imaging provides the doctor with an image of the patient's heart. This is needed to look for any blood clots that are formed in the heart and moved to the brain (embolic stroke) (**Stroke - Diagnosis and treatment - Mayo Clinic, 2021**).

Last but not least, is the CT where x-rays are being used to generate an image of the patient's brain. This will help the doctor to look for any clots (ischemic stroke), bleeding (haemorrhagic stroke) or if it's another disease or even a tumour. Figure (1) and (2) illustrates the difference between a normal CT of the brain (figure 1) and a brain with damage that was caused by a stroke (figure 2).



Figure (1)
(Cuete,
2021):

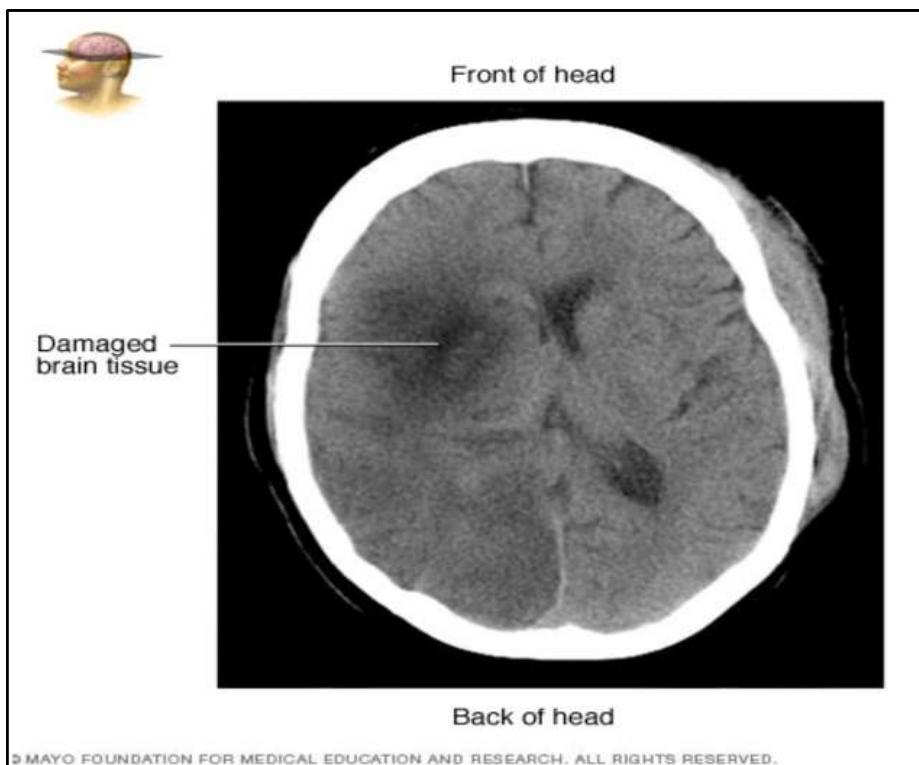


Figure (2) (Stroke -
Diagnosis and
treatment - Mayo
Clinic, 2021):

Moving on, medical imaging is not the only way to diagnose strokes, other ways are implemented as well, such as physical examination and blood tests. Blood tests such as PT (Prothrombin Time) helps the doctor determine the time blood takes to form a clot. "Full Blood count" test is also another example, where a blood sample is taken to determine the number of white blood cells, red bloods and platelets found in the patient's blood. Blood Lipid test is also a very important test since it will give details about the amount of cholesterol, LDL (low density lipoprotein/bad cholesterol) and HDL (high density lipoprotein/good cholesterol) (**Blood Tests to Diagnose Stroke | St. Charles Health, 2021**).

As hypertension is a risk factor of haemorrhagic stroke, the patient's blood pressure has to be checked during the physical examination. The doctor must auscultate the patient's heart for any irregular rhythms, murmurs or gallops which may indicate a potential clot in the heart. The patient must also be examined neurologically to ascertain that the flow of the nervous system is normal and to ensure that another neurological condition will not be mistakenly diagnosed.

EPIDEMIOLOGY

Stroke has to be counted upon one among the eminent global health challenges, as the studies by many around the world testify. In fact, the WHO's 2019 Global Health Estimates had considered it the second leading cause of death and the third leading cause having a toll on disability-adjusted life years (DALYs) to the individual (Global Health Estimates: Life expectancy and leading causes of death and disability, 2021). In the United States, the estimation for one in six deaths from heart disease is a stroke, with the incidence of one stroke every 40 second (**Stroke Facts | cdc.gov, 2021**).

The first statistical review will involve data on mortality, incidence, prevalence, and DALYs attributed to stroke in South, East, and Southeast Asia.

The Mortality Rate will be considered first, which is the number of deaths from a particular disease per 100,000 person-years (**Principles of Epidemiology | Lesson 3 - Section 3, 2021**). Table 1 indicates differences in mortality rates from South Asia, with the highest being Pakistan at 83.3 and lowest Bangladesh showing the rate of 54.8. Mongolia shows the highest rate, at 222.6, while the lowest rate in East Asia is recorded in Japan, recording 43.4. Southeast Asia reflects the highest being Indonesia, at 193.3 and the lowest rate recorded in Singapore, showing the rate of 47.9.

Most of the disparities are because of GNI factors that divide nations into High Income, Middle – emerging, and Low Income (**Gross National Income (GNI), 2021**) (**How are countries classified? 2021**). Being a low-income nation, Pakistan has not been in a position to overcome its shortcomings in health care education and services hence increases in mortality rate. On the other hand, Bangladesh is within middle-income countries and shows greater resources to be spent on health care and education, which gives in a lower mortality rate (**The World Bank In Bangladesh, 2021**). The similar trends can be observed in East and Southeast Asia (**Venketasubramanian, Yoon, Pandian and Navarro, 2021**).

The next to be conversed is the Incidence Rate: a measure that typifies the sum of new cases of stroke over some time. Table 1: Most countries do not have incidence data to permit an overall comparison in all countries of the world. Incidence data, to permit an overall comparison, are available in Japan with the highest rate: 422 per 100,000 men (0.422%) and 212 per 100,000 women (0.212%). Inter-regional comparisons were not possible due to the difference in the period within which the data were collected (**Kenton, 2021**) (**Venketasubramanian, Yoon, Pandian and Navarro, 2021**).

Table 1.

Mortality, incidence, prevalence, and DALY's lost because of stroke

Country	Age-sex standardized mortality /100,000 person-years (2010) ^[1]	Incidence /100,000 person-years	Prevalence /1,000	Age-sex standardized DALY's lost /100,000 people (2010) ^[2]
South Asia				
Bangladesh	54.8	-	9.4 (>30 years) [16]	888.1
Bhutan	58.3	-	-	990.8
India	82.4	119–145 [7]	0.84–4.24 [7]	1,420.3
Nepal	73.5	-	-	1,284.0
Pakistan	83.3	250 [8]	191 (>35 years) [8]	1,467.2
Sri Lanka	65.4	-	0.1 (>18 years) [17]	1,073.6
East Asia				
China	126.9	116–219 [5]	2.6–7.2 [5]	2,101.5
DPR Korea	149.6	-	-	2,698.8
Japan	43.4	422 (M), 212 (F) [10]	27.0 (>65 years) [18]	706.6
Mongolia	222.6	326 (S) [11]	71.3 (>55 years) [12]	4,409.8
Korea	77.4	216 [13]	15.9 [13]	1,117.8
Taiwan	56.8	330 [6]	19.3 [6]	992.1
South-East Asia				
Brunei	68.6	-	-	1,103.2
Cambodia	137.8	-	-	2,627.9
Indonesia	193.3	-	0.02–8.0 [20]	3,382.2
Lao PDR	141.3	-	-	2,727.9
Malaysia	84.3	67 [13]	-	1,480.4
Myanmar	165.4	-	-	2,971.3
Papua New Guinea	56.04	-	-	1,353.1
Philippines	109.6	-	9.0 [21]	2,171.9
Singapore	47.9	180 [14]	36.5 (>50 years) [22]	804.2
Thailand	62.8	-	18.8 (>45 years) [22]	1,108.1
Timor Leste	117.3	-	-	2,236.3
Vietnam	124.5	250 [15]	6.1 [15]	1,955.0

DALY's, disability adjusted life-years; IS, ischemic stroke; F, female; M, male.

Table (1)

Furthermore, to be analysed is the Prevalence Rate, which is the percent of persons diagnosed with stroke during either a defined period or at a specific point in time (**Principles of Epidemiology | Lesson 3 - Section 2, 2021**). More specifically, a high rate of mortality with a low incidence rate leads to a higher prevalence, as more people die from stroke compared to those who are newly diagnosed. In Table 1, it is seen that Indonesia has the lowest average prevalence rate of 0.02-0.8 per 1,000, which is 0.002% - 0.08%. In fact, prevalence rates are very important, especially in public health planning so that with chronic conditions that create much disability like stroke, the right health interventions can be pursued (**Venketasubramanian, Yoon, Pandian, and Navarro, 2021**).

Lastly, the study examines DALYs, a measure that reflects the number of years a person loses due to poor health (**Disability-adjusted life years, DALYs, 2021**). DALYs are important to show the psychological and health burdens of the stroke event survivors. According to the World Health Organization, the highest country was Mongolia, with 4,409.8 per 100,000 persons, and the lowest country was Japan, with 706.6 per 100,000 persons. The fact that Mongolia has the highest mortality rate in East Asia is in accordance with its high DALY rate, which is attributed to low-income status, followed by health-related issues such as the prevalent diabetes, hypertension, and hypercholesterolemia (**Venketasubramanian, Yoon, Pandian and Navarro, 2021**).

PATOPHYSIOLOGY

To begin with, the blood vessels crucial for supplying the brain include the two carotid arteries located in the neck and the two vertebral arteries situated posteriorly in the neck (**Kuriakose and Xiao, 2020; Coronary Artery Disease: Causes, Symptoms, Diagnosis & Treatments, 2021**).

Stroke occurs due to inadequate blood flow to the brain through these vessels, leading to a reduced oxygen supply. This insufficiency can result from two primary types of strokes. The first, termed "Haemorrhagic Stroke," is less common, accounting for approximately 10-15% of cases. This type of stroke is characterized by the rupture or bursting of a blood vessel supplying the brain, causing bleeding. Often, this rupture is associated with hypertension. Haemorrhagic stroke can be further classified into two subtypes. The first subtype, "Subarachnoid Haemorrhage," involves bleeding in the space between the brain and the surrounding membranes, known as the subarachnoid space. This condition may arise from a cerebral aneurysm or head trauma. The second subtype, "Intracerebral Haemorrhage," involves bleeding within the brain's blood vessels. This type is primarily caused by hypertension, and increased use of anticoagulants and thrombolytic drugs can also contribute to its development (**Types of Stroke, 2021**) (**Gomes and Wachsman, 2021**).

The other main type which is more common is the "Ischemic Stroke" (more common found in 85-90%) and this type is caused when there's a blockage in one the blood vessels that supplies blood to the brain. This blockage is usually caused by atherosclerosis. Like the "Haemorrhagic Stroke" the "Ischemic Stroke" is also subdivided into two subtypes. First, we have the "embolic stroke", this occurs when there's a formation of a blood clot anywhere in the patient's body, but it keeps on moving in the blood till it reaches the brain. The moving clot around the patient's bloodstream is called an "embolus" and is usually the result of a cardiological abnormality. Second-ly, the "thrombotic stroke" is unlike the clot in the embolic stroke, this clot happens in the brain's blood vessels. Patients who are old in age that suffer from diabetes or high cholesterol are prone to this type of stroke. These strokes can lead to multiple mini strokes (**Transient Ischemic Attacks/TIAs**) (**Types of Stroke, 2021**) (**Gomes and Wachsman, 2021**).

Moving on, with the understanding that blood flow to the brain is now reduced, figure (3) will help understand the cause of this reduced blood flow, leading to a stroke. Figure (3) clearly illustrates the mechanism in which when the blood flow to the brain is reduced the ATP (Adenosine Triphosphate, an energy provider chemical compound) production is going to be terminated leading to ATP depletion. This depletion in ATP is going to cause both neurochemical and neuroinflammatory injuries (which are mentioned in the figure) thus this injury will result in cell necrosis (death) or damage causing a stroke.

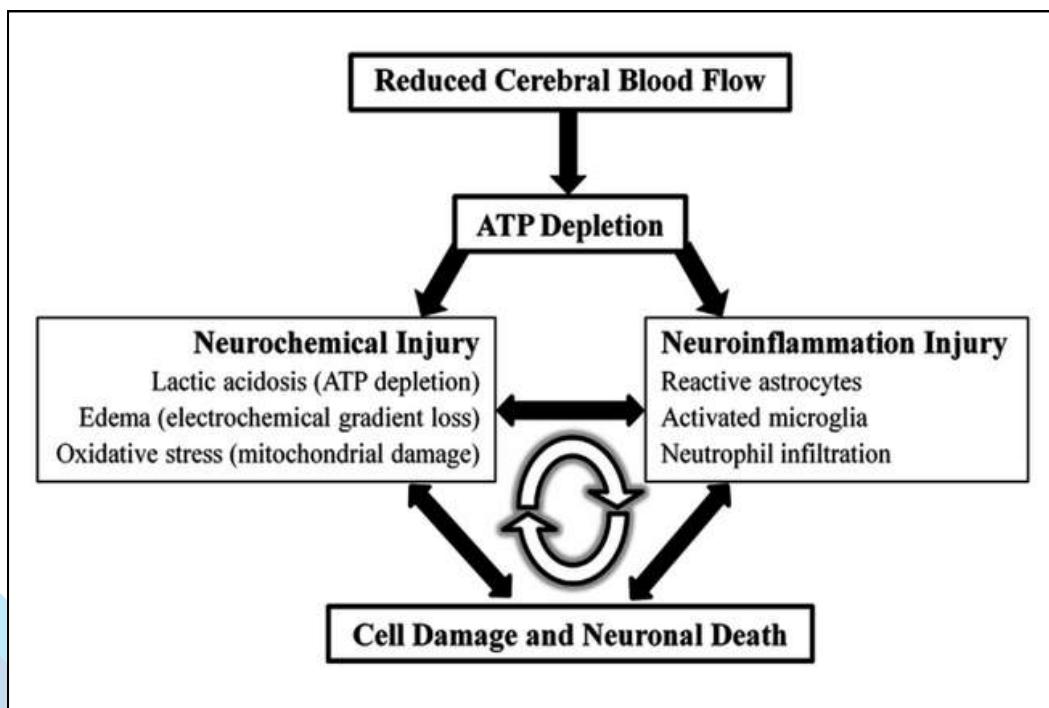


Figure (3)
(N Bodhit, 2021):

MANAGEMENT

Initially, the primary focus in treating ischemic stroke is the restoration of blood flow to the patient's brain. Several medications and procedures are available to achieve this goal.

Firstly, the procedures which are suitable for use in emergency situations, involving intervention by the doctor within the blocked vessel to address the clot obstructing them. The first procedure is the removal of the clot directly using a stent retriever, here the doctor uses a medical instrument that will be attached to a catheter in order to be able of removing the clot directly from the vessel, especially if it's relatively a large clot, however the use of a thrombolytic medicine is sometimes used, which has the job of activating the conversion of plasminogen to plasmin (breakdown clots), this is tissue plasminogen activator (tPA). The second procedure is done through injecting the tPA directly to the site where the stroke happened in the brain. This is done by inserting a catheter into the patient's groin where an artery is found (**Stroke - Diagnosis and treatment - Mayo Clinic, 2021**).

Furthermore, there are some medications that are given to the patient in case of an ischemic stroke, usually done intravenously (IV). When giving medications to a patient having an ischemic stroke, time plays a role especially when intravenously is the way of giving.

The time frame given is a maximum of four and half hours, since the earlier the medicine is given the higher the rate of survival and the lower rate of future complications. tPA is also the medicine injected intravenously which is given to the patient in his arm (**Stroke - Diagnosis and treatment - Mayo Clinic, 2021**).

Proceeding to haemorrhagic stroke, where the main cause is bleeding, thus the priority for the doctor is going to be to stop the bleeding. Initially, the surgical procedure that may be performed to either repair the rupture or prevent its recurrence is considered. The first surgical procedure is the surgical clipping, which is done by placing a clamping at the beginning of the aneurysm, which will prevent it from rupturing or bleeding again by stopping blood from reaching to it (**Stroke - Diagnosis and treatment - Mayo Clinic, 2021**). The second surgical procedure is done through removal of arteriovenous malformation (if it's the cause of the bleeding) if it's small in size and if the location of it isn't deep inside where the doctor can't access, due to a lot of complications that might happen during the surgery. The last surgical procedure is going to be using radiation in order to treat any vessels malformation that might have caused the stroke, this is called stereotactic radiosurgery.

However, when it comes to medications in treating haemorrhagic stroke, doctors tend to think forward to prevent the occurring of seizures and spasms and that's done by giving drugs that's going to decrease the blood pressure by decreasing the intracranial pressure (pressure in brain) (**Stroke - Diagnosis and treatment - Mayo Clinic, 2021**).

Since stroke might affect the patient's psychological health, yielding diseases like depression, anxiety, and other disorders, the patients need to undergo rehabilitation after treatment. The rehabilitation process should be individualized in view of sex, age, occupation, daily life, and caregivers available. Rehabilitation may be provided during hospitalization or after discharge; some also perform it at home, in a clinic, or within the hospital setting. Physicians, therefore, should provide adequate information on rehabilitation facilities to patients to enable them to make proper decisions regarding further care and enable optimizing recovery and improving the quality of life after stroke. Moreover, being part of a support group in which emotional relief can be granted to the patient as they encounter other stroke survivors and make new social relationships which never become lonely (**Stroke - Diagnosis and treatment - Mayo Clinic, 2021**).

Other examples of rehabilitation professionals the stroke survivor may encounter include: occupational therapists, psychologists, recreational therapists, and physiatrists or rehabilitation doctors, among many others (**Stroke - Diagnosis and treatment - Mayo Clinic, 2021**).

How accessible are these treatments and what percentage of patients receive these effective treatments?

Fig. 4: This graph represents the gap among the states of the United States concerning the availability of these treatments and the rate of the pool of patients that received effective care. For instance, sometimes Florida, as represented by this graph, has provided 100 percent of the effective treatments to stroke patients; hence, Florida has been able to keep a higher level of adherence to the practice of ACMs. This measure shows if the necessary and efficacious treatments have been provided to patients having a particular condition, which is then used to ascertain the strength of health care service delivery in Florida.

Lastly, clinical trials are being operated in order to improve the quality of treatment patients with stroke receive and that their quality of life after stroke can be managed better. However, these trial results aren't out yet which is a limitation but gives us a fact that people are working toward making life easier for stroke patients.

There's an ongoing clinical trial that has been going on in JACKSONVILLE where their goal is to see the effect of a care system provider that involves both the patient and their guardians/carer either through rehabilitation or recovery (**Freeman, 2021**). This system is very effective since not only the patient can have an idea of what's going through with him/her but also their family/friends as well which will increase the amount of care the patient receives either physically or mentally, thus improving their quality of life.

PREVENTION

In order to discuss the different levels and types of prevention to each type of stroke, risk factors must be mentioned since they're the ones that must be prevented.

Below is a list of the risk factors that can lead to stroke that are mentioned briefly: Hypertension (Increase in blood pressure = above 120/80), Smoking, Increase in cholesterol levels (increases the chance of clot), Diabetes, Obesity, Any other heart diseases or abnormalities, Increase in alcohol intake, Old Age,

Stroke Core Measure

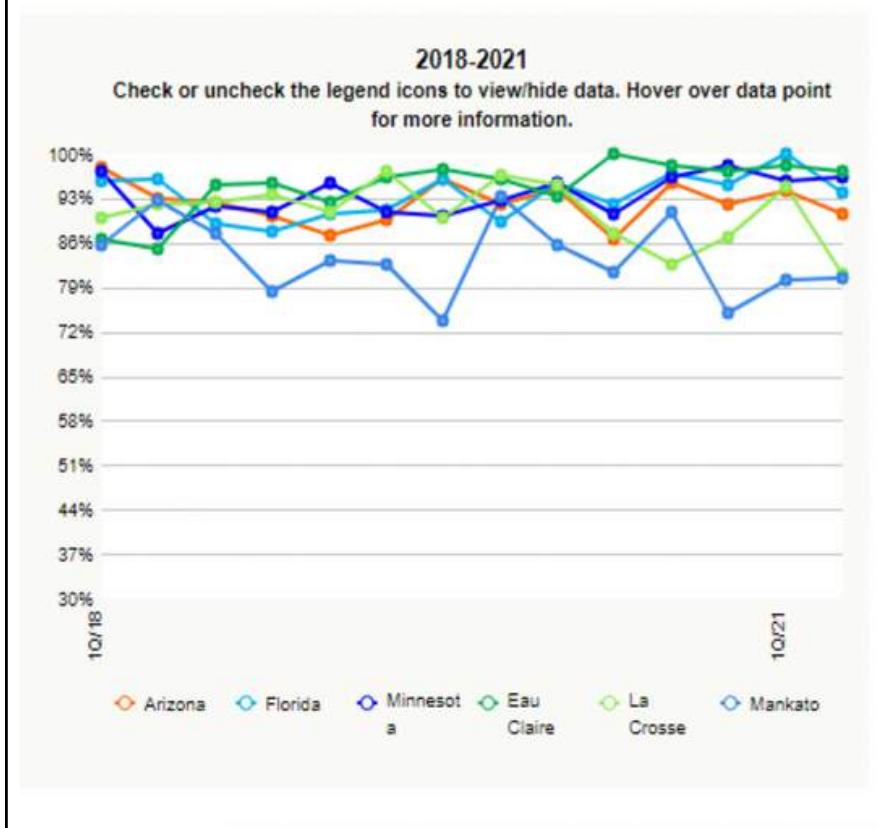


Figure (4)
(TJC, 2021):

Family History/Genetics, Men > Women (Women death from stroke > Men), African Americans (due to high number of hypertension cases within a population), Having a first stroke, Socioeconomic level, and Not exercising (**Risk Factors for Stroke, 2021**).

Proceeding to the prevention, there are 3 types of preventions that are Primary, Secondary and Tertiary Preventions. Keeping in mind that there are risk factors that are mentioned above that can't be prevented since the person doesn't have control over such as age, race, family history/genetics and gender, we call these nonmodifiable risk factors.

First and foremost, Primary prevention where actions are taken before the chronic disease (stroke) happens (**PREVENTION, 2021**). Examples of this include lifestyle and habits changes, such as to stop smoking or not smoking in the first place, exercising, decrease the amount of alcohol intake and following or having a healthy diet and weight. These preventions will cross out a lot of the risk factors stated above and most importantly it will avoid diabetes, hypertension and atherosclerosis which all are considered to mainly lead to a stroke (**PREVENTION OF STROKE, 2021**).

Following this, is the Secondary prevention where actions are taken when a person has one or more of the above stated risk factors, however, still didn't develop symptoms regarding stroke thus preventing it from progressing (**PREVENTION, 2021**).

For example, a patient with hypertension, should keep an eye on his/her blood pressure through blood pressure testing and going through primary preventions in order to keep the high blood pressure under control. Another example is with people with high levels of cholesterol due to genetics, they must start increasing the amount of high-density cholesterol and decreasing the amount of low-density cholesterol in their diet, this will prevent them from increasing the chance of having more blood clots, thus leading to a stroke. People with TIAs (transient ischemic attacks) are recommended going through anticoagulant medicine and keep on doing tests such as carotid duplex (uses sound waves to detect any clot that is causing a blockage in one of the carotid arteries), in order to see if the blockage is large enough so that the patient must go through surgery (carotid endarterectomy) in order to prevent a stroke (**PREVENTION OF STROKE, 2021**).

Lastly, is the Tertiary Prevention where actions are taken towards patients who have already been diagnosed with stroke and experienced, but these actions are taken to decrease or stop the pace of progression of the disease in that case stroke (**PREVENTION, 2021**).

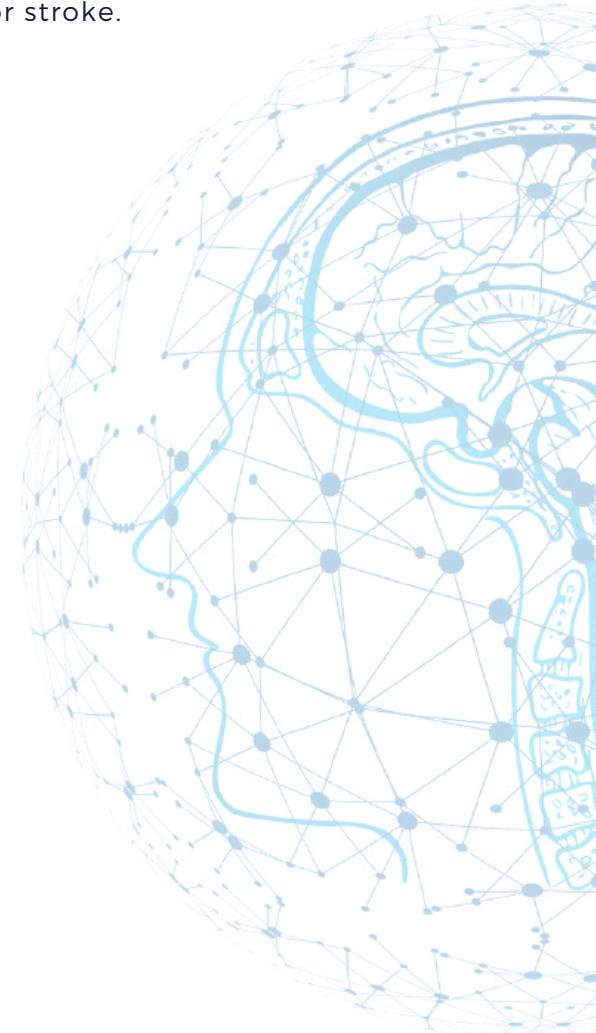
Example of this type is by the patient to keep going through screening in search of any blockage and through rehabilitation in order to increase and ease the quality of life of the patient. Moreover, a lot of countries and governments are providing educational support and support groups for stroke patients to ease their life (**PREVENTION OF STROKE, 2021**). For example, the "STROKE RECOVERY ASSOCIATION" that's located in North South Wales provides optimum care and tries to obtain the effective psychological treatment to patients with stroke by educating people about their recover and how to prevent stroke in the future (**Garbutt, 2021**).

CONCLUSION

Based on the research conducted, it has been evidenced through research that the cost of strokes involves both implicit and explicit costs. The implicit cost is majorly to the health of the patients while the explicit cost, which is often not put into consideration, involves the psychological recovery cost, socioeconomics cost, lifestyle changing, and being unable to do certain things.

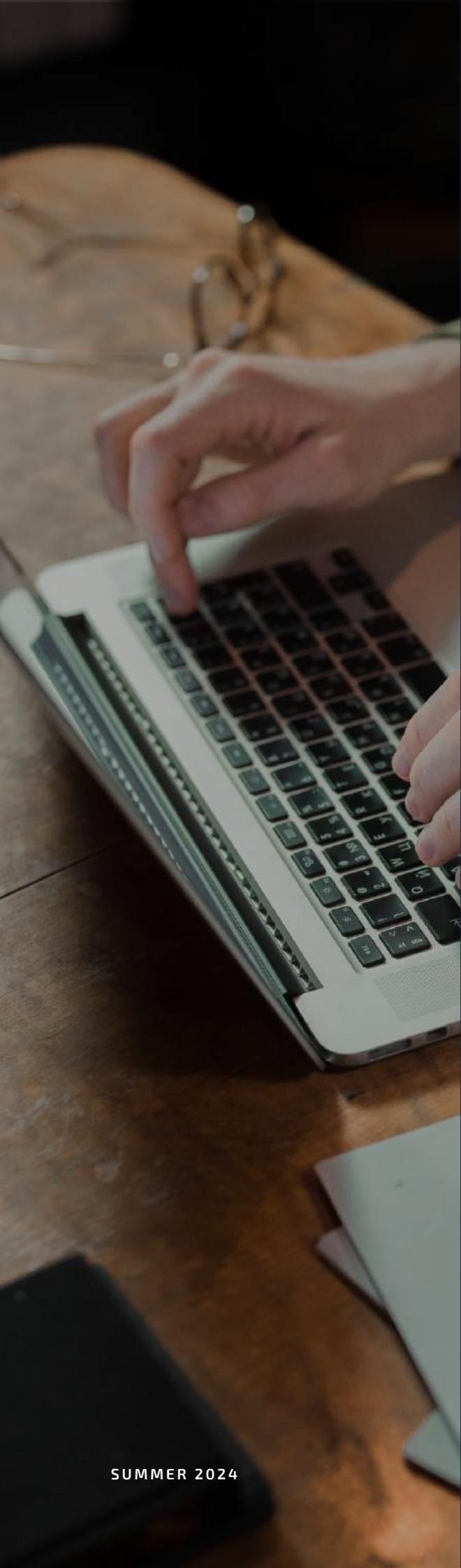
Rehabilitation and psychological treatment are greatly given nowadays. For instance, support groups ensure that stroke patients are able to maintain better mental health by building bridges across people with similar experiences.

These support groups help the formation of social bonds and provide emotional support. Socioeconomic costs at the national level can be addressed by developing education regarding stroke risk factors and promoting healthier lifestyles. Moreover, increasing public awareness about regularly checking blood pressure would avoid hypertension—a major risk for stroke.



REFERENCES





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Exploring Beyond Traditional Angina: Understanding Microvascular Heart Disease

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Heart disease is the leading cause of death globally, claiming millions of lives annually. Angina, a symptom of heart disease, presents as chest pain or discomfort resulting from reduced blood flow to the heart muscle. Traditionally, angina is associated with coronary artery disease (CAD), but recent studies suggest that microvascular heart disease (MVD) is an equally significant yet underrecognized condition. This article delves into the nuances of MVD, explaining why it's crucial to look beyond traditional angina.

Understanding Traditional Angina

Definition: Traditional angina, also known as angina pectoris, is characterized by chest pain or discomfort due to inadequate blood supply to the heart muscles. This condition typically results from CAD, where the coronary arteries are narrowed or blocked by atherosclerotic plaques, thus restricting blood flow and oxygen to the heart [1].

Causes: The primary cause of traditional angina is CAD, where fatty deposits (plaques) build up in

the coronary arteries, leading to a condition known as atherosclerosis. This buildup narrows the arteries and reduces blood flow to the heart. Other causes can include coronary artery spasms, severe anemia, and heart valve diseases [2].

Symptoms: Common symptoms of traditional angina include:

- Chest pain or discomfort, often described as pressure, squeezing, or fullness.
- Radiating Pain in the arms, neck, jaw, shoulder, or back accompanying chest pain.
- Nausea, fatigue, shortness of breath, sweating, and dizziness, particularly during physical exertion or stress [3].

Diagnosis & Treatment: Traditional angina is diagnosed through a combination of medical history, physical examination, and diagnostic tests such as electrocardiograms (ECGs), stress tests, echocardiograms, and coronary angiography. Treatment typically involves lifestyle modifications, medications (e.g., nitrates, beta-blockers, calcium channel blockers), and in severe cases, surgical interventions like angioplasty or coronary artery bypass grafting (CABG) [4].

Introduction to Microvascular Heart Disease

Definition: Microvascular heart disease (MVD), also known as microvascular angina or small vessel disease, affects the small coronary arteries, which are not visible in standard diagnostic tests. Unlike traditional angina, MVD involves dysfunction of the tiny blood vessels within the heart muscle, leading to reduced blood flow and ischemia [5].

Prevalence: MVD is relatively common, affecting an estimated 3-4 million individuals in the United States alone. It is particularly prevalent among women, often presenting with symptoms similar to those of traditional angina but without significant blockages in the major coronary arteries [6].

Risk Factors: Risk factors for MVD include:

- Hypertension (high blood pressure)
- Diabetes
- Smoking
- Obesity
- Sedentary lifestyle
- High cholesterol levels
- Chronic inflammatory conditions like rheumatoid arthritis and lupus [7].

Symptoms and Diagnosis of Microvascular Heart Disease

Symptoms: Symptoms of MVD can mimic those of traditional angina but may also include:

- Chest pain or discomfort, often triggered by physical exertion or emotional stress.
- Fatigue and reduced exercise tolerance.
- Shortness of breath.
- Pain in the arms, neck, jaw, shoulder, or back [8]

Diagnostic Challenges: MVD is challenging to diagnose using traditional methods such as ECG and echocardiography because the small coronary arteries are not easily visible. Patients often experience normal or near-normal results on standard diagnostic tests, leading to under-diagnosis or misdiagnosis [9].

Diagnostic Techniques: Specialized diagnostic techniques for MVD include:

- Coronary microvascular function tests: Assess the function of the small coronary arteries.
- Cardiac MRI: Provides detailed images of the heart's structure and blood flow.
- Positron Emission Tomography (PET) scans: Measure blood flow in the coronary arteries.
- Stress echocardiography: Evaluates how the heart muscles and valves function during stress [10].

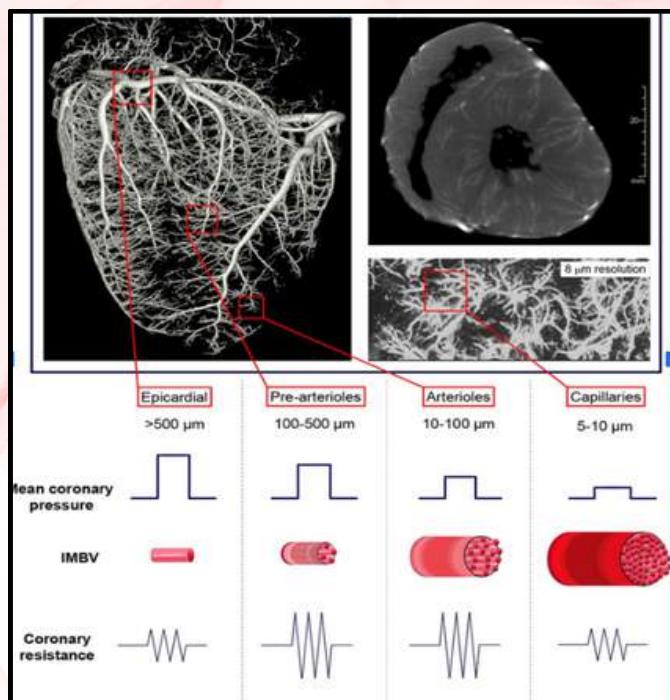


Figure 1

Pathophysiology of Microvascular Heart Disease Microvascular Dysfunction:

The underlying mechanism of MVD involves endothelial dysfunction and impaired vasodilation of the small coronary arteries. Endothelial dysfunction leads to an inability of the blood vessels to dilate properly, reducing blood flow to the heart muscle and causing ischemia. Other mechanisms include smooth muscle cell dysfunction and increased oxidative stress [11].

Research Findings:

Recent studies have shown that microvascular abnormalities can lead to ischemia and angina-like symptoms even without significant blockages in the larger coronary arteries. Research also suggests

that MVD may be linked to an increased risk of heart failure and adverse cardiovascular events [12].

Treatment Options for Microvascular Heart Disease

Pharmacological Treatments:

Managing MVD involves a combination of medications to improve blood flow and reduce symptoms. Commonly used medications include:

- Beta-blockers: Reduce heart rate and blood pressure, decreasing the heart's demand for oxygen.
- ACE inhibitors: Lower blood pressure and reduce strain on the heart.
- Statins: Lower cholesterol levels and stabilize plaques in the arteries.
- Nitrates: Dilate blood vessels and improve blood flow to the heart muscle [13].

Lifestyle Modifications: Lifestyle changes are crucial in managing MVD and improving overall heart health. Recommendations include:

- Adopting a heart-healthy diet rich in fruits, vegetables, whole grains, and lean proteins.
- Engaging in regular physical activity, such as walking, swimming, or cycling.
- Maintaining a healthy weight.
- Quitting smoking and avoiding exposure to second-hand smoke.
- Managing stress through relaxation techniques, meditation, and support groups [14].

Emerging Treatments: Emerging treatments and ongoing research offer hope for better management options for MVD. These include:

- Novel medications targeting specific pathways involved in microvascular dysfunction.
- Advanced diagnostic tools for early and accurate detection of MVD.
- Interventions to improve endothelial function and reduce oxidative stress [15].

Patient Story and Case Study

Real-life Example: Consider the case of Michael, a 62-year-old avid cyclist who began experiencing chest pain during his rides. Despite his active lifestyle and lack of traditional risk factors, Michael's symptoms persisted. Initial diagnostic tests, including an ECG and a coronary angiogram, showed no significant blockages in his coronary arteries. Frustrated by the lack of answers, Michael sought a second opinion from a cardiologist specializing in microvascular disease.

The specialist conducted a coronary microvascular function test, revealing that Michael had MVD. The diagnosis came as a surprise, given Michael's fitness and health consciousness. His treatment plan included medications like beta-blockers and ACE inhibitors to improve blood flow and reduce symptoms. Additionally, Michael adopted lifestyle modifications such as incorporating more antioxidant-rich foods into his diet and practicing yoga to manage stress.

Over time, Michael's symptoms improved significantly. He was able to return to his cycling routine, although with some adjustments to pace and intensity. His story highlights the importance of recognizing MVD, even in individuals who appear low-risk based on traditional heart disease metrics [16].

Outcome: Michael's case illustrates the impact of timely diagnosis and personalized treatment in managing MVD. His improved symptoms and ability to resume his favorite activities underscore the necessity of awareness and specialized care for patients with microvascular dysfunction. This real-life example demonstrates that with proper management, individuals with MVD can lead fulfilling and active lives [17].

CONCLUSION

In conclusion, while traditional angina and CAD remain critical areas of focus, it is essential to recognize and address microvascular heart disease. Understanding MVD, its symptoms, diagnosis, and treatment options can lead to better patient outcomes. Continued research and awareness are crucial in managing this often-overlooked condition. By looking beyond traditional angina, we can improve the quality of life for millions of patients worldwide.

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Is cardiothoracic surgery a dying art ?

What the **future** entails with interventional cardiology
evolving constantly

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ABSTRACT

Cardiothoracic surgery is a medical field that involves surgical intervention in all aspects of the heart and the thoracic area. It remains one in the top ten most competitive specialties in medicine, however some “whispers” in the back row that keep getting louder and louder propose that it is a dying field with the “culprit” being interventional cardiology. As an aspiring surgeon, heavily interested in the specialty of cardiothoracic surgery, in this article I dive deep into this “rumor” and discuss the matter. It is no lie that interventional cardiology is on the rise – it is an impressive modern method of treating cardiac complications with minimal surgical invasion. Regardless, to what extent can it completely replace open heart surgery ?

CONTENT

Cardiothoracic surgery is a surgical field involving the treatment of diseases affecting the thorax, heart, lungs, and lower part of the esophagus. It is a prestigious and old surgical field that has been evolving since 1898 with new surgical methods constantly being practiced. Even though it is regarded as a “veteran” amongst surgical fields, it has yet to be fully replaced by any new fields that are constantly being brought up.

A cardiothoracic surgeon is a surgical resident who has completed their general surgery residency and continued into the specialty of cardiothoracic surgery with an additional 3-year training placement.

Interventional cardiology is a non-surgical field of medicine that involves treating diseases using a small catheter that is inserted into the vascular system and is used to repair small and large damaged or blocked vessels as well some anatomical defects of the heart. Interventional cardiology is a derivant of interventional radiology – in the sense that all procedures are completed in a cath-lab – usually with the use of angiography. What is different in interventional cardiology from cardiothoracic surgery is that even though it is an interventional field of medicine, the doctors practicing are not trained surgeons, yet they are trained specifically on interventional cardiology and get certified specifically on this type of medical practice. This subspecialty of cardiology, which has evolved in the last century, is highly specialised and currently groundbreaking in the medical field.

Ever since interventional cardiology evolved as a specialty, there is the thought of where do cardiothoracic surgeons stand now? Vein and artery blockages, stents, vascular repairs, valve repairs or even replacements can now be treated through interventional cardiology – so what is left for cardiothoracic surgeons to do? How much time is there left until there is no need any more for open heart surgery and how much is the market saturated now and how will that evolve? How are medical students perceiving this and is it an obstacle in choosing this specialty? Are they afraid of completing their residency and then having no jobs? These are valid questions being discussed among doctors and medical students.

Hence a clear overlap between the cases of the two can be noticed. Indicatively, according to the Cleveland Clinic website when researching both specialties an overlap of cases taken can be seen. The specific conditions treated both by interventional cardiologists and cardiothoracic surgeons are; heart valve diseases, aortic aneurysms, coronary artery disease, atrial and ventricular septal defects, hypertrophic cardiomyopathy and heart attacks.

Right now, interventional cardiology is usually favored over cardiothoracic surgery – for numerous and well-vested reasons. Interventional cardiology is recommended to high-risk patients who are ineligible for traditional open-heart surgery and increasingly more patients opt out of the open-heart surgery and prefer the minimally invasive choice. In a statistical analysis done by Ahmed A Alsaddique in 2009 it was found that *15% of patients who undergo selective coronary angiography are referred for surgery. The majority are offered angioplasty and stenting.*

The trend is towards more catheter-based interventions and less towards surgery. The issue is; no patient wants to “go under the knife” – let alone have their chest “cracked-open” and being put into a bypass machine, if there is a less “radical” method of treatment. It is a scary and lengthy procedure however lifesaving. No matter how successful interventional cardiology is, it is still under the microscope. Not every patient is eligible, not every patient is a suitable candidate and not all stories are successful. The only thing holding us back from undergoing open heart surgery are the anesthesiologists’ concerns of the patient being under anesthesia for a long time and the patient fearing having a big surgery done.

Post-operatively both specialties have great prognostics – lengthy post-operation life expectancy and good post-operation quality of life. Nonetheless, cardiothoracic surgery has a lengthy post-operative recovery where patients may need to be placed in the ICU or stay weeks in the hospital under monitoring. On the other hand, interventional cardiology has shorter post-operation hospital stays, making it a favorable option, but in many cases it has less lengthy survival rates when compared to open heart surgery.

When facing the actual rumor at hand, the answer is NO – cardiothoracic surgery is not “dying” it is simply advancing and that is the unequivocal product of medical practice evolving constantly. When investigating the matter in fact, the consensus is that the better long-term results of surgery compared to percutaneous interventions have been well documented and that percutaneous coronary interventions are on the decline and surgical bypass surgery is steady.

Given the current facts, the combination of both practices has been fruitful. A group from Vanderbilt in 2009 reported the feasibility of combining the cath-lab with the operation room, which enhanced the options available to both cardiothoracic surgeons and interventional cardiologists and improving their ability to offer medical care in complex coronary artery diseases. This hybrid approach was patient-centered in the sense that all options were available to the patient at any given moment during the procedure thus creating a less "hazardous" environment and leaving much less room for in-procedure complications to arise. To quote their conclusion; Our data suggest that routine completion graft imaging should eventually become the standard of care in CABG surgery. Furthermore, with the increased complexity of patients referred for cardiac surgery, a team approach, combining traditional cardiac surgical techniques and PCI, may be beneficial, especially in high-risk populations.

It has been supported that the cornerstone of success is the meaningful collaboration between the two specialties – the definition of patient eligibility between the two practices is yet to be distinguished nonetheless the combination of the two has proven to be beneficial in high-risk groups. Notably, the American guidelines for hybrid cardiac revascularization procedures suggest that ; *Hybrid coronary revascularization may be reasonable as an alternative to multivessel PCI or CABG in an attempt to improve the overall risk-benefit ratio of the procedures.*

Last but not least , in an editorial published in PCR Online in 2020, it was suggested that the "Interventional cardiac surgeon" is the new member of the interventional

cardiac team. This unbiased role , of a doctor merging the traditional surgical practice with the interventional practice , was characterized as an innovator cardiac surgeon. The idea of cardiothoracic surgeons completing an additional training in interventional cardiology could be the new future of treating the heart. The editorial suggests that potentially, this could embody a new generation of interventionists, incorporating the skills set of the multidisciplinary team in a single individual . This new angle in this debate offers plenty of food for thought as to what the future entails, however the proof at hand suggests that this scenario may not be as futuristic as it may seem.

REFERENCES



Septal Reduction Therapy in Patients with Obstructive HCM: The sooner, the better?

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INTRODUCTION

In this opinion article, we will examine the significance of early surgical intervention in obstructive Hypertrophic Cardiomyopathy (HCM) cases, alongside the survival rates and complications associated with various treatment options. Hypertrophic Cardiomyopathy is a structural heart condition affecting about 1 in 500 individuals. Most HCM patients experience hypertrophy of the interventricular septum, resulting in Systolic Anterior Motion (SAM) of the Mitral Valve towards the septum. The result is obstruction of the Left Ventricular Outflow Tract (LVOT) during systole, impeding blood flow into the aorta and causing regurgitation into the left atrium due to valvular damage. LVOT obstruction diminishes the survival rate and quality of life in HCM patients. In patients with hypertrophic obstructive cardiomyopathy (HOCM), negative inotropic drugs (such as beta-blockers, calcium channel blockers, and disopyramide) are often the first line of treatment to alleviate symptoms of heart failure and chest pain by reducing the contractility of the heart muscle and thus lowering the left ventricular outflow tract (LVOT) gradient.



However, adherence to long-term medical treatment is relatively low, with only about 5-10% of patients continuing with medication alone. As a result, in patients with an LVOT gradient higher than 50%, or in cases where medications are ineffective in alleviating pain, Surgical Reduction Therapy is recommended. [1]

Septal Myectomy vs Alcohol Septal Ablation

Currently, the two most prevalent surgical interventions for septal reduction are Septal Myectomy (SM) and Alcohol Septal Ablation (ASA). Septal Myectomy involves the surgical reduction of the hypertrophied muscle of the Interventricular Septum. It is an open-heart surgery, where sternotomy and cardiopulmonary bypass are performed. An aortotomy is then performed. Up to 15 g of hypertrophied septal muscle is removed through the aortic valve to enlarge the left ventricular outflow tract (LVOT).

The result is immediate and significant reduction in LVOT gradient, effective in resolving systolic anterior motion of the mitral valve. The recovery period is longer, which makes surgical myectomy preferred for younger patients due to better recovery capacity and longer-term benefits [2]

On the contrary, ASA is a minimally invasive procedure that works by injecting ethanol into the left anterior descending artery, resulting in targeted septal infarction. ASA reduces LVOT gradient and mitral regurgitation in 80-90% of patients and induces regression of left ventricular hypertrophy over time. Since the start of this intervention, ASA has been greatly improved, minimizing complication risk and, most importantly, reducing the effective ethanol dose injected in the myocardium. The utilization of Myocardial Contrast Echocardiography (MCE) helped with the identification of the vessels affecting the septum and the size of infarct after ethanol infusion. [2], [5]

The major question is which of the two procedures is more appropriate for symptomatic obstructive HCM and why. There is no one-size-fits-all answer to the question, as many patients fall into a 'grey zone'. This is why a comprehensive evaluation that includes clinical symptoms, echocardiographic and angiographic findings, surgical risks, and anatomical abnormalities is crucial. That said, it is more reasonable for a younger patient with severe mitral valve disease

and ventricular septal hypertrophy and a multi-vessel CAD to be treated surgically. However, an older patient with less complex CAD and moderate atrioventricular interval is preferred to proceed with ASA. In every case, the skill and experience of the cardiology and surgical teams play a crucial role in the success of either procedure. Centers with high expertise in either SM or ASA may achieve better outcomes with their preferred technique.

Furthermore, according to a cohort study conducted by Nguyen et al, which compared the primary outcome from the 2 surgical interventions, it was found that there were no significant differences in survival rates and no in-hospital mortality between the groups. However, the LVOT pressure gradient decreased more in patients who underwent surgical myectomy, whereas re-intervention of LVOT obstruction was more likely in patients treated with Alcohol Septal Ablation. [3]

In addition, another systematic review (by Liebregts et al) highlighted the necessity for permanent pacemaker implantation in patients who underwent ASA, due to higher risk (over twice as high) of periprocedural adverse arrhythmogenic effect, such as AV block in most cases. Specifically, the complication risk was 10%. Conversely, SM, being an open-heart surgery, entails a longer rehabilitation period but remains the preferred intervention for younger patients [4]

CONCLUSION

In conclusion, SM and ASA significantly alleviate symptoms and enhance overall survival rate. The relief in LVOT pressure is more complete in SM and the likelihood of re-intervention is higher in ASA. Generally, SM is favored for younger patients with more complex CAD and anatomical abnormalities, while ASA is often preferred for older patients with less severe conditions and more favorable anatomy. The decision should ultimately be personalized, considering the patient's specific condition and the expertise of the medical team. Nonetheless, it is advisable that all patients eligible for Septal Reduction Therapy be evaluated by a multidisciplinary heart team, utilizing myocardial imaging echocardiography and other imaging techniques to guide their treatment. [4]

REFERENCES



The Role of Intraosseous Access in CARDIAC ARREST: A Comprehensive Review

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EDITED BY ELENI TZANETOU
DESIGNED BY APHRODITE P. PASCOE

INTRODUCTION

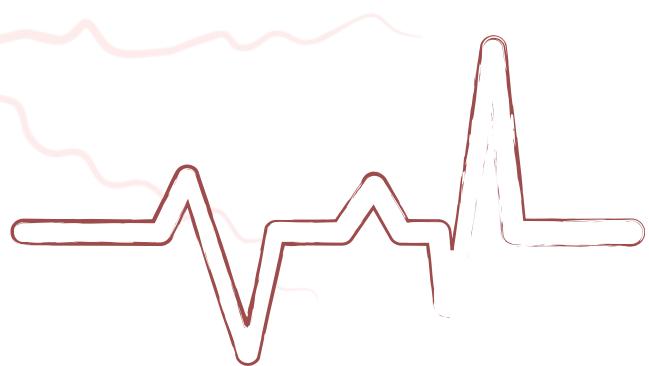
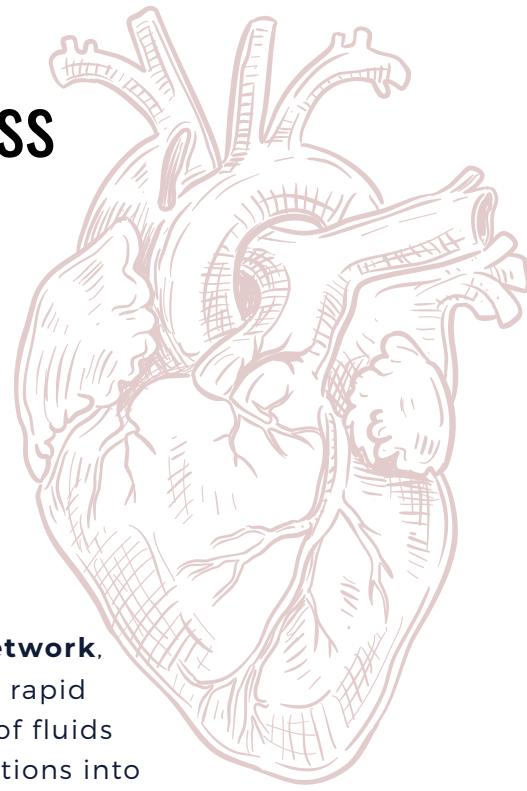
In **cardiac arrest**, rapid and effective administration of medications and fluids is crucial for **successful resuscitation** and improved patient outcomes. While **intravenous (IV) access** remains the **gold standard** for medication delivery, challenges such as vascular collapse, peripheral vasoconstriction, or difficult venous access can significantly delay the time for establishment of IV lines. In such critical situations, **intraosseous (IO) access** provides a vital alternative, offering rapid and reliable access to the systemic circulation through the **bone marrow**. This **comprehensive review** explores the indications, techniques, devices, advantages, considerations, complications, and future directions of IO access in the management of cardiac arrest and other emergent situations.

Anatomy and Physiology of Intraosseous Access:

Intraosseous access involves the insertion of a needle or catheter directly into the marrow space of a bone, typically the **proximal tibia** or **humerus** in adults and the proximal tibia in children. The bone marrow contains a rich

vascular network, allowing for rapid absorption of fluids and medications into the **central circulation**. This route provides an alternative option when peripheral IV access is difficult or impossible, ensuring that critical therapies can be administered promptly during emergencies [1].

The **proximal tibia** is the most **commonly used site** due to its accessibility and relatively **thin cortex**, which facilitates easier needle insertion and reduces the risk of complications such as fracture or needle dislodgement. In **pediatric patients**, the proximal tibia is preferred for IO access due to its proximity to the growth plate and lower risk of injury to adjacent structures compared to other sites [2].



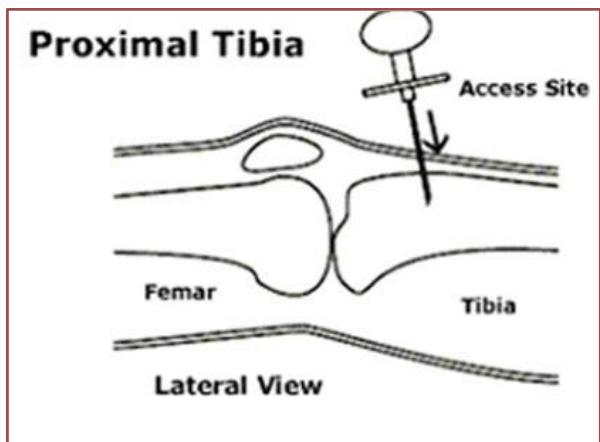


Figure 1

Indications for Intraosseous Access:

IO access is indicated in various emergent scenarios where immediate vascular access is essential:

Cardiac Arrest: During cardiac arrest, rapid administration of medications such as epinephrine, antiarrhythmics (e.g., amiodarone), and sodium bicarbonate is critical for restoring spontaneous circulation. IO access ensures that these medications can be delivered promptly when IV access is delayed or not feasible [3].

Shock and Hypovolemia: In patients with shock or severe dehydration, peripheral veins may collapse, making IV access challenging. IO access provides a reliable alternative route for administering fluids and vasoactive medications, helping to stabilize hemodynamics while efforts are made to establish peripheral or central venous access [4].

Pediatric Emergencies: Children often present unique challenges in vascular access due to their smaller size and limited venous options. IO access is particularly valuable in pediatric emergencies, allowing for rapid administration of medications and fluids without the need for multiple IV attempts [5].

Special Populations: Elderly patients and those with chronic medical conditions may have compromised vascular access due to factors such as arteriosclerosis or previous vascular interventions. IO access ensures that these populations receive timely and effective treatment during emergencies [6].

Techniques and Devices for Intraosseous Access:

Several devices and techniques are available for establishing IO access, each with specific advantages depending on the clinical scenario and patient characteristics. Commonly used devices include manual IO needles, spring-loaded devices, and battery-powered drills designed for **rapid deployment** in emergency settings. The choice of device and insertion site should consider factors such as patient age, bone density, urgency of vascular access required, and provider familiarity with the technique [7].

The procedure for IO access typically involves the following steps:

1. Site Selection and Preparation:

Preparation: The proximal tibia is most frequently selected for IO access due to its accessibility and lower risk of complications. The skin overlying the insertion site is thoroughly cleaned and disinfected to minimize the risk of infection.

2. Needle Insertion:

Using an appropriate IO needle or device, the provider applies firm, steady pressure to penetrate the bone cortex until the needle tip enters the marrow cavity. Proper technique and angle are crucial to ensure successful insertion and minimize patient discomfort.

3. Confirmation of Placement:

Verification of proper needle placement is essential to avoid complications such as extravasation or injury to surrounding structures. Techniques for confirmation include aspiration of bone marrow, visualization of blood flash back, or the use of bedside ultrasound to confirm appropriate needle tip placement within the marrow space.

4. Securing the Device:

Once proper placement is confirmed, the IO device is secured to the skin using adhesive dressings or fixation devices to prevent accidental dislodgement during patient movement or transport.



Figure 2

Advantages of Intraosseous Access:

IO access offers several advantages in emergency situations, particularly in cardiac arrest and other time-critical scenarios:

Rapid Access: IO access can be established quickly, often within seconds to minutes, compared to the time required for peripheral or central venous access.

This rapidity is crucial for administering time sensitive medications such as epinephrine during cardiac arrest [8].

High Success Rate: Studies have demonstrated high success rates for IO access in both adults and children, with success rates approaching 90% in some studies. This reliability ensures that critical therapies can be delivered promptly even when traditional IV access is challenging [9].

Versatility: IO access can accommodate a wide range of medications and fluids, including resuscitation drugs, antibiotics, blood products, and contrast agents for imaging studies. This versatility makes it suitable for diverse clinical scenarios [10].

Considerations & Complications:

While generally safe and effective, IO access is not without considerations and potential complications:

Patient Discomfort: Patients may experience transient discomfort during needle insertion, particularly with manual IO needles. This discomfort is typically brief and can be minimized with appropriate local anesthesia or distraction techniques [11].

Risk of Complications: Rare complications associated with IO access include infection, osteomyelitis, compartment syndrome, and bone fracture. These risks can be reduced through adherence to aseptic technique, proper device selection, and vigilant monitoring of the insertion.

site for signs of inflammation or extravasation [12].

Device-Specific Considerations:

Different IO devices may have specific considerations regarding insertion technique, needle placement, and securing methods. Providers should be familiar with the specific device they are using and adhere to manufacturer guidelines to minimize risks and optimize patient outcomes [13].

Evidence Base and Clinical Outcomes:

Numerous studies, meta-analyses, and systematic reviews have explored the **efficacy and safety** of IO access in various clinical settings, including cardiac arrest, trauma resuscitation, and pediatric emergencies. Meta-analyses have consistently demonstrated the **comparable effectiveness** of IO access compared to traditional IV access in achieving **therapeutic endpoints** and improving patient survival rates.

A meta-analysis by **Jones et al. (2020)** reviewed data from 15 randomized controlled trials and observational studies involving over **5,000 patients**. The analysis found that IO access achieved similar rates of successful medication administration and clinical outcomes compared to IV access, particularly in time-sensitive situations such as cardiac arrest and trauma resuscitation [14].

Similarly, a systematic review by **Smith and Johnson (2019)** synthesized evidence from 12

studies focusing on IO access in pediatric emergencies. The review highlighted that IO access provided rapid and reliable vascular access in children, with success rates exceeding **90%** in most studies. The review also emphasized the importance of early IO access in improving survival outcomes, especially in settings where peripheral IV access was challenging or time-consuming [15].

In addition to **clinical efficacy**, IO access has been shown to reduce time to medication administration compared to IV access, with studies reporting a median insertion time of **less than 30** seconds in experienced providers [16]. This rapid access is crucial for delivering time-critical medications such as epinephrine during cardiac arrest, where every second counts in improving patient outcomes [8].

Furthermore, **long-term outcomes** from registry data and cohort studies have indicated that patients receiving early IO access have comparable survival rates and neurological outcomes to those receiving traditional IV access, underscoring the importance of IO access as a **reliable alternative** in emergency care [3,17].

Future Directions and Innovations:

Advancements in IO access technology continues to evolve, with ongoing research focused on improving device design, insertion techniques, and training protocols. Innovations such as semi-automatic

IO devices, ultrasound-guided insertion techniques, and wireless monitoring systems aim to enhance the safety, efficiency, and reliability of IO access in emergency care settings.

CONCLUSION

Intraosseous access plays a pivotal role in the management of cardiac arrest and other life-threatening emergencies where rapid vascular access is crucial for initiating and sustaining critical interventions. By providing a reliable alternative to traditional IV access, IO access ensures that essential medications and fluids can be administered promptly, thereby improving patient outcomes in high-stakes emergency settings. As medical technology advances and clinical evidence continues to accumulate, IO access remains an indispensable tool in emergency medical care, ensuring that timely and effective treatments reach those in urgent need.

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RABIES:

The Terrifying Disease and How We Fight It

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ABSTRACT

The rabies infection targets the central nervous system (CNS) that impacts global health and especially less developed countries. The disease is spread via the saliva of infected animals and can be fatal if left untreated. The virus progresses from the site of a bite to the CNS, leading to severe symptoms such as hydrophobia, seizures and paralysis. Effective management requires prompt diagnosis and immediate wound care, with vaccination protocols tailored to the patient's immunization status. New treatment protocols using favipiravir are under research, but current clinical trials are showing challenges in delivering the drug across the blood brain barrier.

Rabies is a viral zoonotic disease that primarily affects the CNS and poses a significant public health threat worldwide. The rabies virus is transmitted by the saliva of animals that have been infected by the disease and can be fatal if left untreated. Despite the availability of preventative vaccines and post-exposure prophylaxis (PEP), rabies is still a critical threat for the population of developing countries, where access to preventative measures is limited

and the exposure to the virus is more prevalent. Doctors and scientists are working to create an effective treatment protocol for those infected, but measures to prevent infection in the first place should be made easily available for everyone [1].

Rabies is transmitted via the saliva of infected animals to humans via their bite. In certain instances, the virus has been spread by animal saliva that came into contact with human mucous membranes or open wounds.[2]. A bite is necessary to infect the host as the virus can't penetrate intact skin by itself. When introduced into a human patient, it can start replicating at the muscle cells on the site of the bite. From the muscle cells it can then progress into the nerve cells and into the CNS. It then begins to rapidly replicate, at which point clinical symptoms manifest and severity of the infection increases [3]

In general, rabies is a disease that causes progressive and fatal inflammation of the spinal cord. When the virus first enters the CNS, the immune system will attempt to fight the pathogen, at which stage prodromal symptoms

can manifest. These include fever, fatigue, cough, muscle pain or a sore throat, as well as itching, tingling and numbness in the bite site or the extremities [4].

Rabies can be clinically divided into two types: furious and paralytic rabies[5]. Furious rabies is characterized by tachycardia, hyperventilation, seizures, hyperactivity, hallucinations, a lack of coordination, and, most prevalent, hydrophobia, among others [4,5]. Symptoms are seen to come in waves ("furious episodes"), with periods of calmness in between them [5]. Paralytic rabies, on the other hand, manifests as a fever, neck stiffness, and weakness at the site of the bite that will radiate to the rest of the body, and can even progress to paralysis or even a coma [5].

Research done in 2022 shows a range of 30,000 to 70,000 annual deaths accredited to the rabies virus worldwide. Additionally, less developed countries were also shown to be affected more. The majority of rabies cases in developed countries are caused by wild animals including skunks, raccoons, foxes, and especially bats; domesticated animals (eg. dogs) have only accounted for about 10% of cases [6]. In the US, when a patient shows up with a bite from one of the aforementioned animals, it is assumed that they have the rabies virus, and appropriate measures are taken to treat the infection.. The same procedure is applied for a dog bite in less developed countries [6].

For the treatment to be more effective, prompt diagnosis is essential. Tests include saliva and blood tests, a lumbar puncture to test cerebrospinal fluids (CSF) and a skin biopsy taken directly from the site of the animal bite [4].

In the event of a patient presenting to a hospital with suspected animal-acquired rabies, the first step is to thoroughly clean the bite. Initiating appropriate wound care within three hours of exposure has been shown to be nearly 100% successful in treating rabies on its own without any further treatment[6]. Doctors recommend scrubbing the wound using water and plain soap, making sure to swab deeply enough to puncture the wound to ensure proper cleaning [6].

Because of its fatal nature when contracted, taking rapid action, when a rabies infection is suspected, is essential. Because a standard protocol has not yet been determined, prevention in the form of rabies vaccines are a mainstay of treatment. Because of this, the patient's immunization status determines the subsequent actions for their treatment[6]. In the event the patient was previously vaccinated, they should receive two doses of the rabies vaccine on the day of the exposure and seven days later. Depending on the severity of the case and the risk the patient is in, they may be advised to receive a booster dose, three years after the original two doses [7]. If the patient is not previously vaccinated, they should receive four doses of the rabies vaccine on days 0, 3, 4 and 14.

Doctors can also prescribe rabies immunoglobulin medication that provides the immune system with antibodies against rabies. This drug aims to protect the patient but doesn't attack the virus directly [6,7,8].

The creation of a protocol that highlights the need for neuro-protective features seems to be the best hope for the treatment of the rabies virus [9]. An agent called favipiravir that was originally used to treat influenza symptoms in Japan shows promise for its use in the treatment of rabies in recent studies [9,10]. Favipiravir is a purine nucleic acid that is shown to inhibit a variety of RNA viruses, and past research in animal models showed that it suppressed the replication of the rabies virus. Although the survival period of the mice seemed to be improved, delivery to the CNS via the blood-brain barrier proved to cause difficulties causing the total survival rate to not be improved [9]. Further research with this agent should be done to determine if it could be a new therapy option.

Challenges in the proper diagnosis and treatment of rabies arise predominantly from the lack of research for it. Patients are often misdiagnosed as having psychosis, seizures, or hallucinations, causing the disease to progress to a point where treatment is challenging or even impossible [6]. Additionally, because the infection targets primarily the CNS, effective treatment is hindered by inability of drugs to pass the blood-brain barrier.

In conclusion, rabies remains a neglected tropical infection that endangers a large and vulnerable percentage of the world's population. Despite preventative measures and current treatment regimens, it continues to cause thousands of deaths annually. Research into new treatment protocols that aim to target symptoms after the virus reaches the CNS, harnessing the potential use of favipiravir, shows promise, but also highlights the need for further studies to overcome obstacles such as the blood-brain barrier. Finally, doctors and scientists should fight to make preventative measures more accessible to the populations that need them.

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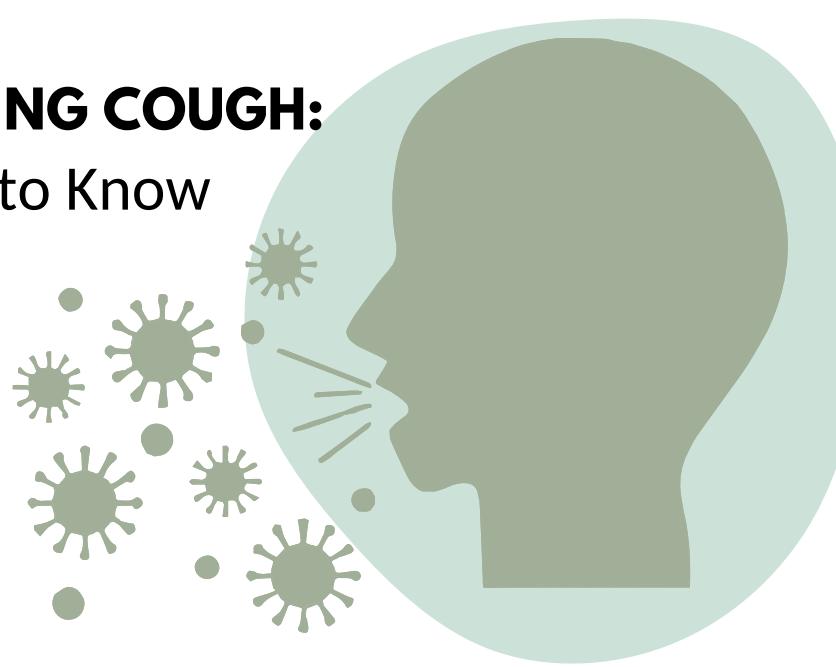


ECHOES OF WHOOPING COUGH:

Everything You Need to Know About Pertussis.

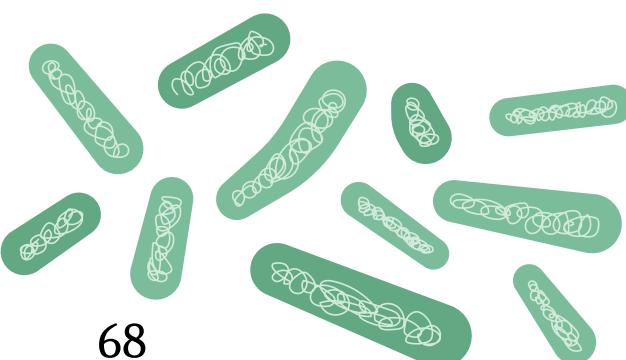
WRITTEN BY NIKOLINA NIKOLAOU
EDITED BY POLYNA ANTONIOU
DESIGNED BY APHRODITE P. PASCOE

Pertussis, or whooping cough is a highly contagious bacterial infection of the respiratory tract affecting people of all ages, with newborns and young children being at higher risk. The disease is typically caused by the gram-negative, obligate aerobic coccobacillus *Bordetella pertussis*. This organism is mainly spread through respiratory droplets when an infected person sneeze or cough. Typically, pertussis progress through three stages, with the second and third being marked by severe and uncontrolled coughing spells (paroxysms), followed by a characteristic highpitched 'whoop' sound on inhalation. Before the vaccine was developed, whooping cough was considered a childhood disease (<1 year of age). Now whooping cough demonstrates high rate of infections in older patients and newborns whose immunity has faded, or they are too young to have gained the full coverage from vaccinations. Deaths caused by pertussis are rare and most commonly occur in infants. [9]



DISEASE PATHOGENESIS:

Primarily, pertussis involves a complex interaction of several virulence factors that contribute to its pathogenicity. Upon entering the upper respiratory tract, the bacterium releases key surface structures, including filamentous hemagglutinin, pertactin, and agglutinins, which facilitate adherence on ciliated epithelial cells of the respiratory mucosa. This adherence is crucial for colonization and subsequent bacterial proliferation. Following this, *B. pertussis* produce additional toxins such as tracheal cytotoxin, which further damage and paralyze the cilia causing inflammation and swelling of the small airways. This disruption will eventually impair the mucociliary clearance mechanism of the respiratory tract, leading to accumulation of pulmonary secretions and contributing to the characteristic severe cough of the disease. Additionally, *Bordetella pertussis* secretes **pertussis toxin**, a major exotoxin that plays a central role in disrupting cellular signaling and immune responses, exacerbating further the disease. [3] [9]



astly, scientists strongly support that pertussis toxin is responsible for most of the systemic manifestations associated with whooping cough.

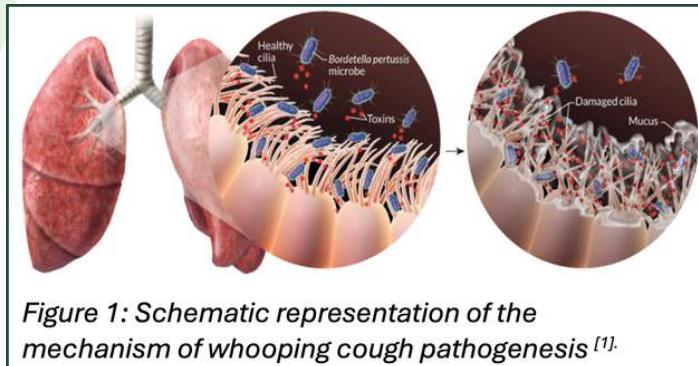


Figure 1: Schematic representation of the mechanism of whooping cough pathogenesis [1].

CLINICAL PRESENTATION:

Typically, on average the incubation period for pertussis is 7 to 10 days, though it can take up to three weeks. Classically the disease progresses through three stages: catarrhal, paroxysmal and convalescent, each differing in symptoms and severity. The **catarrhal** stage is the initial phase of pertussis, presenting the first symptoms of the disease and typically lasting for one to two weeks. During this stage, infected individuals experience nonspecific symptoms resembling those of a common upper respiratory infection (i.e. common cold), including mild cough, fever, watery nasal discharge, and possibly conjunctivitis. Despite the mild symptomatology, patients are highly infectious even in this early stage. Following the catarrhal phase is the cough stage (**paroxysmal phase**), which is more severe and may last another two to six weeks.

This phase is characterized by episodes of intense and vigorous **coughing fits (paroxysms)** that occur during a single breath producing the distinctive 'whooping' sound. These episodes can result in post tussive vomiting, dehydration, exhaustion, and an increased risk of bleeding due to the intensity of the cough. Lastly, the **convalescent stage** (Recovery phase) marks the progressive reduction of symptoms during which the coughing attacks and whooping slowly fading away until the airways are completely clear and heal. This phase usually lasts one to two weeks with the total duration of symptoms extending to about three months. [2] [6] [8]

In general, teenagers and adults often recover from whooping cough without problems. However, the disease tends to be more severe in neonates and unimmunized individuals, where life-threatening **complications** and hospitalizations have been reported. Due to the intensity of coughing, rib fractures, abdominal hernias, and broken blood vessels in the skin and/or around the eyes can occur. Additionally, complications such as otitis media,



Figure 2: Illustration of a baby with whooping cough. [4]

Bordetella pertussis pneumonia, seizures, coma, and even sudden infant death can also happen.

DIAGNOSTIC TESTING:

Diagnosis of pertussis is crucial for confirming the infection and guiding appropriate treatment, as well as implementing a prompt public health intervention. [2] [8]

Tests used to confirm B. pertussis include:

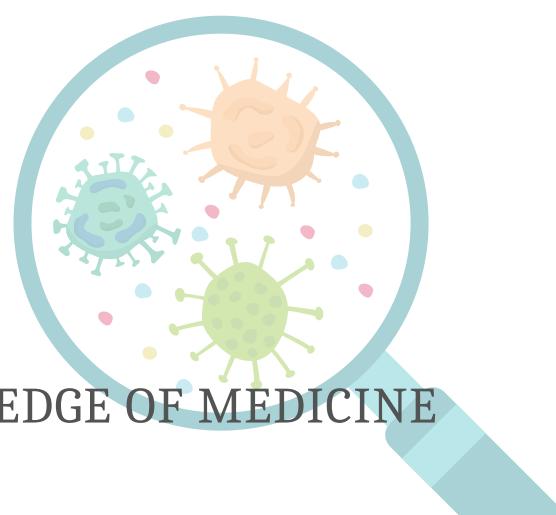
- Polymerase chain reaction (PCR) assay: PCR is considered the **preferred** test for confirming the diagnosis since its results are not affected by recent antibiotic therapy or previous vaccination. For optimal detection of the bacteria, nasopharyngeal swab is recommended, as it is more effective than throat or anterior nasal swabs.
- Bordetella pertussis culture: While culture is less sensitive compared to other diagnostic methods, it remains the **gold standard** for confirming pertussis. However, culture results may take several days, and the test's accuracy can be compromised by current antibiotic use.
- Direct fluorescent antibody test: This diagnostic method requires specially trained personnel and is often associated with high false-positive rates, limiting its reliability and accuracy.

- Serology: Serological testing is particularly useful in the later stages of the infection detecting immune responses against various antigens and toxins produced by B. pertussis.
- Complete blood count (CBC): Absolute lymphocytosis (15,000-100,000 cells/mm³) in infants <3 months.

Suspected case definition for pertussis:

A suspected case of pertussis is identified primarily through clinical presentation, laboratory testing, and epidemiologic linkage. The clinical criteria include a cough illness lasting more than two weeks, accompanied by one or more of the following symptoms: paroxysmal coughing, a whooping sound on inspiration, post tussive vomiting and apnea (with or without cyanosis). Laboratory confirmation involves either the isolation of B. pertussis from a clinical specimen or a positive PCR test. Additionally, epidemiologic criteria include known contact with a confirmed case or residence in an area experiencing a pertussis outbreak. [7]

The presence of fever suggests an alternative diagnosis. !



TREATMENT:

Effective management of pertussis typically involves a multifaceted approach. Early antibiotic intervention is crucial to reduce bacterial load and transmission, whereas supportive care can provide symptomatic relief and aid in patient recovery. This comprehensive strategy helps mitigate the impact of this highly contagious illness. The American Academy of Pediatrics (AAP) advises initiating **macrolide** antibiotic therapy, particularly **erythromycin**, as the first-line treatment for suspected pertussis without awaiting diagnostic confirmation. Prompt treatment, especially during the catarrhal stage, is crucial for reducing bacterial transmission. Erythromycin is typically administered for 14 days. However, due to gastrointestinal side effects and an increased risk of pyloric stenosis in infants under 2 months, alternatives such as **clarithromycin** or **azithromycin** are often preferred. For patients with macrolide allergies or intolerance, a combined antibiotic regimen of trimethoprim/sulfamethoxazole(Bactrim, Septra) should be used. Penicillin as well as first and second-generation cephalosporins are ineffective in managing pertussis transmission and alleviating symptoms. Additionally, centers for disease control and prevention (CDC) along with AAP encourage the use of antibiotics as a **prophylactic** measure to control pertussis outbreaks.

The effectiveness of symptomatic treatment for cough with corticosteroids, antihistamines, and/or albuterol, remains unclear and is not typically recommended as there is insufficient evidence supporting their efficacy or impact on the duration of hospitalization. [2] [8] [9]

PREVENTION:

Pertussis remains a significant cause of childhood morbidity and mortality, particularly in infants under 6 months of age due to their immature immune system, incomplete vaccination status and increase risk of complications. Immunity to pertussis, acquired either from natural infection or through vaccination, does not assure permanent protection. Current estimates suggest that immunity from natural infection lasts between 3.5 to 30 years, while immunity from whole-cell and acellular vaccines may last up to 14 years and 7 years, respectively.

Globally, prevention through immunization is the cornerstone for controlling the spread of pertussis. The CDC recommends that children under 7 years should receive the acellular pertussis vaccine (DTaP) at 2, 4, and 6 months, with a fourth dose at 16-19 months and a fifth dose before starting school. This vaccine also protects against two other serious diseases, diphtheria and tetanus.

For individuals >7 years and older, the Tdap vaccine which is like DTaP is recommended. As vaccine-induced immunity wanes by the age of 11, all individuals aged 11-12 years should be injected with a booster Tdap dose. Additionally, maternal pertussis immunization has been included in national recommendation in several countries encouraging pregnant women to get a one-time dose of Tdap preferably during the third trimester of gestation. [5] [8] [9]

CONCLUSION:

Pertussis, or whooping cough is a highly contagious and sometimes fatal bacterial infection of the respiratory tract especially in children under 1 year of age. The disease manifests through three characteristic phases, beginning with mild symptoms and progressively advancing to severe coughing fits accompanied by the distinctive 'whoop' sound before remission. Preventive measures, including strict vaccination protocols and robust public health surveillance, are crucial in reducing diseases' burden. Unfortunately, despite significant advances in vaccination, pertussis remains one of the leading causes of vaccine-preventable deaths worldwide.



REFERENCES



Can Flushing of Domestic and Public Toilet spread SARS-CoV-2 and other Enteric Pathogens?

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SUMMARY

Microbial transmission has been studied extensively during the SARS-CoV-2 pandemic of the last four years. A new way of transmission of enteric pathogens and enveloped viruses has been suggested, that is infectious aerosols escaping the toilet after flushing, which if true would have serious health consequences. Unlike most enteric pathogens, coronaviruses reach the alimentary canal in a similar manner to some parasites in that their life cycle includes the lung from where they are coughed and then swallowed. Many pathogens, bacterial and parasites, can survive the harsh environment of the stomach, however very few enveloped viruses can survive, such as Coronavirus and Hepatitis B viruses, thus the possibility of their transmission within the toilet environment, even though unlike bacteria and parasites there is no evidence that they can multiply in the intestines, is justifiable. This study was initiated by the addition of bacteria and stain to the toilet bowl and cistern by using simple routine Microbiological monitoring methods; settle plates and stains, to determine whether bacteria or stain-containing aerosols detected within the toilet environment escaped from the bowl or the cistern of the toilet after flushing, when the lid was kept open.

Many different bacteria and fungi were detected, which were both in numbers and types very similar to those recovered prior to flushing, however no bacteria or stain originated from the toilet bowl and when stain was added to the bowl and cistern all aerosols detected originated from the cistern. In conclusion wash-down low-pressure modern gravity-flush toilets do not pose any health threat when the toilet is flushed with the lid open.

INTRODUCTION

It is clear from daily experience that flushing a toilet generates strong turbulence within the bowl and that the speed and flow dynamics of the water in the bowl depend on the type and design of the toilet, with different tank pressure that could be low 10 to 15 psi, pressure assisted 25 to 40 psi or with an electric pump that increases the tank pressure to 60 psi. Anyone who used a squat toilet (also known as squatting, Indian or Turkish toilet) during a sunny day with sunlight entering the room is aware of the presence of rainbows due to water droplets mist ejected in the atmosphere after flushing; the question is: "do the droplets come from the toilet bowl or directly from the cistern?"

The possibility of the toilet being a source of contagion has been studied extensively in the last 70 years¹⁻⁴. The first study to show bioaerosol production during toilet flushing led to improvements in the toilet design not only to prevent the escape of microbes but also to reduce the amount of water needed to remove all faecal matter from the bowl during flushing⁵. About 30 years later, using *Serratia marcescens* and MS2 bacteriophage it was confirmed that high numbers of both the bacteria and the viruses remained in the bowl after flushing, as well as that both the bacteria and the viruses were detected on many surfaces around the domestic toilet⁶.

During the SARS-CoV-2 pandemic of the last four years there has been a great lot of information on the way viruses are spread and survive in the environment. Three very valid mechanisms for the transmission of SARS-CoV-2 were proposed that may also apply in the toilet environment⁷. First, inhalation of faecal and/or urinary aerosol from an individual shedding the virus, a mechanism that can also be applied to all enteric pathogens; second, airborne transmission of respiratory aerosols between users face-to-face or during short periods after use, which only applies to respiratory pathogens⁸; and third transmission from fomites via frequent touching that can apply to both enteric and most respiratory pathogens.

Though SARS-CoV-2 is an enveloped virus, like Hepatitis B can survive the harsh acidic conditions of the stomach and can cause a variety of gastrointestinal symptoms such as anorexia (39.9%), diarrhoea (2%), vomiting (3.6%), nausea (1%), abdominal pain (2.2%) and gastrointestinal bleeding (4%)⁹. However, neither the viral infective load nor the concentration of the virus in faeces is known, and with diarrhoea that may persist between 4 and 6 days there is a great risk of transmission if aerosols containing the virus escape the toilet bowl during flushing. The possibility of SARS-CoV-2 transmission via floor drains was first investigated in an outbreak in Hong Kong in 2003¹⁰ and this possibility was also confirmed to exist for SARS-CoV-2 in apartment buildings¹¹.

The influence of flushing on the spread of SARS-CoV-2-containing aerosol particles was studied using computational fluid dynamics (to explore and visualise the characteristics of fluid flow during toilet flushing) and has showed alarming simulation results¹². They observed a massive upward transport of particles with 40 – 60% of these particles that reach above the toilet seat above the toilet seat and may linger in the air or deposited onto surrounding surfaces. If these computational fluid dynamics are also true for domestic and public toilets, and the particles escaping after flushing are ejected from the toilet bowl, they may pose serious health risks to anyone using or entering the toilet (breathing or acquiring

the microorganism from fomites i.e., by touching) after an infected individual used it.

There are many diarrhoea-causing pathogens. viruses and bacteria that can be spread in the manner described above, such as Enteropathogenic & Enterohaemorrhagic Escherichia coli, Salmonella, Shigella, Vibrio cholerae, Campylobacter, Cryptosporidium but none more than Norovirus with a concentration of $\approx 10^{11}$ virions/gram of diarrhoeal fluid, and an infective load of only 100 virions (Table 1)¹³⁻¹⁵. The microbial load during diarrhoea as well as in carriers has been studied for many enteric bacterial pathogens and was found to vary considerably among individuals^{13,16}. Microbial load in the infected individual and survival of the microbe in the environment are two of the major factors that can influence the spreading and development of disease in the recipient¹⁷.

Microorganisms present in faeces have the potential to contaminate surfaces in toilets and bathrooms⁶, particularly with the young and very old who are either prone to accidents or exhibit poor hygiene. As mentioned above infectious gastroenteritis-causing bacteria and viruses are excreted in very large numbers, $10^{10} - 10^{11}$ /g faeces during episodes of acute diarrhoea so this study was designed to investigate whether flushing modern wash-down low-pressure gravity-flush domestic or of similar design public toilets, will induce turbulent flow that can expel aerosol particles containing microorganisms that have been added into the bowl.

Experiment	Toilet	Petri Dishes	Microorganism	Exposure Time, min
1	1	BA	Micrococcus	2 & 10
2	1	BA	Micrococcus	2
3	1	BA	Micrococcus	2 & 10
4	1	MAC	E. coli	2 & 10
5	2	<u>BA&MAC</u>	E. coli	10
6	2	BA	Micrococcus	10
7	3	<u>BA&MAC</u>	E. coli	10
8	3	BA	Micrococcus	10

BA- Blood Agar, MAC- MacConkey Agar

Table 1: The Experiments performed showing the Petri dishes and Microorganism used and the exposure time after flushing

MATERIALS AND METHODS

Toilets: Three different, but of similar design wash-down low-pressure gravity-flush toilets were used; water pressure 10-15 psi. Two domestic toilets, the first was situated in a 5 m² bathroom (T1) and the second in a 2.3 m² toilet room (T2) in the home of one of the authors (MAP). The third in a 2.5 m² toilet room which could be considered as a public toilet was in Archbishop Makarios III Hospital (T3) for use by staff.

The water tanks or cisterns of the three toilets had a reservoir containing 10 Litre of flush water and the toilet bowls contained 1.5 Litre of water. For T1 and T2 the cistern was attached to the bowl whereas for T3 the cistern was mounted approximately 1.5m above and was connected to the toilet with a 5cm diameter plastic pipe.

Before each experiment, the toilet bowl and all porcelain surfaces were scrubbed with a hypochlorite-containing disinfectant (4.5%) and flushed twice to eliminate traces of the cleaning compound. The same disinfectant was also used to decontaminate the toilets and surfaces after each experiment.

Toilet flushing: In most diarrhoea cases the affected person will open the lid, and using the toilet brush will clean everything that was splashed or attached to the sides of the bowl at the same time as flushing the toilet; therefore, the lid was kept open for all experiments.

Background bacteria found in the toilet environment: Settle plates were used to determine both the types and amount of background bacteria 2 days before of each experiment, by placing Blood, MacConkey and Sabourauds Agar plates around each toilet and its vicinity for 1 min, 10 min, 30 min and 2 hours. The same procedure was repeated during each experiment and the plates were exposed for 2 min (average time an individual remains in the toilet after flushing the toilet), 10 min (assumed maximum time that someone may remain in the toilet) and 30 min (time by which most particles/aerosols will settle onto surfaces). The experiments were also carried out after spraying with disinfectant, with a spray that contained 57.81% ethanol and 0.09% Alkyl-Dimethyl-Benzyl-Ammonium (Dettol©) with the doors closed.

Plate distribution in the toilet

Room: Figure 1 shows the distribution of plates on the surfaces around the toilet as well as the plate tree at different heights during each experiment. The plate tree represented people of different heights and was prepared by drilling 1 cm holes into a 180x4 cm pole and inserting 34x1 cm rods leaving 15 cm exposed on each side of the pole. The height increased by 20 cm for each set of plates as shown. Petri dish lids were glued to the edges of rods so that the agar plates could rest securely on them.

After the plates were added to the plate tree they were kept closed and the lids were removed seconds before the toilet was flushed. After the 1st timed exposure, lids were added to half of the plates, one on each level and all the plates were closed and removed after completion of the experiment. Except for the first and second set of experiments the entire room, ceiling, surfaces, and the plate tree were sprayed with disinfectant, 30 min prior to each experiment and the surfaces and the plate tree were re-sprayed with the disinfectant and scrapped clean after each use. All experiments were performed with the toilet doors open.

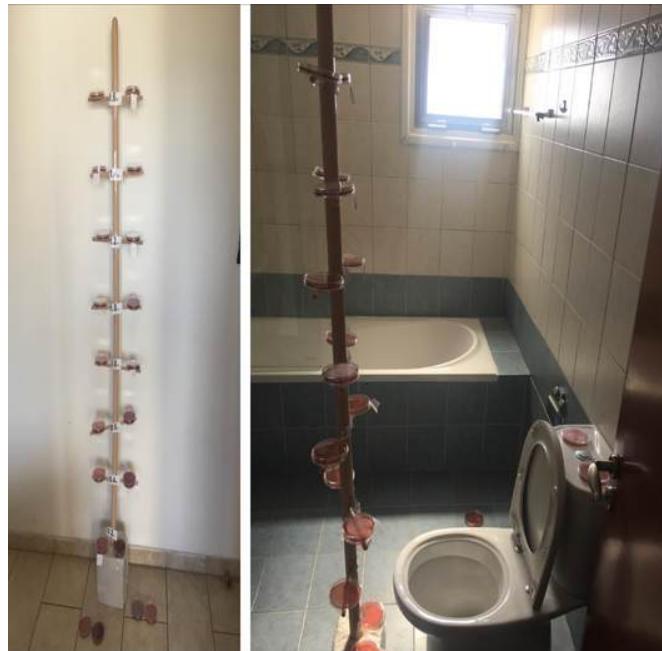


Figure 1: The plate-tree after construction and in position in toilet 1 (T1) after flushing

Bacteria strains used for toilet seeding:

Clinical isolates of *Micrococcus* spp. (BSL 1) which is non-pathogenic, grows very easily on many BA plus due to its colour easy to count the colonies and a fully sensitive and *E. coli* (BSL 2) an organism never recovered in during the experiments with the *Micrococcus* spp bacteria were chosen. Both isolates were identified using the Phoenix 100 (Becton Dickinson). Using a 48-hour culture on Blood agar a heavy suspension with a similar concentration to enteric pathogens during diarrhoea, stock solution of $>10^{10}$ cfu/mL was prepared in sterile saline. The stock solution was checked for viability as well as concentration (semi-quantitatively) by subbing 10 μ L onto BA plates; after which was sealed tightly and mixed rigorously before it was gently added to the pre-cleaned toilet bowl in a manner that coated the entire surface of the lower bowl. The viability of the added solution was checked by subbing 10 μ L from the toilet bowl onto a BA and MAC plates before the toilet was flushed. Only BA plates, 20 per experiment were used for this isolate and each experiment was repeated twice for each toilet. The 20 Petri dishes used for each experiment were 10 BA and 10 MCA or 20 MCA plates only (**Table 2**).

Incubation of Plates: All the plates were incubated at 37°C under aerobic conditions and were examined daily for 4 days. Results were recorded after 4 days incubation; after which all the plates were left at Room Temperature and were re-examined after 6 days (total incubation period 10 days).

Droplet production after toilet flushing:

This is a similar experiment to that described previously⁴ where a dye was added to the bowl or the water tank to determine whether the water droplets ejected and escaped into the air during flushing originated from the bowl or the water tank.

Crystal violet dye (Merck) was added either to the bowl (100 mL) or the water tank (300 mL) of the two domestic toilets only. Sheets of white absorbent kitchen paper were placed in the same positions as the Petri dishes (**Figure 1**) as well as on the top of the bowl and the floor around the toilet as shown in **Figure 2**. The toilet was flushed, and the room was left undisturbed for 30 min before examining the white paper for visible blue droplets. The experiment was repeated with T1 using cleaning aromatic balls as shown in **Figure 2(C)**.

The bowl and the water tank were cleaned with 1.5% Sodium hypochlorite, which removed all traces of the dye between experiments.



Figure 2: The toilet and white tissue distribution during and after flushing with blue dye.

Figure 2a.: Dye added to the toilet bowl (A1, A2 & A3) no drops outside cistern

Figure 2b. Dye added to the cistern (B1, B2 & B3) drops noted 40 cm away from the toilet (B3)

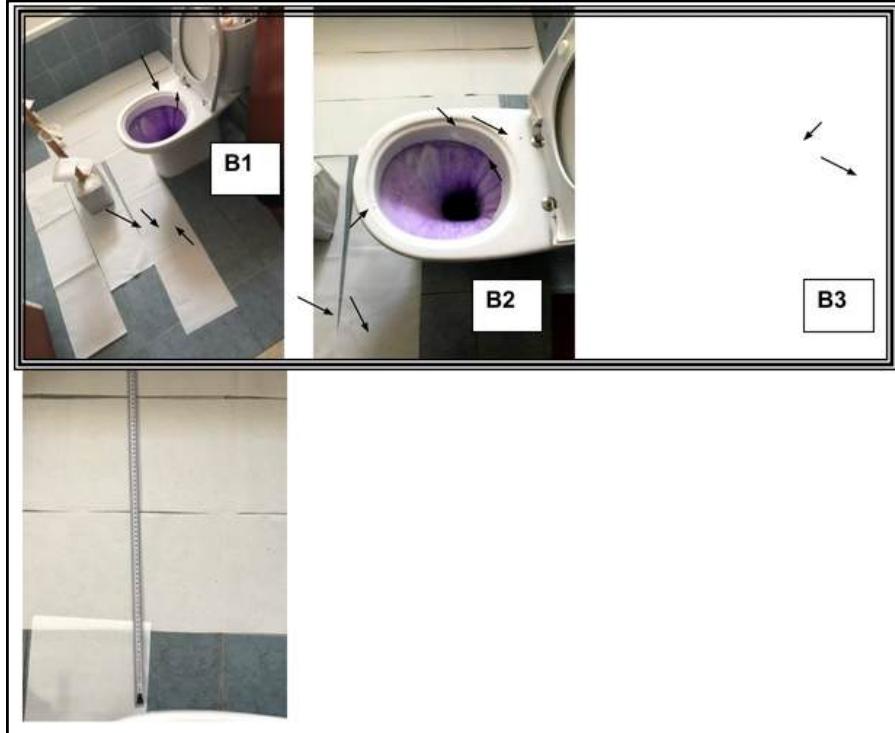


Figure 2b.: Dye added to the cistern (B1, B2 & B3) drops noted 40 cm away from the toilet (B3)



Figure 2c.: Dye added to the cistern with cleaning aromatic balls in the toilet (C) drops not shown



Enlarged photo of B2

RESULTS

Background Bacteria found in the toilet environment: Many different types of Bacteria and Fungi were grown and the amount of both increase with an increase in the exposure time. The yellow Micrococcus spp colonies numbers after 10 minutes of exposure were very similar to those in the experiments where Micro-coccus spp. was added to the bowl of the toilet, ranging from 1 to 15, average 6 colonies, which increased to an average of 12 and a maximum of 21 colonies at 30 minutes of exposure.

Spraying the air and ceiling of the toilet with disinfectant while the door was open and moving around did not alter the numbers of bacteria or fungi recovered when compared to the experiments without spraying. However, spraying the air and surfaces prior to the experiments without disturbance in the toilets, however (doors closed) reduced the number of colonies for all bacteria and fungi by >80% when compared to the first two experiments and to the experiments with the doors open and movement; in an additional experiment where the door was opened and closed several times during exposure of the Petri dishes the number of colonies were similar to those with the doors kept open.

Micrococcus spp. experiments: The organisms recovered and the colony counts are shown in **Table 2**. Though the highest number of colonies was seen nearest to the floor, recovery of yellow Micro-coccus spp was independent of height, with similar numbers to those of the background ranging from 1 to 15 colonies. The numbers recovered after flushing the toilets when compared to the back-ground colonies prior to the experiment proved that there was no statistical difference. It was concluded therefore that this organism was not the ideal indicator, due to the recovery of high numbers of Micrococcus spp. colonies, both before and after seeding the bowl. A single mucoid colony of Enterobacteriaceae was isolated during experiment 3, and was identified as Klebsiella spp. To avoid confusion E. coli, being an organism that was not recovered on any plate during the first three sets of experiments, was selected for further investigations.

Table 2: The distribution of bacteria and fungi recovered during the eight experiments post flushing after 2 and 10 minutes exposure, N=the total number of plates used in all experiments.

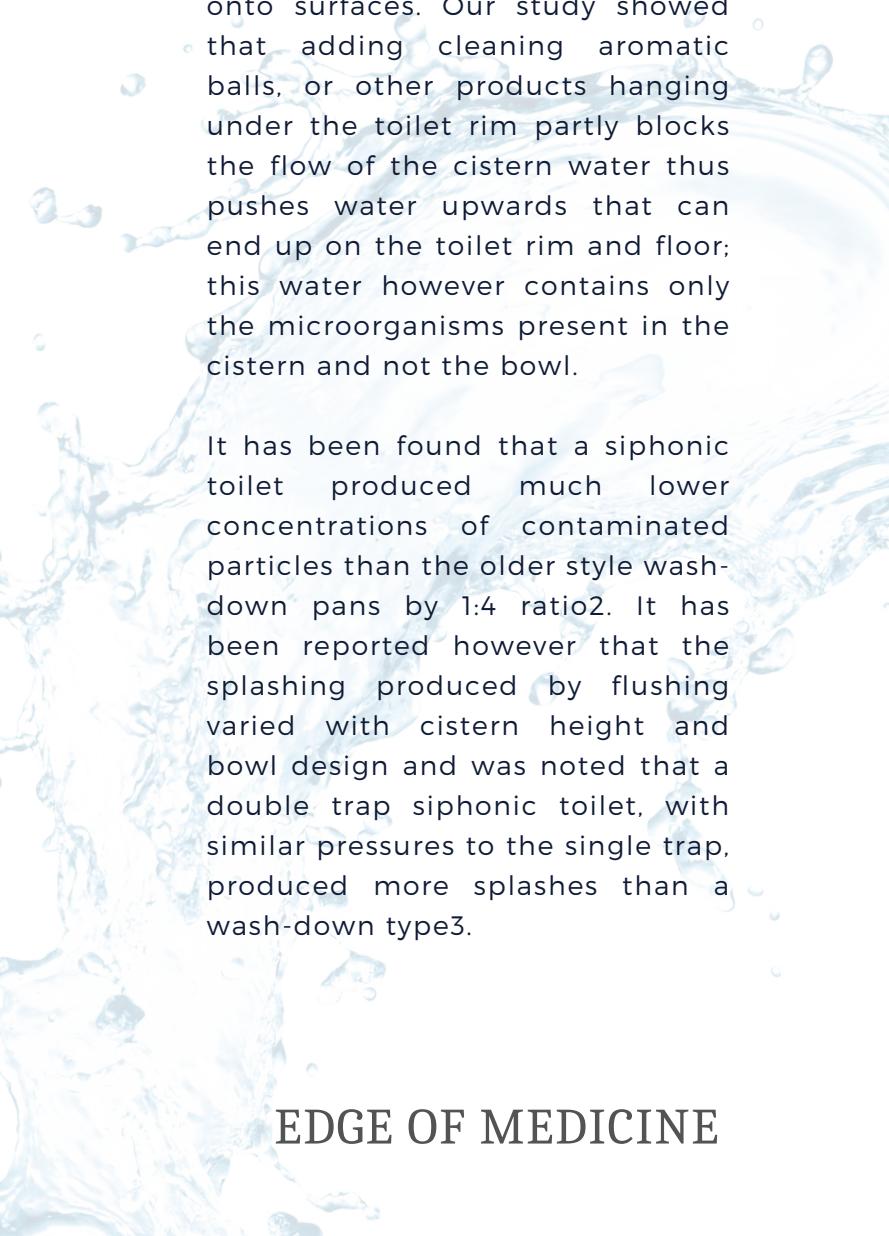
Microorganism	Exposure 2 min		Exposure 10 min	
	(Plates with Growth N=80)	Total No of Colonies	(Plates with Growth N=70)	Total No of Colonies
Micrococcus spp Yellow	47	182	46	251
Micrococcus spp Red	17	25	12	17
Coag Negative Staphylococcus	47	129	52	169
Staphylococcus aureus	30	41	36	50
Proteus spp	1	1	0	0
Klebsiella spp	0	0	1	1
Bacillus spp	34	70	37	77
Yellow Aerobic Spore Bearer	13	13	10	11
Flat Aerobic Spore Bearer	21	32	16	33
Nocardia spp	7	8	11	13
Yeast	3	5	0	0
Acremonium spp	1	1	1	1
Aspergillus <i>flavus</i>	1	1	1	1
Mucor spp	0	0	1	1
<i>Cladosporium</i> spp	1	2	1	1
Penicillium spp	9	30	8	10
Chaetomium spp	2	3	4	5

E.coli experiments: No E. coli was recovered in any of the three experiments. The numbers of other bacteria and fungi on BA plates were similar to the experiments with Micrococcus spp. Table 2. On MAC plates only moulds and Bacillus spp. were recovered with 75% of plates having no growth.

Droplet production: No blue colour was seen on any white tissue surface when the Crystal violet dye was added to the bowl of the toilet before flushing **Figure 2a**. Blue stain on the white tissue was seen only on tissues close to the toilet rims and the floor surrounding the toilet as shown on **Figure 2b (B1, 2 & 3)**, when the Crystal violet dye was added to the cistern of the toilet before flushing. The number of droplets increased, particularly on the floor on the side where the cleaning aromatic balls were hanged **Figure 2c (C)**.

DISCUSSION

The greatest risk of environmental contamination with infectious gastroenteritis causing bacteria and viruses is in the toilet/bathroom. The risk increases during acute diarrhoeal illness when faecal material containing billions/trillions of microorganisms is present in the bowl of the toilet both on the porcelain surfaces and the liquid. There is considerable variation both in the design, water pressure and size of modern flush toilets and these in turn will affect the amount of turbulence, splashing, and aerosol production^{3,19}.



In a modern wash-down low pressure gravity-flash domestic or public toilet when the flush button is pressed water pours into the toilet bowl where it splits in three; one goes down to the bowl and two travel under the rim one to the right and the other to the left and when they meet on the opposite side create vortices that elevate and fall into the centre of the water contained in the bowl. Depending on the toilet design these vortices may continue upward into the air above the bowl^{3,12}. This elevation may carry small droplets above the toilet rim and seat and if they are dispersed as many studies claimed, they can float in the toilet environment and potentially be inhaled or settle onto surfaces. Our study showed that adding cleaning aromatic balls, or other products hanging under the toilet rim partly blocks the flow of the cistern water thus pushes water upwards that can end up on the toilet rim and floor; this water however contains only the microorganisms present in the cistern and not the bowl.

It has been found that a siphonic toilet produced much lower concentrations of contaminated particles than the older style wash-down pans by 1:4 ratio². It has been reported however that the splashing produced by flushing varied with cistern height and bowl design and was noted that a double trap siphonic toilet, with similar pressures to the single trap, produced more splashes than a wash-down type³.

This study investigated the infection risk after flushing a toilet contaminated with indicator organisms at concentrations that mimic pathogen shedding during infectious diarrhoea which could be $>10^{10}$ particles per ml¹³. Using domestic wash-down toilet, a type used widely in Cyprus, the UK and most of the other European Countries, we examined the dynamics of aerosol formation and contamination of environmental surfaces after flushing and found that the only droplets/aerosols escaping after flushing originated from the cistern and not the bowl. Droplets/aerosols from the cistern might be a cause of concern for pathogens like Legionella but seeing the amount escaping and comparing it to that created when a person has a shower it's insignificant; however, the cistern ought to be cleaned regularly to eliminate biofilms.

Many studies recommend that the toilet lid must be closed before flushing, however, in many countries, including the United States, the toilets in public restrooms are often without lids, particularly the urinals¹⁸ and many suggested that this poses a serious hazard⁸. Most investigators also suggested a better toilet design that would include a lid or better one that closes automatically before flushing. Another factor that maintains the lid open during flushing and contributed to keeping the lid open in our study as mentioned above, is the fact that during diarrhoea faecal material coats most of the internal porcelain of a toilet.

thus the person involved will use a brush to clean the area while the water is running in the bowl.

Bioaerosol impactor samplers were employed to detect aerosols as well as microorganisms with and without faecal waste in the toilet bowl and the study concluded, like others before them as mentioned above, that microorganisms remaining in the bowl after flushing²⁰. Unfortunately, the authors of this study did not provide a list of the microorganisms they suggested escaped the bowl after flushing. The fact that they did not find any difference between flushes with and without waste in the bowl suggests that the microorganisms did not originate from the bowl but from the environment as we found in our study. Their finding of higher concentrations of particles after flushing is not surprising as water flushed at such pressure, just like opening and closing the door, will create turbulence with-out necessarily any emission of aerosols, a fact that reinforces the suggestions of other studies that all toilets and those available to the public must be adequately ventilated²¹.

There are many factors affecting bioaerosol generation during toilet flushing^{13,22}. There are also many interactions between liquid, the air, and the flushing mechanism and above all the structures of toilet²². The description by the Authors²² of the way the water enters the bowl splashes against the wall as well as their schematic representation in their Figure 2 might represent many types of public and domestic toilets but differs from all three toilets used in this study, the amount of water in the bowl, and in particularly at the point of entry of the water to the bowl. Therefore, the formation of fine droplets or droplet film containing bacteria that can be aerosolized does not apply to the model of toilets used in this study. Any upward airflow vortex produced in the toilets used in this study will be forced down into the bowl thus flushing cannot expel any bioaerosols from the bowl to the air above the toilet.

Two studies using commercial toilets with high tank pressures, 60 psi demonstrated both the emission and spread of aerosols^{23,24}. The toilets used in these two studies vary considerably from the domestic toilets used in our study. The high pressure which was four-fold higher than those of simple domestic toilets must be responsible for the emission and dispersal of aerosols. Another study which used similar methods and comparable toilets to our study demonstrated the aerosolization of *Clostridium difficile* and splashing of food colouring²⁵.

the Authors however, pointed out that the single toilet they tested, produced more droplets than the standard wash-down design, furthermore the Authors question the reproducibility of their findings if newer toilet designs were to be tested, in particular those that use less water, as are those used in our study.

Households, local authorities, other organisations and in particular personnel looking after public toilets must adhere to regulations and follow simple rules and common sense as clearly outlined⁷ to prevent acquisition of potentially fatal infections from domestic and public toilets.

CONCLUSION

The evidence from many studies indicates that there is a potential risk of acquisition of infectious agents, bacteria, viruses, and protozoa from the toilet and in particular from airborne bioaerosols produced during flushing. Our study has shown that the toilet environment contains many different types of microorganisms mainly skin bacteria, environmental bacteria and fungi as was shown in a review study before²⁶ however, it was shown that bacteria do not escape from the toilet bowl during flushing. The aerosols detected were from the cistern and not the bowl. Using three different toilets but with similar water flow distribution in the bowl after flushing this study showed that the toilet design is the major

factor determining the escape of aerosols from the toilet bowl and whether the lid is closed or open does not necessarily influence microorganisms escaping. Keeping the lid closed has been shown by others to reduce the number of aerosols escaping after flushing and from their distribution of these aerosols in our study we can safely add that the cistern escaping aerosols seen in our study would have been reduced or totally prevented from escaping if the lid had been kept closed²⁷. It is evident that many studies ought to be carried out with the many different types of toilets available and in particular squatting toilets, a type of toilet preferred in some countries²⁷ to establish which which types expel bioaerosols during flushing so that the manufacturers can modify them to prevent emission and potential infections.

ACKNOWLEDGEMENTS

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DECLARATION OF INTEREST

There are no relevant declarations of interest for any of the authors. This study was financed in full privately by Dr Markella Marcou and Dr Michael A Petrou. The experiments, result interpretation and writing were evenly shared by all three authors.

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Melanoma: Overview of causes and new advances in treatment

WRITTEN BY CHRISTINA MASTORI KOURMPANI & MAGDALINI RIGINA FRANGOUΛΙΗ

EDITED BY ANNA ANGELAKI

DESIGNED BY ELENI PARADEISI

What is melanoma and how can we differentiate it from normal normal moles? This article provides a comprehensive overview of:

- The Pathophysiology of melanoma
- Primary causes
- Differentiation from normal moles
- Prevention
- Treatment strategies

Melanoma is a malignant tumor arising from melanocytes, the cells responsible for producing melanin. Melanin is the pigment responsible for skin color. Melanocytes are derived from neural crest cells and are primarily located in the basal layer of the epidermis. The pathophysiological process can be divided into several key stages.

The initial step in melanoma development is **Genetic Mutations and Oncogene Activation**. The mutations can occur in oncogenes (genes that promote cell growth) or tumor suppressor genes (genes that inhibit cell growth). Common mutations associated with melanoma include those in the BRAF, NRAS, and KIT genes.

The BRAF V600E mutation, for instance, leads to the activation of the MAPK/ERK signaling pathway, promoting uncontrolled cell proliferation.

Then follows the Tumor Suppressor Gene Inactivation. Inactivation of tumor suppressor genes such as CDKN2A and PTEN further facilitates melanoma progression. The CDKN2A gene encodes proteins that regulate the cell cycle, and its loss leads to unchecked cellular division. PTEN mutations result in the activation of the PI3K/AKT pathway, enhancing cell survival and growth.

The third stage is the **Immune Evasion**. Melanoma cells often develop mechanisms to evade the immune system. They can downregulate the expression of antigen-presenting molecules or secrete immunosuppressive factors, reducing the ability of immune cells to recognize and destroy them.

Furthermore, the fourth stage is Tumor Microenvironment and Angiogenesis. The microenvironment surrounding melanoma cells supports their growth and survival. Melanoma cells can secrete factors that promote angiogenesis, the formation of new blood vessels, which supply the tumor with oxygen and nutrients.

Finally and above all, is the Metastasis stage. As melanoma progresses, it gains the ability to invade surrounding tissues and metastasize to distant organs. This involves changes in cell adhesion molecules and the extracellular matrix, allowing melanoma cells to detach, migrate, and establish secondary tumors.

The cause of melanoma is not specific and its development can be influenced by a combination of genetic, environmental, and lifestyle factors. Exposure to Ultraviolet radiation from the sun or tanning beds is the most significant environmental risk factor for melanoma. UV radiation can cause direct DNA damage, leading to mutations. It also generates reactive oxygen species (ROS), which induce oxidative stress and further genetic damage. Intermittent, intense UV exposure, such as that causing sunburns, is particularly harmful. Individuals with a family history of melanoma (Genetic Predisposition) are at higher risk, suggesting a genetic component. Inherited mutations in genes such as CDKN2A and MC1R (melanocortin 1 receptor) are associated with increased melanoma susceptibility. MC1R variants, for example, are linked to red hair, fair skin, and a tendency to freckle, all of which are risk factors for melanoma. Another important factor is the Phenotypic Characteristics. Certain physical traits, such as having fair skin, light eyes, and a high density of moles, are associated with an increased risk of melanoma.

NORMAL MOLES VS. MELANOMA

Normal moles (nevi) are common skin growths that develop when melanocytes grow in clusters. They are usually benign and exhibit the following characteristics. While in contrast melanoma may present with the following atypical features, often summarized by the ABCDE rule. Recognition of these differences is crucial for early detection and treatment of melanoma, which can significantly improve prognosis.

Nevi	Melanoma
typically symmetrical	asymmetrical, with one half differing from the other
smooth, well-defined borders	irregular, notched, or blurred borders
uniform in color, ranging from tan to dark brown	display multiple colors, including shades of brown, black, red, white, blue
smaller than 6 millimeters in diameter	larger than 6 millimeters but can be smaller when first detected
remain relatively stable in size, shape, and color over time	change in size, shape, or color over time

PREVENTION

The increasing rates of melanoma and non-melanoma skin cancers have been mainly attributed to increased ultraviolet radiation exposure, therefore preventative measures are crucial to decrease the incidence and promote early detection. Currently, prevention mainly involves the education of patients concerning sun avoidance and protection. Some measures include:

- Use of broad spectrum (UVA/UVB) sunscreen with an spf of 15 and above every day and for extended outdoor activity an spf of 30 and higher.
- Avoid getting sunburns
- Avoid using tanning beds
- Monthly self-examination from head to toe
- Professional skin examination by a dermatologist at least once a year for non-high risk groups

However, some risk factors for cutaneous melanoma cannot be prevented such as:

- Excessive amount of moles
- Dysplastic nevi
- Familial Atypical Multiple Mole and Melanoma Syndrome (FAMMM)
- Lighter physical features (Fitzpatrick classification)
- Immunosuppressive medication and conditions such as HIV

TREATMENT

Different types of treatment are available for patients with melanoma including standard treatment as well as clinical trials in which patients can choose to take part in. The primary treatment of all stages of melanoma is Surgical excision. Based on the tumor thickness and penetration the excision margins differ. The current guidelines according to Breslow's depth recommend the following:

Breslow's Depth	Recommended excision margin (cm) ²
IN SITU	0.5-1.0
Thin Melanoma (less than 1 mm thick)	1.0
Intermediate Melanoma (1-4 mm thick)	1.0-2.0
Thick Melanoma (more than 4 mm thick)	2.0

In addition, lymph node mapping and sentinel lymph node biopsy are equally important to monitor for possible metastasis. Chemotherapy can also be given as adjuvant therapy following surgical excision to decrease the risk of melanoma recurrence. External radiation therapy can also be used alone or in combination with chemotherapy in advanced stages of melanoma as well as a form of palliative therapy to relieve symptoms and improve the quality of life.

Last but not least, **I(i)mmuno-therapy** used in the treatment of high-risk melanoma cases is quite promising and has led to great improvements in patient outcomes. Immunotherapy has led to reductions of melanoma recurrence following surgical resection as well as improvement in patient survival in those that cannot undergo surgical resection. Prior to the introduction of **I(i)mmuno-therapy**, the median survival of patients with advanced melanoma was 6-9 months. Following the approval of first and second generation immune checkpoint inhibitors for use in immunotherapy, survival has improved vastly and has reached nearly 6 years. At this moment, the immune checkpoint inhibitors mainly used in the treatment of melanoma are Pembrolizumab and nivolumab which are both PD-1 inhibitors. PD-1 is a checkpoint protein that is found on T cells and PD-L1 is found on tumor cells. Both aid at keeping the immune responses in check.

The binding of PD-L1 to PD-1 blocks T cells from killing tumor cells. Therefore, with the use of an immune checkpoint inhibitor this path is inhibited and the T cells are allowed to kill the tumor cells.

Despite these recent advances, progression of disease in patients is still a major issue indicating an ongoing need for novel therapies to combat advanced melanoma. New types of treatment are currently being tested in clinical trials including angiogenesis inhibitors, a type of targeted therapy, as well as vaccine therapy which is being tested in stage III melanoma patients.

TREATMENT

Although it accounts for a small percentage of skin cancer cases, melanoma is responsible for the majority of skin cancer-related deaths due to its aggressive nature and potential to metastasize. Understanding the pathophysiological mechanisms underlying melanoma and the various risk factors involved is crucial for developing effective prevention and treatment strategies. Ongoing research continues to unravel the molecular intricacies of melanoma, paving the way for targeted therapies and improved patient outcomes.

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Comprehensive overview of RESPIRATORY SYNCYTIAL VIRUS (RSV)

Pathogenesis, Diagnosis & Treatment

WRITTEN BY MARIA MUÇA

EDITED BY BANO IMTIAZ

DESIGNED BY MARGAUX KOURKOULIOTIS

ABSTRACT

Respiratory Syncytial virus is a negative single-stranded RNA enveloped virus, which causes lower respiratory disease and is the leading cause of children less than one year old to be hospitalized. RSV was first discovered in Chimpanzees and then two years later in humans. It is divided into two subgroups RSV A and RSV B. The virion of the virus is composed of the G protein, F protein, SH protein, and M protein. RSV is transmitted through respiratory droplets that enter via the eye or the nose. To rapidly diagnose RSV the most common rapid tests used are the lateral flow immunoassays and the reverse transcription polymerase chain reaction. To date, the production of vaccination against this virus is still in progress since the previous ones produced had many safety concerns. Ribavirin to this day is the only antiviral treatment that is approved by the FDA, however, careful evaluation and discussion among healthcare professionals should be taken into consideration to decide whether it is a good idea to administer this medication.

PATHOGENESIS

Respiratory Syncytial Virus (RSV) is a human respiratory pathogen, that causes acute lower respiratory tract infections leading to bronchiolitis or pneumonia. In severe cases it causes infants to be hospitalized during their first year of life. [1]

RSV is a negative single-stranded RNA enveloped virus, that is around 15.2Kb lengthwise. It is a member of the Genus Pneumovirus which comes from the Paramixoviridae family. [2]

RSV was first discovered in 1955 in the monkey species, specifically Chimpanzees with respiratory diseases. It was then isolated from babies with severe lower respiratory disease in 1957. [3]

RSV usually occurs in healthy infants. However, conditions such as premature birth, cardiopulmonary disease, lack of initial infection, and absence or limited levels of maternal antibodies responsible for protection against RSV, are associated with an increased susceptibility of the RSV disease. The elderly and immunocompromised individuals can also be affected by RSV. [2]

The symptoms of RSV are similar to those of a common cold which can range from mild to severe and affect each age group differently. For instance, mild symptoms in babies are fever, coughing, changes in their breathing pattern, fussiness, and decreased appetite. Mild symptoms in children are fever, cough, runny nose, difficulty eating and swallowing, and breathing slower than normal. However, severe RSV in infants can cause noisy breathing, wheezing, flaring of nostrils, short or fast breathing, and pauses while breathing [4].

The genomic composition of RSV is composed of 10 genes that code for 11 proteins [2]. Two of the proteins produced are nonstructural proteins known as NS1 and NS2, that suppress the innate immune system signaling. NS1 regulates the host response by inhibiting the type one interferon response (IFN), dendritic cell maturation, and the stimulation of the inflammatory response. Whereas the suppression of the ubiquitination of inactive forms of retinoic acid-inducible gene-1 (RIG-I), melanoma-associated protein 5 (MDA5), and the blocking of the production of the subsequent signaling event and type 1 IFN are caused by the attachment of NS2 to the host cell [3].

RSV consists of a filamentous or spherical enveloped virion that has multiple viral glycoproteins including an attachment glycoprotein (G), a fusion glycoprotein (F), and a small hydrophobic glycoprotein (SH) [5].

The G protein enables the binding of the virus to the host cell. During infection, this type of protein exists in two forms : either the membrane-bound form that is responsible for viral attachment of the viral envelope to

the host cell or in the form of secreted isoform which functions by avoiding the immune system [5]. The F protein functions by fusing the viral envelope to the host cell [2]. Lastly, the SH protein exists as a pentameric ion channel found in small amounts and is believed to be linked with the delay of apoptosis of infected cells [3].

RSV is divided into two subgroups: RSV A also known as A1-23, which has twenty-three genotypes, and RSV B also known as B1-B6, which has six genotypes. The classification of their genotypes is based on their antigenic reactivity and genetic variation within the variable G protein [6]. Antigenic reactivity refers to the proteins responsible for enabling RSV to enter the host immune system increasing the likelihood of reinfection [7]. Moreover, the RSV virion is also composed of a viral matrix (M) protein located beneath the envelope. This protein is important for maintaining the integrity and stability of the virion particles. Lastly, the viral genome is preserved by specific proteins found inside the viral particle known as nucleoprotein (N), phosphoprotein (P), and RNA-dependent RNA polymerase (L). These proteins also facilitate replication in addition to a transcription processivity factor (M2-1) [2].

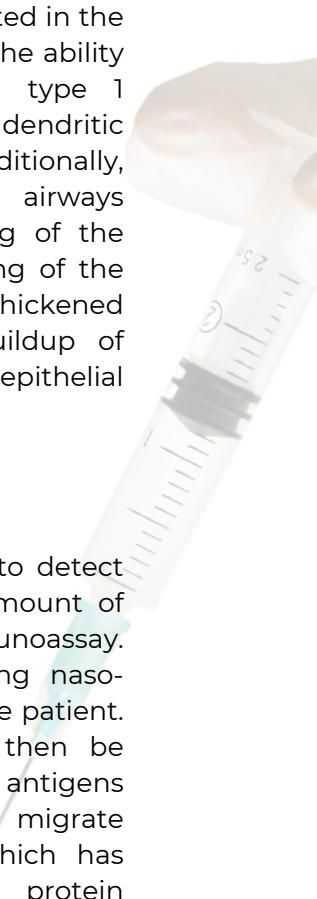
Moving on to the transmission, RSV is transmitted through large respiratory droplets that enter the body via the nose or the eyes. The period between the onset of the disease and the appearance of symptoms ranges between two to eight days. This virus easily spreads around as it persists for a long time on hard surfaces, approximately six hours, on the skin for about twenty minutes, on rubber gloves for ninety minutes, and other objects [8].

From a pathological standpoint, RSV spreads across the lower respiratory tract by infecting the epithelial cells. The ciliated cells in the bronchioles of the lower tract are targeted by the virus after it has been replicated in the epithelial cells. This leads to the ability of detecting the virus in type 1 pneumocytes, intraepithelial dendritic cells, and basal cells. Additionally, obstruction of the small airways occurs due to the shedding of the epithelial cells from the lining of the airway, the accumulation of thickened mucus, as well as the buildup of luminal and intraluminal epithelial cells [8].

DIAGNOSIS

A common rapid test used to detect RSV in infants in a short amount of time is the lateral flow immunoassay. This test works by collecting nasopharyngeal aspirates from the patient. The sample collected will then be added to the strip. The RSV antigens within the sample will migrate laterally along the strip, which has monoclonal antibodies (F protein antibody) absorbed onto the membrane that will recognize and bind to the F protein antigen, forming complexes. These complexes will move along the strip and will be detected by the membrane-absorbed monoclonal anti-RSV F protein at the test line, causing the appearance of a pink to red colored line. Conveniently, this test requires only fifteen minutes to receive results [9].

Alternatively, the reverse transcription polymerase chain reaction (RT-PCR) can be used to detect the genetic material of RSV by collecting a patient's sample of nasopharyngeal aspirates or swabs [10]. The quantitative RT-PCR test is a modified version of the PCR test that uses rapid, specific, and sensitive methods to detect, subgroup and quantify the



virus. Firstly, the reverse transcriptase enzyme will transcribe the RNA and form a single-stranded contemporary DNA (cDNA) which will then be transformed into a double-stranded DNA with the use of DNA polymerase. Then these DNA molecules will be utilized as templates for the PCR amplification [11]. The assay uses two sets of primer probes that target nucleocapsid or fusion genes to detect RSV A and RSV B respectively [12]. This test takes twenty to thirty minutes to receive the results [13].

TREATMENT

Since the discovery of RSV, it has been a necessity to produce a vaccine against this disease in order to lower the mortality rate. Therefore, in 1966, the first RSV vaccine was produced, and it consisted of a formalin-inactivated virus (FI-RSV) from the beret strain. During the initial phases of the clinical trial, the vaccine was tested on guinea pigs, cynomolgus monkeys, and rabbits. When results proved effective, researchers moved onto infants between two and seven months old, administering the vaccine in three doses. Surprisingly, the results received were not as expected as the vaccine failed to provide a sufficient response of neutralizing antibodies and resistance to infection. Additionally, the vaccinated infants experienced more severe pulmonary disease and peribronchiolar infiltration of eosinophils to the extent that two infants aged fourteen and sixteen months passed away [14].

When the virus entered the body, it did not stimulate the protective memory of the immune system leading to the vaccine being ineffective in preventing the disease, causing the discontinuation of the vaccine. Subsequent vaccines, including live attenuated and causing

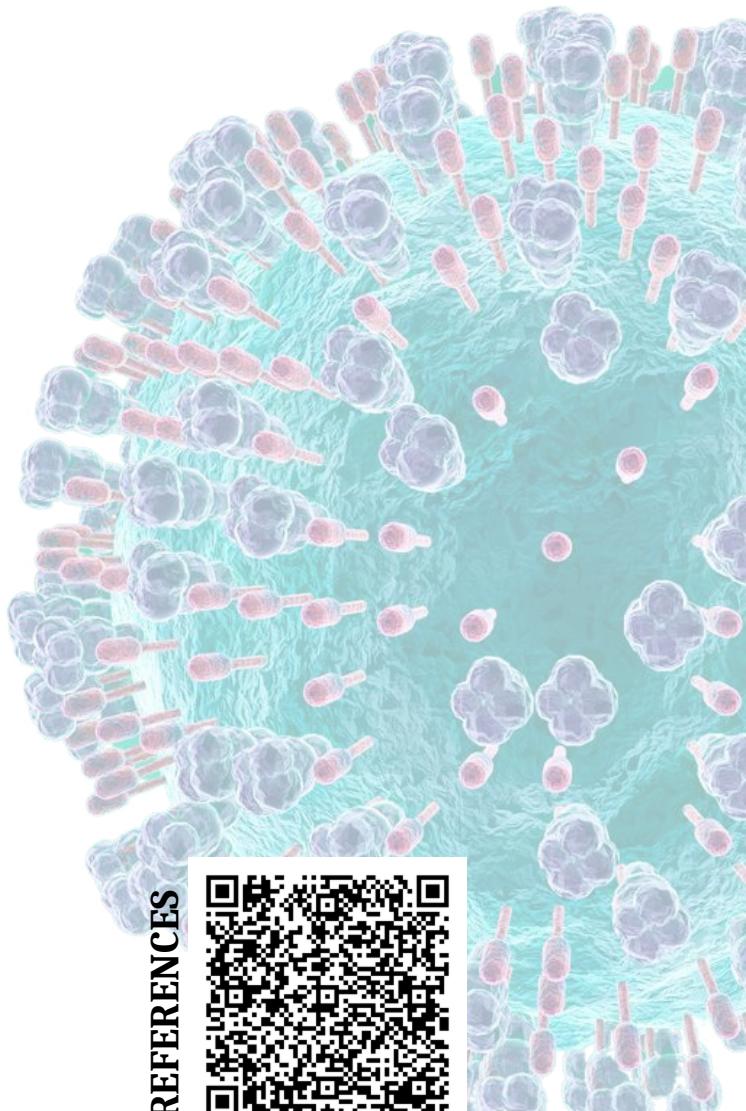
the discontinuation of the vaccine. Subsequent vaccines, including live attenuated and chimeric vaccines, showed potential but raised safety concerns [14]. However, in 2023, Arexvy was the first vaccine to be approved by the FDA, and the European Union, for patients aged 60 years and older [15].

Ribavirin is an antiviral treatment used to treat patients with severe RSV. It is the only antiviral treatment that is approved by the FDA. Ribavirin functions by suppressing the replication of the DNA and RNA of the RSV virus, which is accomplished by direct or indirect mechanisms. In the direct mechanism, the treatment interferes with RNA capping, polymerase inhibition, and lethal mutagenesis. As for the indirect mechanism, it inhibits the inosine monophosphate and has an immunomodulatory effect. There are three ways in which Ribavirin can be delivered [16]: intravenously for seven days, orally for seven to ten days [17], or by aerosolization. This treatment is usually given along with IV immunoglobulin (IVIG) [16]. As with any other treatment, this antiviral treatment also has potential side effects such as chest pain, shortness of breath, skin rashes, and bronchospasm. There are also other side effects such as vomiting and headaches which could impact healthcare providers and family members, even though proper methods of administering the treatment to the patient were applied [18].

However, the cost of this medication and potential side effects lead it to not being administered to previously healthy individuals. Given the advantages that have been observed in severely immunocompromised patients, the decision to utilize this

treatment among these patients, is still a matter that needs careful evaluation, consideration, and discussion among healthcare individuals [18].

To sum up, RSV is a negative single-stranded RNA enveloped virus, causing lower respiratory disease primarily in infants. RSV is transmitted through respiratory droplets and detected using rapid tests. Ribavirin to this day is the only antiviral treatment approved by the FDA, primarily in severe cases. As of 2023, the RSV vaccine approved by the FDA, is only administered to patients aged above 60 years, meaning the fight for an RSV vaccine for all still continues.



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Air Quality

and how it affects our health

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ABSTRACT

Air pollution, consisting of various contaminants like dust, fumes, and particulate matter, poses significant health risks by impacting the respiratory system, heart, and brain, leading to diseases such as stroke, ischemic heart disease, and lung cancer. It contributes to over six million deaths annually, with children being particularly vulnerable. Both short- and long-term exposure to pollutants like ozone and nitrogen dioxide is harmful, exacerbating conditions such as asthma. Climate change worsens air quality, increasing pollutants and allergens. While more research is needed to fully understand air pollution's broader impacts, it is recognized as a leading cause of non-communicable diseases globally. Individuals can improve indoor air quality through regular cleaning and ventilation, while public health measures, such as increasing urban greenery, improving public transport, and transitioning to cleaner energy sources like nuclear and renewables, can mitigate air pollution. Public education on air quality is crucial, especially for vulnerable populations.



Every day we take about 20 thousand breaths on average. 20 thousand breaths of air of dubious quality in the Western world. Have you ever sat down and wondered how the air we breathe might affect our health? In this short article, we will explore this topic that might have intrigued your mind at one point or another.

So, what is air pollution exactly? Air pollution means that one or more contaminants can be found in the atmosphere. Examples include, but are not limited to dust, fumes, smoke, or vapor. These contaminants enter the respiratory tract through our nose or mouth and can lead to general inflammation, oxidative stress, and even immunosuppression. It is not only the respiratory system that is impacted by these molecules, since the heart and brain can also be affected indirectly, leading to an increased risk for several different diseases. Air pollution is a risk for all-cause mortality, as well as specific diseases. However, the ones we have the strongest links for are stroke, ischemic heart disease, COPD, lung cancer, and cataract.



Overall, air pollution is a major threat to global health and is responsible for more than six million deaths per year worldwide, with approximately 1.7 million of these being children under the age of 5. This number has sadly kept increasing in the past 20 years.

Now you might be asking which particles specifically do we care for as a society? The pollutants that public health experts are mostly concerned with are carbon monoxide, ozone, nitrogen dioxide, and sulphur dioxide. There is also particulate matter, which is mainly emitted by the exhausts of vehicles and burning wood. All these particles are minuscule and therefore can penetrate deep into the lungs and travel through the vessels to other organs like the heart, where they can cause further harm. Of course, with their small size comes their ability to be invisible to the naked eye, however their pungent smell alerts most of us of their insidious nature. To give you an idea of how small some of these particles are, a subset of them is 30 times thinner than a human hair. [1] [2]

We used to think that air pollution was only a problem in the long run, however, we now know that both short- and long-term exposure to air pollutants is harmful. This is because we have found that for some pollutants there is no threshold below which no harmful effects occur. To give you an example, even low levels of particulate matter exposure, can aggravate asthma and/or reduce lung function. Asthma, which is a chronic lung disease affecting people of all ages, can in fact be caused or made worse by several air pollutants like ozone, nitrogen dioxide, and sulphur dioxide.

Climate change can severely impact air quality since it leads to more frequent and more severe droughts, which in turn create better conditions for dust and dust-borne pathogens to accumulate and enter buildings. The increase in temperature has led to more forest fires, which in turn has led to more carbon monoxide released in the atmosphere. Global warming also extends the growing season for plants in specific areas, which leads to higher amounts of pollen in the air, leading to more severe allergies. [3] [4]

It is important to highlight the fact that, even though we know a lot about air pollution and our health, we do not know everything. We have evidence for example, that suggests that air pollution may affect diabetes and neurological development in children, but the strength of such a link is not yet clearly defined. Moreover, to fully comprehend how climate affects factors like temperature, humidity, ventilation, mold, fungus, biological pollutants, and volatile organic compounds that are present in indoor air, more research is required.

What we do know though is that air pollution is one of the leading risk factors for disease burden as you can see in the chart below. In fact, air pollution ranks second after child maternal malnutrition, which is usually encountered in third-world countries. Air pollution is something that almost every country suffers from, and it has

Furthermore, try to keep humidity between 30 and 50 percent. Keep in mind that limiting pets' access to bedrooms and generally keeping them healthy and clean should also be a top priority. As a general tip, try to ventilate your home every day, by letting some windows open for time to time. [5]

Leading Risk Factors for Disease Burden (2021)

The values represent the percentage of total DALYs attributable to each risk factor

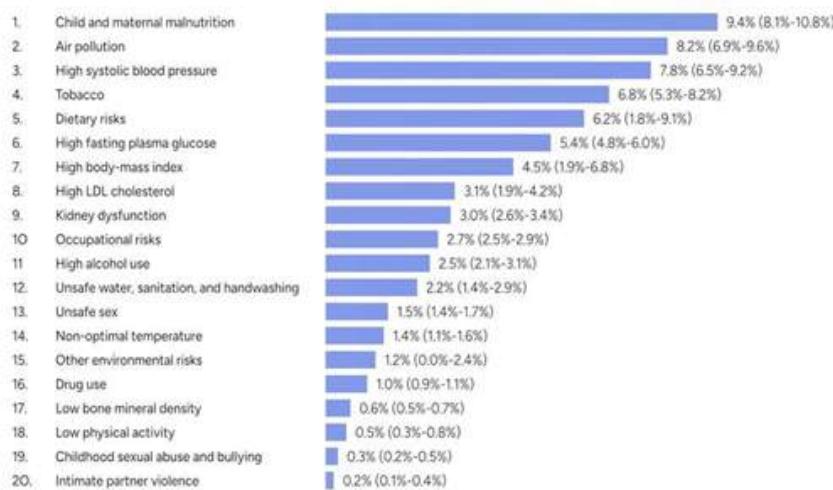
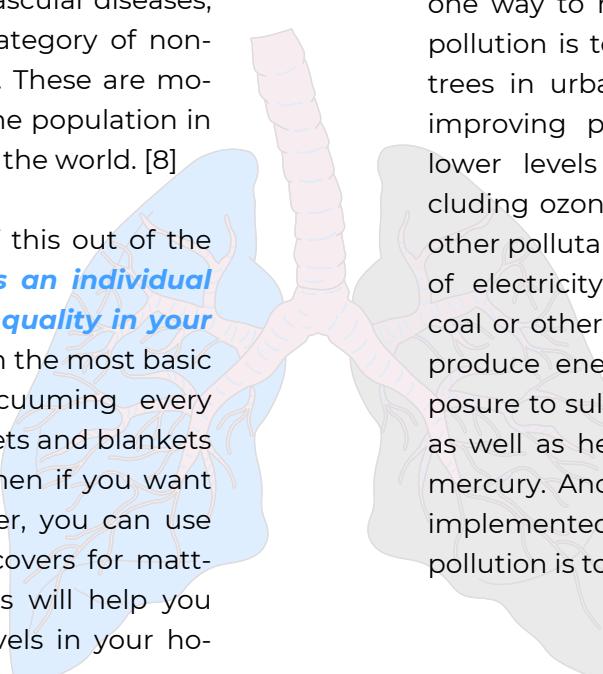


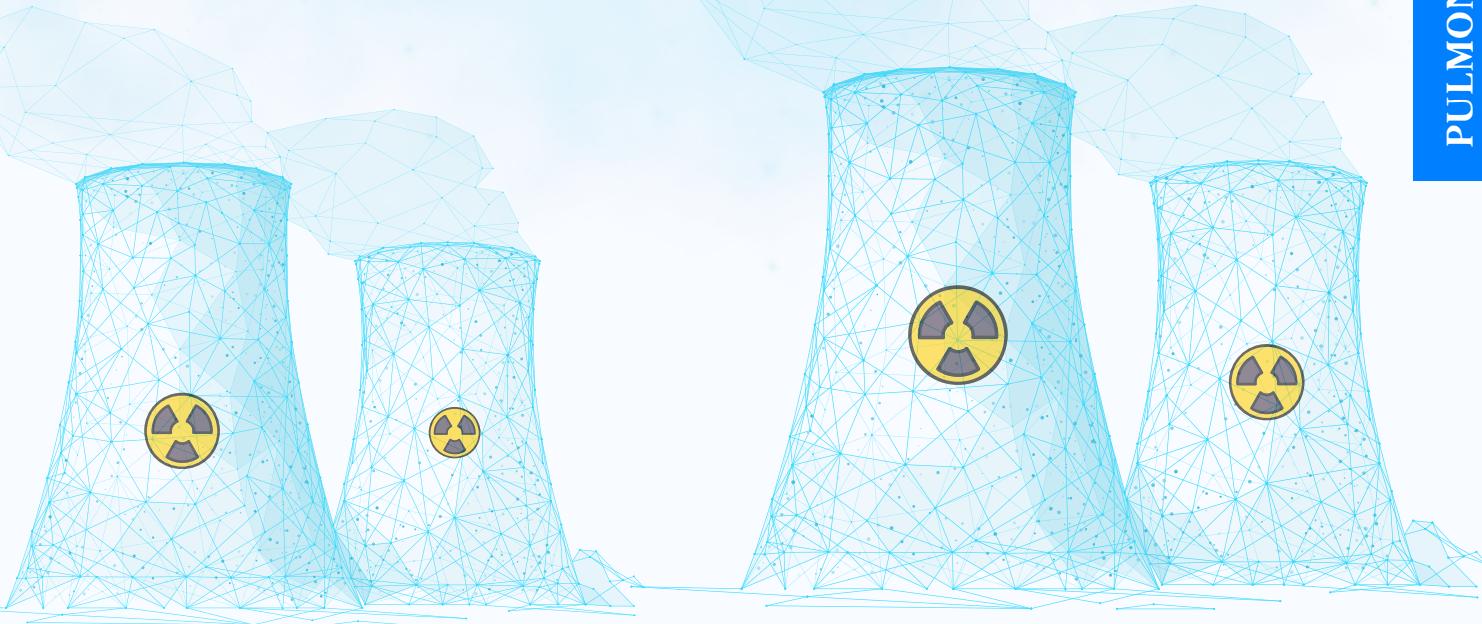
Fig 1: The Leading Risk Factors for Disease Burden (2021)

been shown to lead to an increase in respiratory and cardiovascular diseases, which fall under the category of non-communicable disease. These are mostly what kill most of the population in almost every country in the world. [8]

Now that we got all of this out of the way, **what can you as an individual do to improve the air quality in your house?** Let us start with the most basic things, which are vacuuming every week and washing sheets and blankets weekly in hot water. Then if you want to take it a step further, you can use special allergen-proof covers for mattresses and pillows. This will help you reduce the allergen levels in your home.



As for public health improvements, one way to reduce the impacts of air pollution is to increase the number of trees in urban settings. Besides that, improving public transportation can lower levels of fume emissions, including ozone, particulate matter, and other pollutants. Reducing the amount of electricity used in regions where coal or other fossil fuels are burned to produce energy can help reduce exposure to sulphur and nitrogen oxides, as well as heavy metals like lead and mercury. Another change that can be implemented to massively reduce air pollution is to burn less coal.



This has been achieved in some countries by gradually replacing coal-fired power stations with clean nuclear energy, as well as renewable energy sources like solar and wind energy. [6]

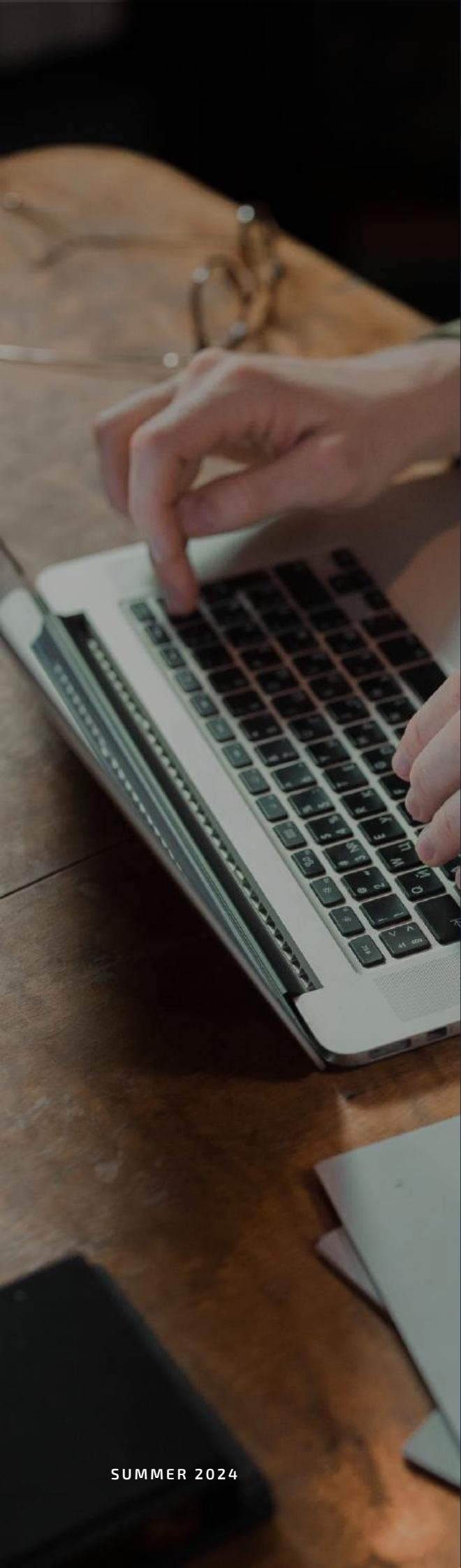
Since the 1960s, legacy nuclear energy has been stigmatized as dangerous even though it has been the safest method of producing electricity. Legacy nuclear designs were involved in the three well-known nuclear accidents at Three Mile Island, Chernobyl, and Fukushima. Even though advanced nuclear has the finest safety record of all electricity generation methods, the population mistakenly links it to the now abandoned legacy nuclear. The nuclear waste of legacy nuclear energy takes tens of thousands of years to decay, while with advanced methods we see a reduction to about 400 years. When it comes to advanced nuclear energy, we need to consider the fact that no deaths or negative health effects raised after the three-mile island incident, and the amount of radioactive energy released in a well-maintained facility is trivial.

On the other hand, unlike the fossil-fuelled factories, advanced nuclear reactors do not produce any air pollutants while operating. [7]

Finally educating the population on air quality and the environment is important, especially for those who are sensitive, like patients with asthma or severe allergies. Those who suffer from such conditions, need to be guided by their physicians and be understood by those near them. Clean air is something that should be a given to all humans, it should be something we strive for. It shouldn't be something we ignore or take for granted.

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Bottle Feeding: What Is the Risk for Ear Infections?

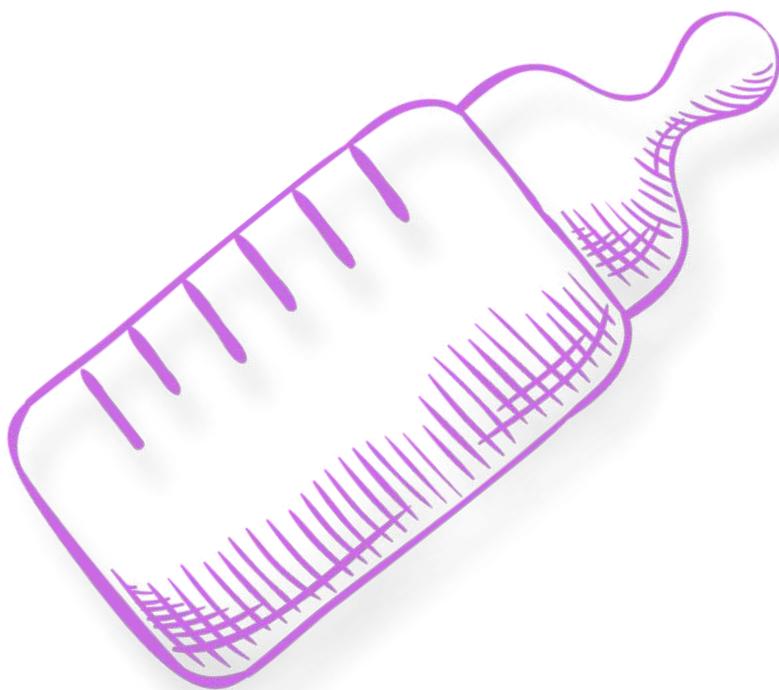
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INTRODUCTION

Breastfeeding is a precious gift for neonates. Literature recommends exclusive breastfeeding for the first six months of life, with a gradual reduction in frequency as solid foods are introduced. [3] Numerous studies highlight the protective effects of breastfeeding against various diseases, including those affecting the upper respiratory system, such as acute otitis media (AOM). [3] Human milk transfers specific IgG antibodies targeting *Haemophilus influenzae*, a primary pathogen responsible for AOM. [1] However, bottle-fed infants, whether fed with human milk or formula, are at a higher risk of developing AOM. [1,2] Key factors contributing to this increased risk include feeding position, bottle design, and the anatomical connection of the Eustachian tubes.

Nonetheless, the pathogenic mechanism of which milk reaches the Eustachian tubes and causes AOM has been well-established. [2,4] Unlike breastfeeding, which involves nipple sucking it, allows milk to flow directly into the oral cavity, bottle feeding—particularly with poorly ventilated bottles—creates a different pressure gradient. [2] The strong negative pressure combined with an improper feeding position can lead to milk being propelled from the throat into the middle ear via the Eustachian tubes. [2,4]

The anatomical structure of the Eustachian tubes in infants, which are wider and shorter, increases the likelihood of milk entering the middle ear. This pooling of milk creates an environment prone to bacterial overgrowth. [1,2]



Interestingly, AOM in bottle-fed infants does not always have an infectious course. Research in specific populations of bottle-fed infants has shown AOM episodes do not respond to standard therapeutic interventions. [4] For this reason, chronic granulomatous otitis media was considered as diagnosis.

[4] There are three stages of this disease. [4] Overall, it is an atypical otitis media. It is characterized by the absence of fever and typical pathognomonic pain, with instead presenting as an acute onset of sterile discharge with recurrent episodes. [4] The condition could progress with scarring of the tympanic membrane, resulting in mild to moderate hearing loss.

[1,2,3,4] The pathogenic mechanism involves the formation of a foreign body granuloma due to milk pooling, which triggers a granulomatous process. [4] Additionally, bottles with a faster flow rate than a natural nipple exacerbate the feeding issues.

CONCLUSION

Pediatricians observing recurrent episodes of acute otitis media with atypical presentations should closely examine the feeding practices. New parents should be advised to minimise bottle feeding and adhere to specific guidelines when bottle feeding is necessary. Infants should be positioned upright with their heads elevated at approximately 30 degrees. Bottles should be designed to closely mimic the mother's nipple to ensure a slow milk flow, and fully ventilated bottles can help manage the pressure gradient. Maintaining a controlled feeding pace is also crucial. Implementing these measures can help prevent new episodes of AOM of unclear etiology.

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Brain Organoids in Disease Modelling and Drug Testing

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ABSTRACT

Brain organoids, lab-grown collections of neurons and other brain tissue, are revolutionizing the fields of disease modeling and drug testing. These organoids can be cultivated from a person's skin cells, provide a more realistic sample of human brain tissue for scientific study, and pharmaceutical testing. Traditional methods like animal models, autopsies, and imaging techniques have limitations in accurately representing the human brain's function and disease.

INTRODUCTION

For starters, let's explain in simple words how brain organoids come to be and why they are important. The brain organoid is a collection of lab-grown neurons and other brain tissue that scientists can use to learn about full-grown human brains. This is all grown from a simple "sample" of skin cells, allowing scientists to ethically test drugs in a more realistic approach... Why would such a technique exist?

Neuroscientists face a challenge: the human brain is shielded by our thick skulls and swaddled in layers of protective tissue, making it extremely difficult to observe in action.



For centuries, scientists have tried to understand them using autopsies, animal models, and in recent years, imaging techniques. We've learned a lot through all these methods, but they have limitations. Conditions such as Alzheimer's and schizophrenia, or diseases such as Zika, affect the human brain and due to its hidden view, there is a lack of understanding. Furthermore, when it comes to the development of medicine for such conditions it is important to be able to test them in "realistic" environments. What do we mean by "realistic" environments? Just as scientists used mice, autopsies, screening techniques, and more recently "body in a chip" methods; they each lacked a fundamental trait that was essential for efficient drug development and comprehension of the brain's function. Mice brains could not represent human brains accurately since they are a different species, corpses lacked brain function, screening techniques could not allow us to freely interact with the brain, and "body-chips" lacked the complex 3D "terrain" of an organ since they are composed of simple cell layers that lacked the natural form and function of a human brain.

Brain organoids function like human brains, but are not part of an organism. Each one comes from an undifferentiated stem cell that can develop into any tissue in the body, from bone to brain. Scientists can make undifferentiated stem cells from skin cells. That means they can take a skin sample from a person with a particular condition (or not) and generate brain organoids from that person. However, the hardest part of growing a brain organoid, which stumped scientists for years, was finding the perfect combination of sugars, proteins, vitamins, and minerals that would induce the stem cell to develop a neural identity. That was only discovered in 2013. The rest of the process has been revealed however, there has been issues with financial support. A neural stem cell essentially grows itself, similar to how a seed grows into a plant, all it needs are the brain's equivalents of soil, water, and sunlight. A special gel to simulate embryonic tissue, a warm incubator set at body temperature, and a bit of motion to mimic blood flow. These growth factors strictly require quite a few resources to maintain their function such as an oxygen-rich environment.

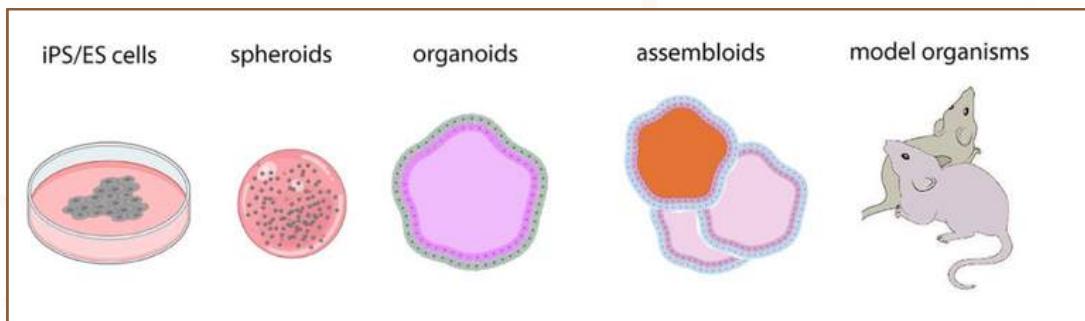


Figure 1

The stem cell grows into a very small version of an early-developing human brain, complete with neurons that can connect to one another and make simplified neural networks. As the mini brain grows, it follows all the steps similar to fetal brain development.

ETHICS

By observing this process, we can learn how neurons develop, as well as how it results with so many more of them in our cortex, the part responsible for higher cognition like logic and reasoning, that other species have deficiency. Being able to grow brains in the lab, even tiny ones, raised ethical questions, in particular: Can they think for themselves, or develop consciousness? And the answer is no, for several reasons. A brain organoid has the same tissue types as a full-sized brain, but isn't organized the same way. The organoid is similar to a computer that's been taken apart and reassembled at random; the CPU, the RAM memory, and other parts could still be studied, but the computer could never properly function. Similarly, a brain organoid allows us to study different types of brain tissue, but can't think.

Even if mini-brains were organized like real brains, they still wouldn't be able to reason or develop consciousness due to size, lack of chemical signals that would occur in a normal brain supplied by blood.

A big part of what makes our brains so smart is their size, and mini-brains have only about 100,000 neurons compared to the 86 billion in a full-sized brain and scientists aren't likely to grow larger brain organoids anytime soon. Without blood vessels to feed them, their size is limited to one centimeter at most. However, it is still up to debate whether these tiny brains actually do have a consciousness or not. Despite what is known about the brain's basis of consciousness, there is no reason to believe currently that brain organoids, as of 2022, are conscious in any meaningful sense.

Studies that Involved Brain Organoids

What methods exactly were used to prove that brain organoids have such potential? Scientists at Stanford University put human brain tissue into a rat because they wanted to see if the human neurons would merge with the rat's brain, enough to control its behavior. In more detail, organoids that were formed and closely resembled the human cerebral cortex, (the brain's outermost layer) were transplanted into the brains of rat pups that were just two to three days old. This early stage was chosen because the developing rat brains could integrate the human embryonic cells more effectively, allowing the human neurons to form connections and mature alongside the rat brain cells.

After transplantation, the human organoids integrated well with the rat brain. Rat endothelial cells formed blood vessels within the human tissue, providing necessary nutrients and removing waste. The human neurons grew significantly, expanding to occupy about one-third of the hemisphere, and formed complex connections with the rat brain, including connections to the thalamus, a key sensory relay center. The transplanted human neurons were shown to influence rat behavior. In one experiment, human neurons that were modified to respond to blue light were activated, prompting the rats to associate the light with a water reward. This demonstrated that the human cells could function as part of the rat's reward circuitry and visual processing. This aided in understanding the development of the brain and unlocked the possibility of performing "partial brain transplants" in the future. This innovative process could result in replacing the diseased parts of a brain returning it to good condition especially in still-developing brains (infants).

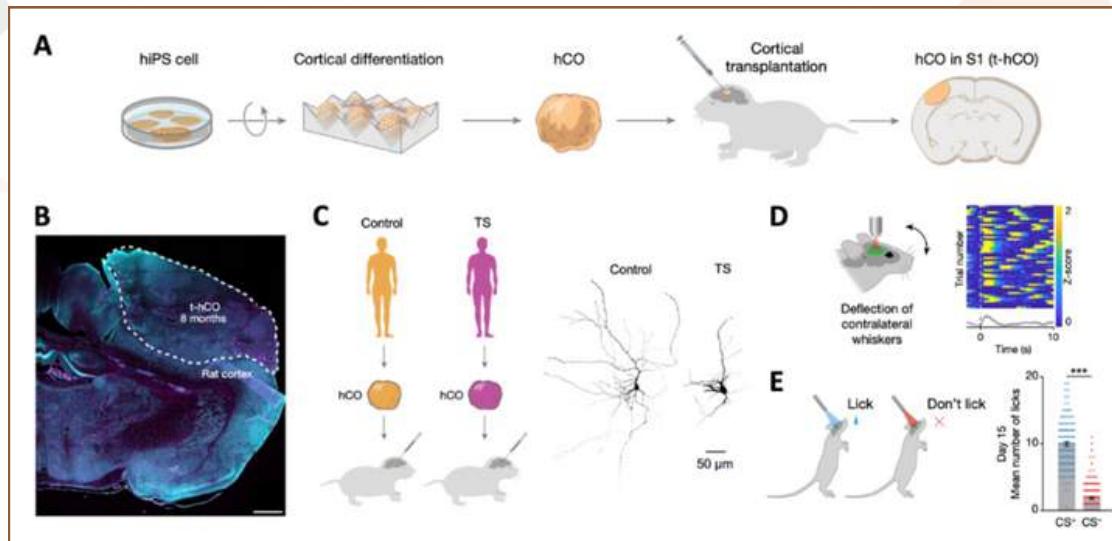


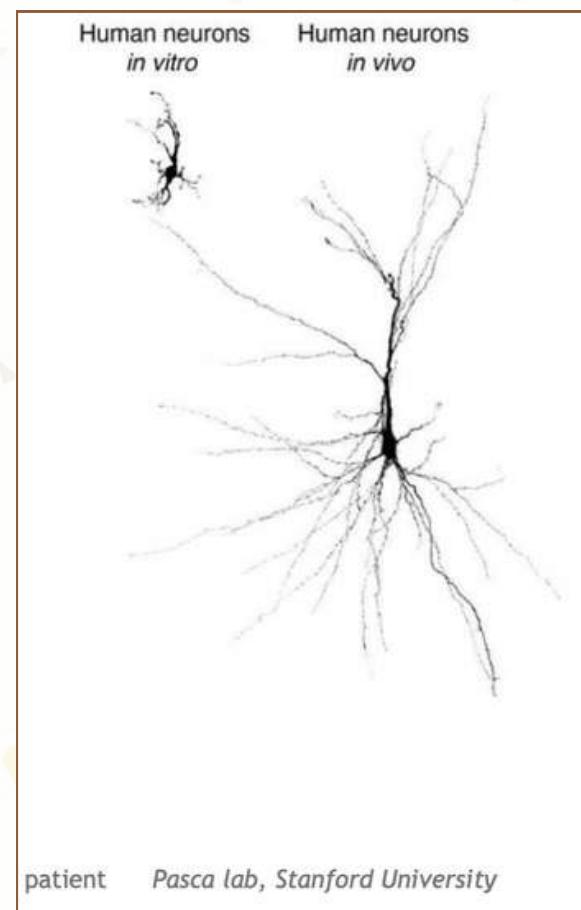
Figure 2

But of course, some may ask "Was the licking behavior really due to optogenetics (a technique that involves genetically modifying neurons to express light-sensitive proteins, allowing researchers to control the activity of these neurons with light), or just seeing the blue light?" A separate group of rats (control group), with a transplant but no optogenetics, also completed the red/blue light water training. They showed no significant difference in licking behavior during red and blue light. This suggests that the differences were really due to optogenetic stimulation of the organoid (not, for example, seeing the light).

Another interesting study that its success relied on brain organoids was a study done on the reliable drug testing technique, that happened recently (24th of April 2024). Researchers have become ambitious about planning for future cures since they successfully modeled a rare condition called "Timothy Syndrome", which neurologically causes developmental delays, epilepsy, and autism spectrum disorder.

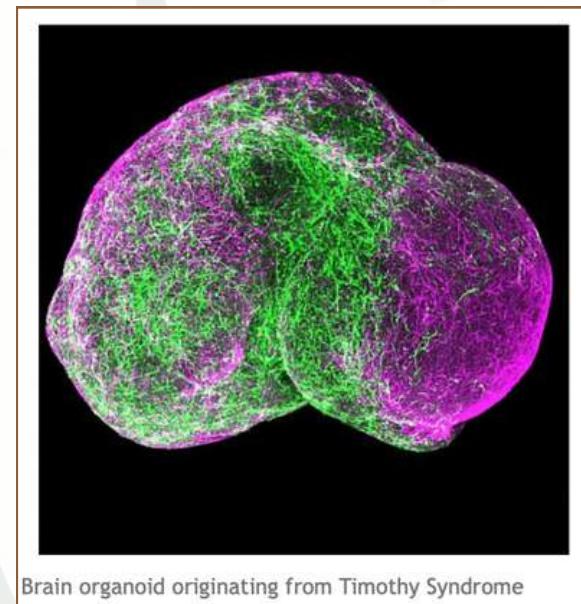
This disease is caused by a mutation to a single gene called "CACNA1C" which is responsible for calcium channels that help control signals in the brain and body. In more detail, After the CACNA1C gene is transcribed into RNA, splicing can produce different protein versions. Normally, one version is made during development, then another later. In Timothy syndrome, the first version continues, leading to overactive calcium channels and abnormal cell activity. However, researchers managed to develop antisense oligonucleotides (ASOs) to treat genetic disorders. ASOs bind to RNA to affect its processing. Dr. Sergiu Pașca's team at Stanford University tested ASOs to block the RNA changes causing Timothy syndrome.

They proceeded to grow brain organoids from stem cells of people with Timothy syndrome and found that the ASOs reduced abnormal RNA splicing. The most effective ASOs restored normal calcium channel function in these organoids. To assess the treatment's impact on brain development, they created assembloids from fused organoids to mimic the forebrain. Treating these assembloids with ASOs normalized brain cell movement during development. Testing in newborn rats involved transplanting human-derived organoids into rat brains. The organoids integrated well, and ASO injections reduced abnormal RNA splicing. This normalized calcium channel function and cell appearance under a microscope.



patient Pasca lab, Stanford University

Figure 3



Brain organoid originating from Timothy Syndrome

Figure 4

The last thing to mention for this article, is to demonstrate the spectrum of scientific fields that brain organoids cover, and their recent potential to bring in a new era of computing . The most recent news in computing science was the creation of the “Quantum Computer” but brain organoids have brought forth the age of “Bio-Computing” and “BIO-AI”. In more detail, a Swiss startup called FinalSpark, has created a biocomputer using 16 brain organoids each containing roughly 10,000 neurons. These organoids are integrated into silicon chips with electrodes, allowing for two-way communication between the neurons and digital systems.

This setup mimics neural networks and processes information with far less energy than traditional silicon-based processors. The Neuroplatform, which sustains the organoids in a controlled environment, enables other researchers to study artificial intelligence and other fields. This new form of computing and artificial intelligence isn't exactly an “upgrade” but an entirely different form of technology. It is about an AI that aims to harness the unique properties of biological neural networks, potentially offering advantages in processing tasks that involve more nuanced understanding and adaptation. For instance, brain organoids could potentially mimic certain cognitive processes more closely than traditional algorithms, possibly improving tasks that require complex pattern recognition or adaptive learning.

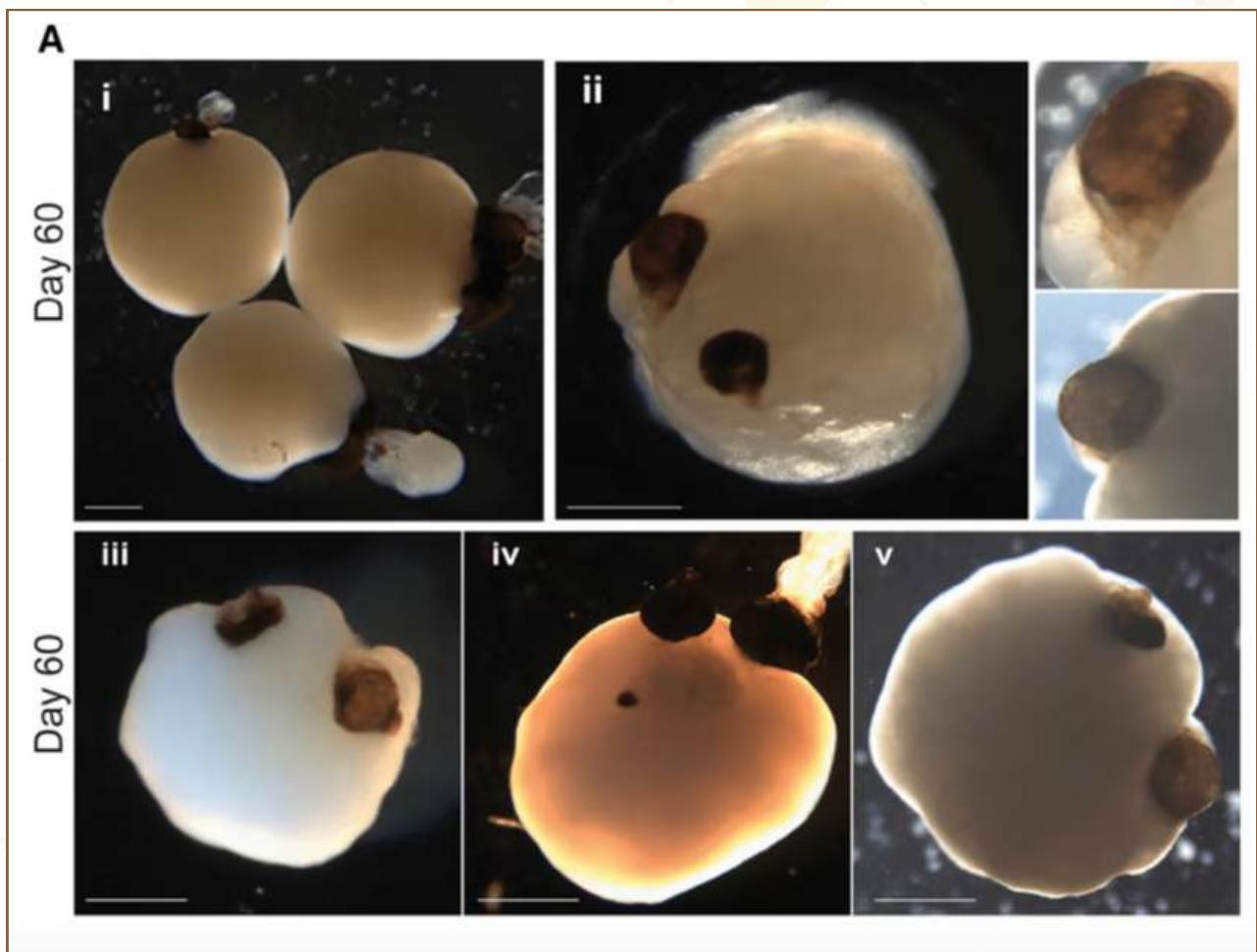
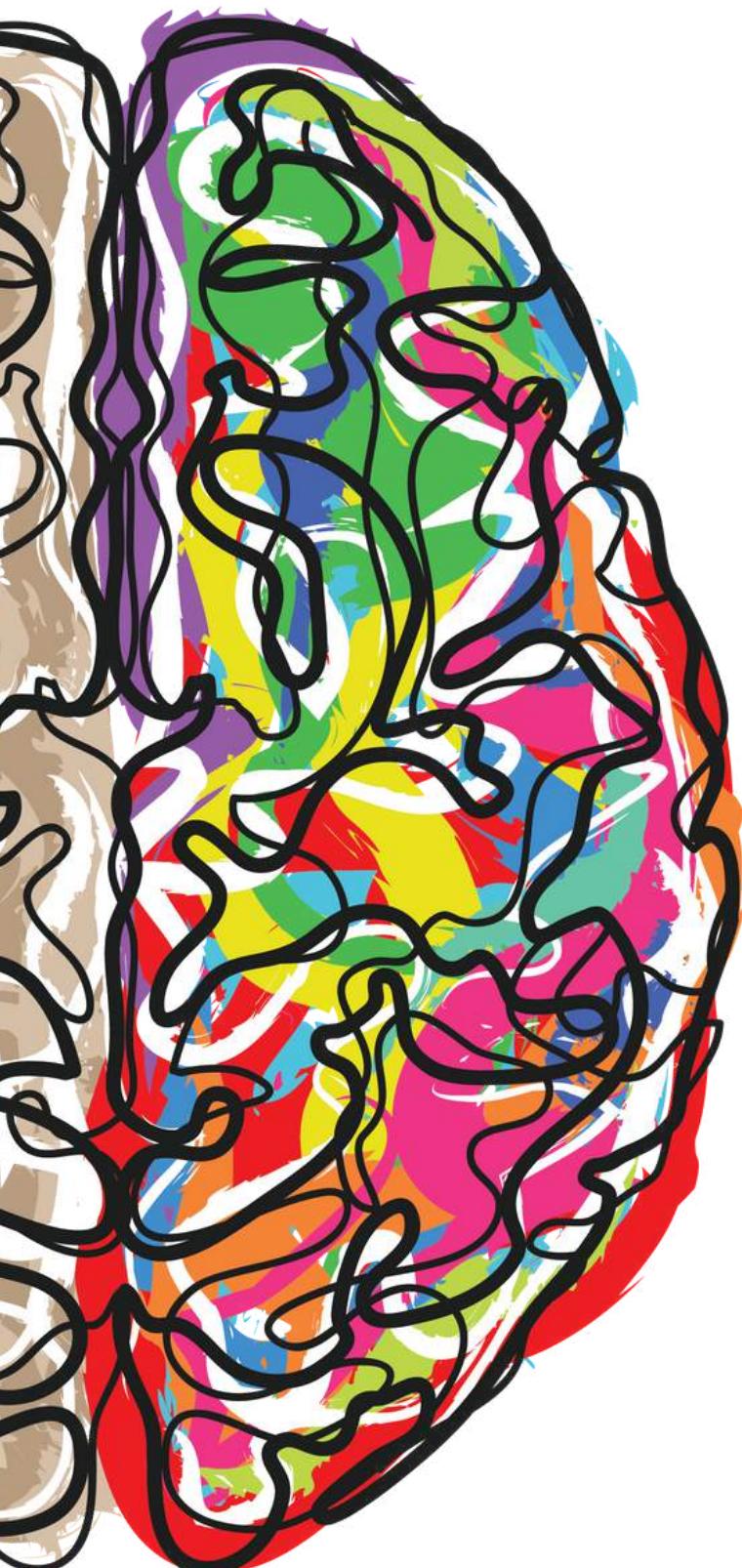


Figure 5



CONCLUSION

Finally, before the above experiments and uses of brain organoids came to be, brain organoids were believed that they couldn't interact with the outside world, in other words, to gain senses. However, just by these examples we have offered we have essentially disproved that. Some brain organoids have even managed to develop "eyes", also referred to as "optic cups" that are able to process light without the usage of optogenetics. So, the theory of them "not being able to develop senses" began to "crack" early on, as scientists continued their research on them. Now, since 2013, when Jürgen Knoblich, and his team at IMBA discovered the secret of creating neurons from undifferentiated stem cells on a Petri dish; Resulted in research about brain transplantation, which furthered understanding, and aided in regulating conditions like autism, epilepsy, Timothy's syndrome, including the innovative form of Artificial Intelligence.

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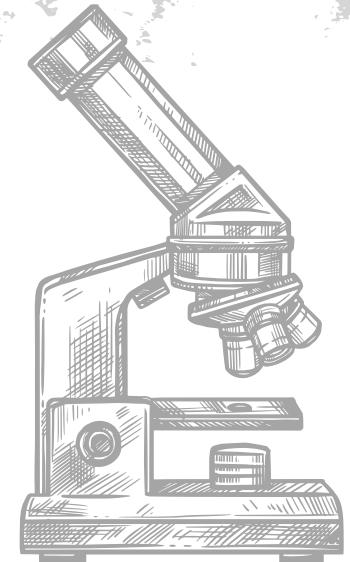
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3D BIO-PRINTING IN AIRWAY RECONSTRUCTIVE SURGERY

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An essential part of our respiratory system, the trachea, can become narrowed or damaged due to various conditions such as thyroid cancer, congenital anomalies, and trauma. Traditional treatments frequently fail to restore the trachea to its former state, however, the advent of 3D bioprinting technology offers a new approach, potentially revolutionising the reconstruction of airway defects and providing new hope for patients with severe and complex issues. [1]

The bioprinting process begins with a CT scan of the trachea, which is then converted to a digital file in order to be readable by the printer. The printer works much like an everyday office printer, with ink, bio-ink in this case, which consists of a bio-compatible material such as hydrogel and various cell types, often taken directly from the patient to ensure optimal histocompatibility. There are different forms of bioprinting, with extrusion-based bioprinting being the most commercially used, where the cell-enriched bioink and scaffold material (usually a biodegradable polymer) are loaded into cartridges, which are then attached to printheads, once researchers manually set specific parameters.



the machine begins to print layer by layer to produce the desired tracheal shape. Once the printing is complete, the structure must be stabilised via the process of crosslinking in which the construct is treated with UV light or ionic solution; upon completion, the researchers may then submerge the trachea into an appropriate cell medium and place it within an incubator to allow for cell cultivation. [2] The 3D bio-print is now ready to be surgically implanted within the patient.

Which scaffold material is superior is debated within the scientific community, with the desired quality being resorbable biomaterials with non toxic byproducts and strength, such as poly- ϵ -caprolactone (PCL), which is particularly favoured due to its structural similarities to tracheal cartilage, polylactic acid (PLA); commercially favoured due to its Food and Drug Administration approval, polyglycolic acid (PGA), and poly(lactic-co-glycolic) acid (PLGA).

PGA and PLGA are recommended due to their high porosity, allowing for cells to infiltrate the scaffold to allow for neovascularization, while also being relatively quickly absorbed by the body, however, this paired with its subpar mechanical strength, has made these biomaterials not ideal for long-term treatment. Whereas, PCL is greatly preferred for long-term treatments due to its low porosity, good biocompatibility, and slow degeneration within the body, paired with its superior mechanical strength compared to PGA, PCL is optimal for cartilage scaffold material. [3]

There are four possible options for the design of the construct: stent, non-circumferential reconstruction, circumferential reconstruction, or mini plate. Airway stents have existed before bioprinting as being made from silicone, however, recent advances have created stents from bioresorbable materials which degrade over time. A study conducted by Robert Lischke et al. endoscopically implanted 20 polydioxanone (PDS) stents within six patients (median age of 41.5 years) who had post-transplant bronchial anastomotic stenosis over a 4 year period. The median stent diameter was 12 mm, and the median length was 20mm. After implantation, evaluation by bronchoscopy and computed tomography (CT) showed that the stenosis was relieved in all the patients initially with no bleeding or movement of the stent, however, four of the patients needed multiple stents implantation due to anastomotic re-stenosis.

with the median time for restenting being 5 months. A year after the last stent was implanted, one of the patients died due to a pulmonary embolism, and the 5 other survivors were in good clinical conditions up to 4 years of follow up since their first stent, and were intervention free for up to 44 months. [4]

Non-circumferential reconstruction refers to surgical repair which reconstructs only part of the trachea rather than the entire circumference. In this approach, surgeons mainly use PCL printed into varying shapes and sizes, with studies claiming the use results in no stenosis and minimal tissue granulation over time, while histologically, a regeneration of ciliated epithelium and neurovascularisation on the luminal surface of the tissue. However, in larger animals, results have varied, such as with a study conducted by Jakob M. Townsend et al. in which sheep were implanted with PCL tracheal patches (originally 2.5×3.5 cm) cut to be slightly larger than their defect (measured 1.5×2.5 cm), to create an airtight seal of approximately 5 mm overlap around the periphery. After 10 weeks since the implantation (2 weeks before schedule), four of the five sheep had to be euthanized due to respiratory distress.[5]

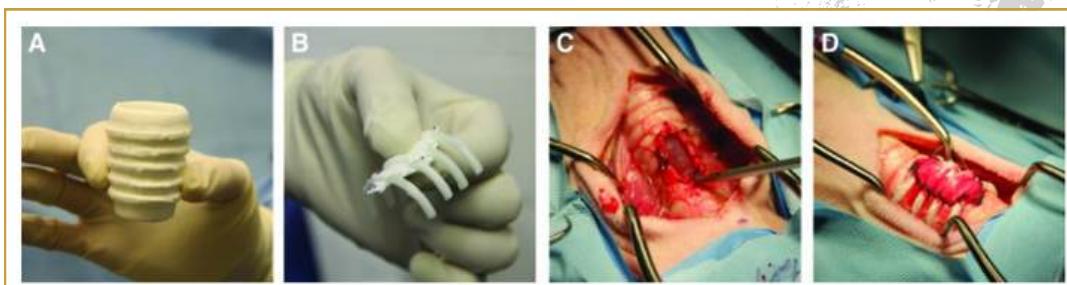


Figure 1

Whereas, a study conducted by Sadiq S. Rehmani et al., where a 4cm defect was manually made and later reconstructed using a PCL implant into the 7 pigs, resulted in successful tracheal reconstruction in all cases, and 5 of the 7 pigs outliving the 3 month study period. Post euthanasia examination revealed a well incorporated graft with respiratory mucosal coverage and vascularity.[6] Circumferential reconstruction is notorious for being more tasking, with results showing greater degrees of granulation and stenosis leading to respiratory distress. The dominant hypothesis for this is the increased inflammatory response; however, a study conducted by Jae Yeon Lee et al. set out to test this hypothesis by administering immunosuppressive drugs to rabbits after undergoing a tracheal reconstruction with a PCL scaffold, which discovered that the use of cyclosporine and/or azathioprine had no beneficial effects. In addition, the use of cyclosporine harmed the rabbits due to side effects, including extreme respiratory distress, diarrhoea, and weight loss. [7]

In an example of mini-plate usage, a graft for an anterior laryngotracheal reconstruction (LTR), defined as a surgery to enlarge the airway by placing a graft in the narrowed area, [8] was 3D printed with PLA, the scaffolds were then seeded with mature chondrocytes and collagen. After allowing the scaffolds to culture for 3 weeks, they were evaluated for cell viability and proliferation; the assessment showed 87.5% viability

and that the cell population doubled within the first 7 days of the study period, and histological findings illustrated that the cells maintained their cartilaginous properties throughout the 21 day study period. The LTR was then performed on 9 rabbits with the scaffolds, three of which were sacrificed at the predetermined time points (4,8,12 weeks), and their grafts were assessed with a bronchoscopy and histology. Results showed all the animals surviving the duration of the study, bronchoscopy findings showed a mucosalized tracheal lumen with no evidence of tissue granulation or scarring, and histology conveyed new forming cartilage in the area where the graft was placed. [9]

Incorporating cells such as chondrocytes or ciliated epithelia in cases of artificial trachea production is often done via a hydrogel. The materials which the hydrogel is made of vary, with naturally derived components, for example, collagen, glycosoaminoglycans (G-AG), extracellular matrix (ECM), adhesive glycoproteins, Pluronic F-127, gelatin, or hyaluronic acid. [10] [11][12] These materials are endorsed due to their biocompatibility and neovascularization, yet, implants solely containing natural materials lack the mechanical strength for structures such as a trachea.[13] This leads to the conclusion that combining naturally derived materials to reap the benefits of biocompatibility with artificial materials due to their superior structural integrity is preferable.

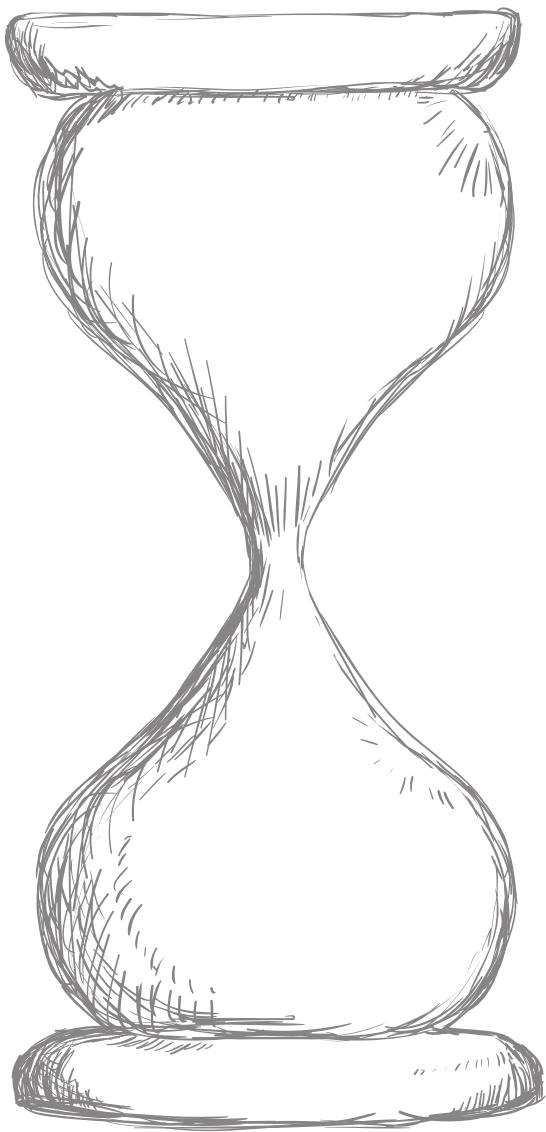
One example of this is a 3D-printed PCL scaffold reinforced with silicone rubber bands, which was sequentially layered with tmdECM hydrogel and hTMSC sheets on the scaffold's luminal surface. These were prepared via the decellularization of porcine tracheal mucosa and the creation of hydrogel, the isolation and culture of hTMSCs from human inferior turbinate tissues, and the formation of hTMSC sheets using temperature-responsive culture dishes. Once implanted into the rabbits, an evaluation was performed two months post-implantation, indicating a complete luminal surface regeneration in the tracheal grafts, nonetheless the authors noted some granulation. [14] In regards to cartilage regeneration, one option is bone marrow multipotent stem cells (bMSC), which, when under stimulation, can differentiate into chondrogenic phenotypes; studies have shown that rabbit MSC cultured with chondrocytes on hydrogel differentiated into chondrocytes. [15] Another popular option is chondrocytes, although, their limited availability and the challenge of maintaining their phenotype during in vitro culture have hindered their broader use. [16]

In August of 2023, a group of South Korean surgeons collaborating with Seoul St. Mary's Hospital of the Catholic University of Korea and Gachon University claimed to have manufactured and implanted the first custom-made 3D bio-printed trachea into a woman in her fifties who suffered partial tracheal

loss after a thyroid cancer surgery. The manufacturing process used 3D printing using a printer from T&R Biofab, which involved using a bioink derived from adult nasal stem cells from standard procedures like nasal turbinate surgery, and cartilage cells obtained during nasal septum surgery, which were sourced from other patients. This resulted in the artificial trachea being made of mucous membrane and cartilage, while the scaffold was made of PCL to ensure structural integrity. In a 6 month follow up, Professor Kim Seong-won and his team claimed that the trachea had healed and that new blood vessels had developed. [17][18]



In conclusion, 3D bioprinting shows a remarkable advancement in medical technology, offering an innovative and promising solution to tracheal defects. While challenges remain, the progress made inspires hope for a future where personalised and effective treatments are accessible to all patients. As research and technology continue to evolve, the potential for 3D bioprinting to transform lives becomes increasingly tangible, paving the way for a new era in reconstructive medicine.



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Endometrial Hyperplasia:

Alternative approaches for this long-standing challenge

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ABSTRACT

Endometrial hyperplasia is a precancerous condition that is caused by a hormonal imbalance which allows the thickening of the endometrium followed by abnormal changes. Abnormal bleeding, which might be heavier than normal, might be the first symptom to arise from this condition. There are two types of endometrial hyperplasia; hyperplasia without atypia with normal-looking cells and atypical hyperplasia where the abnormal cells are considered precancerous. Treatment options include reduction of the risk factors, management with progesterone therapy, and, as ultimate solution, hysterectomy.

INTRODUCTION

As far as conditions of the female reproductive system go, endometrial hyperplasia represents the most frequent among developed countries. This precancerous condition occurs when the inner lining of the uterus, the endometrium, becomes irregularly thick. For premenopausal women, the upper normal limit of endometrial thickness is set at 15mm, while for postmenopausal women a thickness of more than 5mm is considered abnormal [1]. Normally, this uterine lining is formed every month during a woman's reproductive years and serves multiple roles. If conception takes place,

the growing fetus in the uterus is cushioned by this exact lining, while in the case where conception does not occur, then the lining is shed during menstruation and the cycle starts over every month.

The origin of this hypertrophy is primarily the imbalance of two important hormones; progesterone and estrogen, which have significant roles in the menstrual cycle. Progesterone signals cell shedding, while on the other hand estrogen promotes cell growth. Therefore, the increased estrogen levels in combination with the insufficient levels of progesterone counteract the proliferative effects of estrogen on the tissue and this hormonal imbalance arises. This may occur in a variety of settings, including obesity, polycystic ovary syndrome (PCOS), estrogen related tumors and certain formulations of estrogen replacing therapies.

Endometrial hyperplasia may cause many unpleasant symptoms to the female population suffering from it including heavy menstrual bleeding, bleeding between menstrual cycles, polymenorrhagia (menstrual cycles that are shorter than 21 days), bleeding after menopause, and even amenorrhea (not having period at all). [2],[3]

CLASSIFICATION

According to the World Health Organization (WHO) latest classification that was published in 2014, endometrial hyperplasia could be differentiated between two categories; 1. Hyperplasia without atypia, and 2. Atypical hyperplasia/endometrioid intraepithelial neoplasia, as shown in the table below.



New term	Synonyms	Genetic changes	Coexistent invasive endometrial carcinoma	Progression to invasive carcinoma
Hyperplasia <i>without</i> atypia	Benign endometrial hyperplasia; simple non-atypical endometrial hyperplasia; complex non-atypical endometrial hyperplasia; simple endometrial hyperplasia without atypia; complex endometrial hyperplasia without atypia	Low level of somatic mutations in scattered glands with morphology on HE staining showing no changes	< 1%	RR: 1.01–1.03
Atypical hyperplasia/endometrioid intraepithelial neoplasia	Complex atypical endometrial hyperplasia; simple atypical endometrial hyperplasia; endometrial intraepithelial neoplasia (EIN)	Many of the genetic changes typical for endometrioid endometrial cancer are present, including: micro satellite instability; <i>PAX2</i> inactivation; mutation of <i>PTEN</i> , <i>KRAS</i> and <i>CTNNB1</i> (β -catenin)	25–33% <small>5</small> 59% <small>2</small>	RR: 14–45

Figure 1: New WHO classifications of endometrial hyperplasias. [4]

This change in the differentiation of the types of this condition was made to understand better the molecular genetic changes. Regarding the first category, hyperplasias without atypia do not display any relevant genetic changes and are characterized by their benign nature. On the other hand, atypical endometrial hyperplasias present numerous mutations related to invasive endometrioid endometrial carcinoma. [4]

DIAGNOSIS

Foremost, to diagnose endometrial hyperplasia, it is of outmost importance to take a good medical history of the patient, where the female patient is going to be asked about any irregularities during her menstrual bleedings, as well as details about her menstrual history like when it started, when it stopped (if applicable), how

long the cycle is/was and if the patient was ever pregnant. In addition, the patient should be also asked about any medication usage, with emphasis given on estrogen-related drugs.

Furthermore, attention should be paid to the physical examination of the patient. Most of the time, pelvic examination may be normal, however this does not exclude endometrial hyperplasia from being present. The most reliable test to confirm this diagnosis is endometrial biopsy. It is performed with the assistance of transvaginal ultrasound, which depicts the thickness of the uterine lining. However, in some cases, a procedure called hysteroscopic-guided uterine sampling with dilatation and curettage (D&C) could also be performed under sedation.

During this procedure, a hysteroscope (tube adapted with a light and a camera) is being inserted inside the vagina, through the cervix, and into the uterus, which enables the visualization of the uterus. Regarding the D&C phase of this procedure, the cervix is dilated to allow access to the uterus, and then a device called curettage aims at the removal of the uterine lining for further testing. Another procedure that can be performed to examine the cells of the endometrium is pipelle biopsy. Pipelle endometrial biopsy is widely used in females with abnormal uterine bleeding where a small sample of endometrial tissue is obtained to be examined. [3],[5],[6]

TREATMENT – ENDOMETRIAL HYPERPLASIA WITH WITHOUT ATYPIA

Undoubtedly, endometrial hyperplasia is a particularly important precancerous finding that should be closely monitored and treated to prevent further progression and to improve the patient's quality of life.

It is quite unusual for endometrial hyperplasia to progress into endometrial cancer in the absence of atypical cells. In fact, according to studies only roughly 5% of the population with endometrial hyperplasia without atypia are at substantial risk of developing endometrial cancer. This type of hyperplasia is also likely to dissolve on its own over time. Crucial to the treatment plan is to try to minimize important risk factors such as obesity, since fat cells contribute to excess estrogen production.

In addition, it is recommended to start treatment with progestin to neutralize the thickening effect of the excess estrogen on the endometrium. Usually, an oral progesterone or a progesterone containing intrauterine device (levonorgestrel IUD) might be suggested for this purpose. Due to the overall effectiveness of progesterone therapy and the insignificant risk of getting cancer in this stage, few are the cases where hysterectomy is advised as a first line therapy. [5]

TREATMENT – ENDOMETRIAL HYPERPLASIA WITH ATYPIA

In this case, the course of treatment should be more aggressive since the risk of cancer progression is much higher. Many studies claim that disease resolution is more likely to be achieved with hormonal therapy and specifically with progestin, a synthetic progestogen, with success rates ranging from 89% up to 96%. Conventionally, progestins have been the mainstay of conservative treatment for atypical endometrial hyperplasia and in combination with GnRH analogues, metformin, and hysteroscopic resection, appear to enhance the efficacy of the treatment. For the female population in their reproductive years, levonorgestrel intrauterine devices (IUDs) not only yield a higher histologic regression rate for complicated hyperplasia without atypia and atypical hyperplasia when compared to oral progestogens, but also offer a higher local dose concentration of progestins compared to the oral route, avoiding any adverse effects related to the systemic administration of progestogens.

All these render IUDs as the preferred route of therapy administration. Moreover, another option applicable to those who no longer wish to become pregnant is total hysterectomy, a surgical removal of the uterus which eliminates the possibility of getting endometrial cancer. [5]

CONCLUSION

If left untreated or managed poorly, endometrial hyperplasia could result in a variety of complications with the most significant being the development of endometrial cancer. Abnormal endometrial cell proliferation raises the risk of malignant transformation, especially in complex or atypical endometrial hyperplasia. Untreated hyperplasia can worsen irregular uterine bleeding, which in turn can lead to chronic anemia and its associated complications such as fatigue and impaired physical functioning. There is a higher chance of aggravating hormonal imbalances in situations where hyperplasia is hormonally driven, such as in tumors that secrete estrogen or ailments like polycystic ovary syndrome. This could lead to additional issues with the patient's reproductive health or metabolic disorders. Furthermore, dealing with a disease that increases one's risk of developing cancer can have a profoundly negative psychological impact on those who are affected. Ultimately, to minimize the likelihood of these complications and to enhance patient outcomes, endometrial hyperplasia must be diagnosed promptly as possible and managed appropriately. [3]



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