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Microbiology and Pathology

S2 Autoimmune Pathogen

Melioidosis an Emerging Disease

Highlights

Case Series Study in Mayotte

Review on Lipoprotein(a) Infection

Discovering Thoughts, Inventing Future

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CONTENTS OF THE ISSUE

- i. Copyright Notice
 - ii. Editorial Board Members
 - iii. Chief Author and Dean
 - iv. Contents of the Issue
-
- 1. Melioidosis an Emerging Disease in the Indian Ocean Region: Case Series Study in Mayotte. **1-4**
 - 2. Plausibility Review on Lipoprotein (A) Infection Path of S2 Autoimmune Pathogen. **5-11**
 - 3. Artificial Intelligence (AI) in Family Medicine– A Summary. **13-20**
 - 4. Biochemical, Cytological and Microbiological Profile of Cerebrospinal Fluids Analyzed at Thedouala General Hospital Laboratory. **21-37**
-
- v. Fellows
 - vi. Auxiliary Memberships
 - vii. Preferred Author Guidelines
 - viii. Index



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Melioidosis an Emerging Disease in the Indian Ocean Region: Case Series Study in Mayotte

By Abdoulaye Diallo, Yacouba Dembele, Amadou Cheick Tidiane Cisse
& Issifou Yaya

Abstract- Background: Burkholderia pseudomallei is the agent of melioidosis. It is a bacterium from the hydrotelluric environment, highly pathogenic for humans. The geographical distribution of this disease is spreading and now affects the southwest of the Indian Ocean and in Mayotte

Case presentation: We report four new cases of melioidosis with a case that was complicated by a failure of several organs (case 2) which were observed on Mayotte Island. The last two affected cases came from Madagascar. Burkholderia pseudomallei was isolated from blood cultures, confirming the diagnosis. Prolonged treatment with ceftazidime or Ertapenem intravenously followed by cotrimoxazole alone or combined with oral doxycycline led to complete recovery.

Keywords: burkholderia pseudomallei, melioidosis, Mayotte.

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Melioidosis an Emerging Disease in the Indian Ocean Region: Case Series Study in Mayotte

Abdoulahy Diallo ^α, Yacouba Dembele ^σ, Amadou Cheick Tidiane Cisse ^ρ & Issifou Yaya ^ω

Abstract- Background: *Burkholderia pseudomallei* is the agent of melioidosis. It is a bacterium from the hydrotelluric environment, highly pathogenic for humans. The geographical distribution of this disease is spreading and now affects the southwest of the Indian Ocean and in Mayotte

Case presentation: We report four new cases of melioidosis with a case that was complicated by a failure of several organs (case 2) which were observed on Mayotte Island. The last two affected cases came from Madagascar. *Burkholderia pseudomallei* was isolated from blood cultures, confirming the diagnosis. Prolonged treatment with ceftazidime or Ertapenem intravenously followed by cotrimoxazole alone or combined with oral doxycycline led to complete recovery.

Conclusion: Melioidosis poses a potential threat in the Indian Ocean region in general and Mayotte and should be carefully monitored. The high incidences of diabetes and climatologic conditions such as rainy seasons with the occurrence of tropical cyclones make Mayotte a possible setting for melioidosis. It would therefore not be surprising to see a marked increase in the incidence rate of melioidosis in the years to come.

Keywords: *burkholderia pseudomallei*, *melioidosis*, Mayotte.

1. INTRODUCTION

Melioidosis is a bacterial zoonosis in humid tropical areas, caused by a Gram-negative bacillus *Burkholderia pseudomallei*, an invasive germ, transmitted by inoculation, inhalation or ingestion. Although inhalation is the first route of infection described, it is now well known that inoculation is the most common mode of infection [1]. It was described in 1912 by Whitmore in Burma (Myanmar) [2]. It is a severe, opportunistic infection, difficult to treat, with high mortality. It is an emerging disease in the process of spreading. It mainly affects susceptible persons who are directly in contact with contaminated wet soils. Immunosuppressed elderly persons (e.g., those suffering from diabetes mellitus and/ or alcoholism, chronic kidney and lung disease) are at increased risk of developing infection. It can reach all the organs and especially the lungs. The disease has protean manifestations ranging from localized abscess formation

to disseminated abscesses, septicemia, shock [3–4]. Ceftazidime or meropenem are the therapeutic choice for treating severe cases of infection and can be given by the IV route for several weeks, followed by oral treatment (up to 20 weeks) with trimethoprim-sulfamethoxazole and doxycycline [5]. Here, we report four new cases of melioidosis that were observed in Mayotte, which is a French overseas department.

Case summary 1

In 2016, 73-year-old Comorian with a history of high blood pressure, chronic renal failure, insulin-requiring diabetes, does not smoke, non-alcoholic. Living in Mayotte for many years, with no notion of recent travel. He consults in the emergency room for fever and chills with an infectious focus on the left on the chest X-ray. The clinical examination found crackles from both bases. The general condition of the patient allows return home with amoxicillin / clavulanic acid. Three days after going to the emergency room, he consults again for persistent fever. The biological assessment shows a moderate inflammatory syndrome with GB 15 G / L with PNN 12.2 G / L, thrombocytopenia at 86 G / L, CRP 222 mg / L, urea 34 and creatinine 369 and HbA1c at 11%. A blood culture taken during its first emergency visit highlights *Burkholderia pseudomallei* after 6 hours of incubation on the aerobic sample. A chest CT scan showed necrotizing pneumonitis with bilateral effusion and small parenchymal condensation of the focal right upper lobe. Based on the antibiogram, treatment with Ertapenem (1 g / day) and cotrimoxazole 960 mg (1 tablet / day) for 14 days was started. Apyrexia is achieved on the fifth day of treatment. The control blood cultures will all come back sterile. After two weeks of dual antibiotic therapy, the patient is treated with cotrimoxazole alone for a total of 3 months. A good clinical-biological evolution at the end of the treatment without relapse was observed.

Case summary 2

In March 2018, 54-year-old Comorian woman with type 2 and hypertensive diabetes. Living in Mayotte for many years, with no notion of recent travel, does not smoke, does not drink alcohol. Farmer. For the past month and a half, she had had a deterioration in general condition with weight loss, fever with chills, headache with a dry mouth, tongue, pallor and an imbalance of diabetes. She complains of diffuse abdominal pain, constipation on physical examination. On admission, the

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biology found GB 10.5 G / L, PNN 9.19 G / L, thrombocytopenia: 105 giga / L, prothrombin level: 42%, CRP 257mg / L. Cytolysis three times normal, moderate cholestasis without jaundice, HbA1c 13%. Three blood cultures (aerobic Falcon) grow to *Burkholderia pseudomallei*. The Thoraco-Abdo-pelvic CT scan performed on admission found moderate bilateral pleural effusion, predominantly on the left, and a thin layer of pericardial effusion at the mediastinal window. At the parenchymal level, there were multiple diffuse nodular lesions of central and peripheral distribution, bilaterally and predominantly on the right with bilateral hilo-basal peri-broncho-vascular thickening with left postero-basal parenchymal condensation. There were also multiple hypodense lesions on the hepatic parenchyma evoking micro-abscesses and stable appearance of the intra-splenic abscessed collections and Thrombosis of the splenic vein associated with several lymphadenopathies at the level of the splenic hilum thus confirming the image of the thrombus at level of portal division of the left liver. The brain scan did not find any argument in favor of an abscess. Initially treated with Ceftriaxone then adapted to the results of blood cultures with Ceftazidime (6g / day) plus intravenous Cotrimoxazole (3200mg / day) for 14 days then relay maintenance treatment with cotrimoxazole (960mg) oral (6 tablet / day) and doxycycline (200mg / day). She also benefited from a curative anticoagulation by Lovenox then Rivaroxaban for 3 months. At 6 months of treatment, there was a good clinical-biological and CT evolution with almost complete regression of the pulmonary, hepatic and spleen lesions. No relapse after 3 months of follow-up

Case summary 3

In July 2018, 61-year-old Mahorais, whose only history was a benign prostate enlargement with a first placement of a permanent catheter in Madagascar a month before his hospitalization. Addressed to the emergency room in front of a table of febrile glairo-bloody diarrhea evolving for 3 days, a general examination found fever. Biology finds an inflammatory syndrome (22 G / L of leukocytes, CRP 339mg, a 2N cholestasis without hepatic cytolysis and an increased free bilirubinemia and PSA at 14.88. A vesico-prostatic ultrasound found in the bladder a clot of hematoma measuring 73 mm long transverse axis 54 mm thick and 54 mm high or 113 ml in volume. The prostate was enlarged, homogeneous, without image of a nodule. Cytobacteriological examination of the urine found leukocyturia at 19200 / mm³, red cells 1686 / mm³, as well as Gram-negative bacteria live Put on ceftriaxone and Ofloxacin Cytobacteriological examination of urine and two aerobic blood cultures confirmed the presence of *Burkholderia pseudomallei* Diagnosis of hemorrhagic shock secondary to massive hematuria within the framework of a septicemia with urinary starting point by

Burkholderia pseudomallei was posed. Passage with the block for clot removal vesical I by the upper route and retropubic adenomectomy. Introduction after antibiogram of Ceftazidime (6g / day) for 14 days with then switch with Doxycycline (300 mg / day) for 3 months. The evolution is quickly favorable both urologically and infectiously. Note that the blood cultures and Cytobacteriological examination of the urine carried out after the treatment returned sterile and an abdominopelvic scanner showed nothing.

Case summary 4

In December 2018, Mahorais, 62, type II diabetes and high blood pressure. After a month's stay in Madagascar, presents to the emergency room three weeks after his return for feverish cough; a hypothesis of right lung disease was raised and treated with amoxicillin / clavulanic acid with return home. Returns to the emergency department two days later for increases in the pulmonary picture with stage IV dyspnea, productive cough and chest pain. The clinical examination is without particularity. Biology GB 14.3G / L, including PNN 10.0G / L, P 407G / L, CRP 295mg / L and HBA1c 9.8%. A Thoraco Abdomino-Pelvic CT scan found at the mediastinal level: infra-centimetric lymphadenopathy at the level of the Baret's compartment and right bronchopulmonary, a bilateral pleural effusion larger on the right. At the parenchyma level, there were several bilateral pulmonary foci, the largest of which was located at the level of the upper right lobe with an aspect of early collection abscess 43 mm in diameter located in the posterior sub pleural. Several other foci of pseudo-nodular appearance are found at the level of the right apex, at the level of the lingula and at the level of the two lower lobes. Abdomino-pelvic no abnormality. Aerobic blood culture returns positive to *Burkholderia pseudomallei*. The diagnosis of a hypoxemic pneumonia with *Burkholderia pseudomallei* was confirmed with initiation under meropenem (6 g / day) and cotrimoxazole (960mg) oral (4 tablet / day) for 14 days then relay with Doxycycline (200mg / day) and cotrimoxazole (960mg) even dose for 3 months. Significant improvement at the clinical level with oxygen and biological withdrawal. No relapses were reported after three months of follow-up.

II. DISCUSSION

We report two indigenous cases and two imported cases of melioidosis from Madagascar observed between 2016 and 2018 in Mayotte which is the last French overseas department, located in the Indian Ocean region. Melioidosis is a seasonal condition, the incidence of which increases with each rainy season [6]. In fact, 75 to 81% of cases are detected during the months when rainfall is highest [7]. Hygiene conditions and access to drinking water could be at issue because a study carried out in 2013 in

Thailand shows that ingestion of non-drinking water is clearly criminalized in low-income countries [8]. According to INSEE in 2017, almost a third of the inhabitants of Mayotte did not have access to water in their accommodation. To obtain water, the Mahorais use an outdoor tap shared between several dwellings. Those who do not have them call on "neighbors or relatives". "The others, mainly residents of sheet metal houses, get their water from a fire hydrant, from a well or directly from a river or stream," said INSEE. A review of the literature published in 2017 shows that 13 cases of melioidosis have been documented in the Indian Ocean region since 2004 [9,10,11]. In the Indian Ocean region, most of these cases occurred after a stay in Madagascar [10,12], like our two imported cases. The incidence of melioidosis in Madagascar may be more important than assumed because it is likely that many cases are never diagnosed or treated. The number of cases diagnosed is probably lower than reality, due to the lack of diagnostic means in developing countries, and the ignorance of this pathology by doctors. These recent clinical reports suggest that this infection is endemic in the Indian Ocean region. In our case series, three-quarters of our patients were diabetic. Various studies clearly demonstrate that almost 50% of melioidosis patients have varying degrees of diabetes mellitus. Additionally, *B. pseudomallei*-infected diabetics have impaired IL12P70 production that results in decrement of IFN- γ [13]. It was also found that pulmonary localization was the most frequent with almost 75% of cases. According to the literature, melioidosis is expressed in the majority of cases by pneumonia, regardless of the endemic area [14]. This is often severe and may require the use of intensive care. Pulmonary involvement occurs in the form of pneumonia, lung abscess, pleural effusion or even pleural empyema [15]. Genitourinary disorders with prostatic abscess have also been reported in Australia, while a significant proportion of hepatic or splenic abscesses have been found mainly in Thailand [14,16]. Our patients were treated during the attack phase with either a carbapenem or ceftazidime as monotherapy for at least two weeks and then relayed with trimethoprim sulfamethoxazole or doxycycline alone or both. Study confirms that ceftazidime or meropenem are the therapeutic choice for the treatment of severe cases of infection and can be administered IV for several weeks, followed by oral treatment (up to 20 weeks) with trimethoprim sulfamethoxazole and doxycycline [5].

III. CONCLUSION

Melioidosis poses a potential threat in the Indian Ocean region in general and Mayotte and should be carefully monitored. The high incidences of diabetes and climatologic conditions such as rainy seasons with the occurrence of tropical cyclones make Mayotte a

possible setting for melioidosis. It would therefore not be surprising to see a marked increase in the incidence rate of melioidosis in the years to come. In addition, clinicians examining travelers with severe pneumonia or sepsis returning from subtropical or tropical regions should consider the differential diagnosis of acute melioidosis especially that novel molecular methods of diagnosis (e.g., PCR) are being increasingly implemented for routine diagnosis. Report to the laboratory to avoid accidental contamination on the one hand and on the other hand, it is feared that *B. pseudomallei* will be used as a biological weapon

Key learning points

- *Burkholderia pseudomallei* is the causative agent of melioidosis, which is prevalent throughout Southeast Asia.
- This bacterium is an important bioweapon and bioterrorism risk worldwide.
- The overall fatality rate of septicemia in melioidosis is very high, and bacteria are intrinsically resistant to many antimicrobial agents.
- Melioidosis increasingly affects travelers visiting endemic areas, thereby leading to septicemia.
- Clinicians should consider acute melioidosis as a differential diagnosis.

Top five papers

[1] Allou N, Martinet O, Allyn J, Bouchet B, Jaffar-Bandjee M-C, Galas T, et al. (2017) Emergence of melioidosis in the Indian Ocean region: Two new cases and a literature review. *PLoS Negl Trop Dis* 11(12): e0006018. <https://doi.org/10.1371/journal.pntd.0006018>

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Abbreviation

B. pseudomallei: *Burkholderia pseudomallei*
 CRP: C-REACTIVE PROTEIN
 CT scan: Computerized Tomography
 GB: white blood cells
 HbA1c: glycated hemoglobin
 IV: Intravenous injection
 INSEE: The National Institute of Statistics and Economic Studies
 IL12P70: Interleukin-12, p70

IFN- γ : Interferon-gamma receptor
 PNN: Polynuclear neutrophils
 PSA: Specific Prostate Antigen
 P: Platelets
 PCR: Polymerase Chain Reaction



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Plausibility Review on Lipoprotein (A) Infection Path of S2 Autoimmune Pathogen

By Yang I. Pachankis

Abstract- Introduction: The review is motivated by COVID-19 vaccination poisoning paths in human hosts from a sebaceous immunobiological perspective, purposed to facilitate pharmacokinetic targeting solutions.

Review: The review evaluates the sebaceous immunobiological chain in the downstream and upstream human physiology. It is incentivized by the lipoprotein correlations to COVID-19 severity in human hosts, and it considers the post-vaccination risk factors and neuronal infection paths. The review is guided by the generation pathways of reactive oxygen species.

Keywords: adenosine monophosphate; COVID-19; micropinocytosis; mitochondria; mitosis; oscillation analysis; proton-motive force; SARS-CoV-2; sebaceous immunobiology; scission point.

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Abstract- Introduction: The review is motivated by COVID-19 vaccination poisoning paths in human hosts from a sebaceous immunobiological perspective, purposed to facilitate pharmacokinetic targeting solutions.

Review: The review evaluates the sebaceous immunobiological chain in the downstream and upstream human physiology. It is incentivized by the lipoprotein correlations to COVID-19 severity in human hosts, and it considers the post-vaccination risk factors and neuronal infection paths. The review is guided by the generation pathways of reactive oxygen species.

Results: The plausibility elimination of the steroidogenesis pathway has narrowed down the neuronal infection paths to stem cell migration pathways for the unvaccinated, and stem cell and leukocytes for the vaccinated.

Conclusions: The review suggests even though SARS-CoV-2 vaccination postponed collective infection severity in the initial outbreak, its long-term lethality and harms outweigh the short-term economic benefits.

Registration: The review is prospectively registered on Open Science Framework with the DOI: [osf.io/39x6r](https://doi.org/10.31233/osf.io/39x6r), and the relevant clinical trials are registered on ClinicalTrials.gov with the numbers NCT05839236 and NCT05930912.

Keywords: adenosine monophosphate; COVID-19; micropinocytosis; mitochondria; mitosis; oscillation analysis; proton-motive force; SARS-CoV-2; sebaceous immunobiology; scission point.

I. INTRODUCTION

Lipoproteins have been an important intersectional carrier between cardiac and hormonal functions. Lipopeptide LPK (L-PEG₁₂-(KIAALKE)₃) is involved in membrane destabilizing with the electrostatic activity of LPE (L-PEG₁₂-(EIAALEK)₃) in membrane fusion activities ⁽¹⁾; cell entry of the hepatitis C virus, for example, is aided by apolipoprotein C-I (ApoC-I) for membrane fusion ⁽²⁾. High-density lipoprotein (HDL) is differentiated to cell-penetrating peptides' mutants and fusogenic lipids at mildly acidic pH, with the latter showing higher affinity to the cell plasma membrane during the process ⁽³⁾. Endocytic uptake of SARS-CoV-2 S2 protein induces fusogenic activities ^(4, 5), which is key to the pathogenic severities not only limited to SARS-CoV-2 ^(6, 7). The correlational study of low-density lipoprotein - cholesterol (LDL-C) to COVID-19 severity ⁽⁸⁾ and clinical results of NCT05711810 trial led to the hypothesis on S2 proteins' hibernation concentration being on LDL-C.

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HDL and LDL's steroidogenesis capacities ⁽⁹⁾ further justified a sebaceous immunobiological review. While Apolipoprotein B (apoB)-containing lipoproteins, including chylomicrons, very-low-density lipoprotein (VLDL), and LDL, carry and deliver triglycerides and cholesterol, HDL mediates Reverse Cholesterol Transport (RCT), with apoA-I for anti-atherogenic properties ⁽¹⁰⁾. An LDL and a molecule of apolipoprotein B100 covalently bound, via disulfide bonds, to a plasminogen-like particle apolipoprotein(a) [Apo(a)], compose of the plasma lipoprotein lipoprotein(a) [lp(a)] ⁽¹¹⁾. Insulin levels play a critical role in lp(a) degradation through the hepatic synthesis of Apo(a), whereby lp(a) particles have the capacity to cross the endothelial barrier and the arterial intima in promoting atherogenesis and delivering LDL-C ⁽¹¹⁾.

The internal mitochondrial synthesis paths have thus become the focus of the review. Mitochondrial functions include DNA segregation, oxidative phosphorylation efficiency, reactive oxygen species (ROS) production, and apoptosis ⁽¹²⁾. ROS is considered the key physiological response biomechanism in the review ⁽¹³⁾. From the clinical trial experience, it is hypothesized that SARS-CoV-2 S2 protein competes for ROS with host physiology, and it is thereafter anchored for practical safety concerns in the review with the potential pharmacokinetic targeting solution purpose.

II. REVIEW

The review is structured from the opening on interactions between melatonin and melanin. Melatonin actions are mediated through its cognate membrane bound type 1 and 2 (MT1 and MT2) receptors or through receptor-independent mechanisms; they can affect the phenotype of normal human melanocytes ⁽¹⁴⁾. Melatonin can downregulate the paracrine factors Endothelin-1 (ET-1) and prostaglandin synthase 2 (PTGS2) in the keratinocytes by inhibiting the janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) pathway, which reduces melanogenesis and melanin production in pigment cells ^(15, 16).

With the neuronal-sebaceous ROS dynamics, the second subsection reviews the mitochondria-driven adenosine triphosphatase (ATP) synthesis. Endocytotic pathways are evaluated after the downstream mitochondrial activities revolving around the ROS. The third subsection examines the upstream

steroidogenesis, specifically focusing on macropinocytosis. RCT in the fourth subsection concentrates on SARS-CoV-2's main pathogenesis by the complexities in autophagy and the autophagy-lysosome pathway. With the sebaceous immunobiological pathways, SARS-CoV-2's vaccination poisoning trails in human hosts are analyzed. The fifth subsection reviews the melanin involvement in adrenocorticotrophic hormone (ACTH)^(17, 18).

a) *The Downstream Basis of Sebaceous Immunobiology*

Melatonin synthesis involves both hydroxylation and decarboxylation with the aromatic L-amino acid, and acetylserotonin O-methyltransferase (ASMT)⁽¹⁹⁾; it occurs in the mitochondrial matrix in some species, where chloroplasts are also capable of⁽²⁰⁾. Melatonin secretion is reported to have direct and varying associations with leukocytes and leukocyte levels⁽²¹⁾, and melatonin nuclear binding receptors are identified in human lymphocytes and monocytes⁽²²⁾. Statistical experiment exhibits a circadian effect on human melatonin inhibition of leukocyte levels⁽²³⁾. Its impact on neutrophils is involved in apoptosis in carp and zebrafish^(24, 25).

The chemo-physiological associations between melatonin and sebaceous immunobiology are intertwined with the circadian effect. *Ex vivo* study evidenced melatonin and its metabolites' protection function on melanocytes from ultraviolet B radiation (UVB), including its adverse impact on keratinocytes⁽¹⁴⁾. Methoxytryptamine receptor independent protective effects against UVB-induced DNA-damaging ROS generation from epidermal melanocytes stimulate UVB irradiated melanocytes' expression of major antioxidant enzymes, including catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GSTP1), superoxide dismutase (Cu/Zn-Sod and Mn-SOD), glutamylcysteine synthetase (GCS), and NAD(P)H dehydrogenase, quinone 2 (NQO2)⁽¹⁴⁾. Albeit melatonin promotes melanin synthesis in the human SK-MEL-1 melanoma cells, it also inhibits, with a different chemical process, melanin synthesis from UVB irradiation induced melanin pigmentation⁽²⁶⁾.

b) *Mitochondrial Pathway in Adenosine Triphosphatase*

The phenomenon of mitochondrial flashes (mitoflashes) is considered a biomarker for mitochondrial energy metabolism under certain conditions, and protons produced by photolysis or electroneutral proton ionophores act as a powerful mitoflash trigger⁽²⁷⁾. Combined with my previous proton-production review, where protons are made in reactions in which ATP is hydrolyzed or the oxidized form of nicotinamide-adenine dinucleotide (NAD⁺) is reduced ($\text{RH}_2 + \text{NAD}^+ \rightarrow \text{NADH} + \text{H}^+ + \text{R}$)⁽²⁸⁾, and cardiac mitochondria regulate and energize ATP levels⁽²⁹⁾;

anions inhibit mitochondrial ATP production and decrease mitoflash frequencies, and vice versa, cations trigger mitoflashes⁽²⁷⁾. Electron transport chain (ETC) from proton-coupled electron transfer (PCET) provides energy with heat generation to ATP synthesis; less concise is the evidence for ROS interactions with proton-motive force (PMF) and cation fluxes, possibly contributed by the rapidly shifting dipole fields^(27, 29).

Hydrogenic (cation-based) and oxidative (anion-based) phosphorylation differences provide further insights. Even though cations, in general, promote mitoflashes, phosphine (PH_3) toxicity exists with its functions on lipid peroxidation from its superoxidation of ROS, by intoxicating mitochondria and by changing the latter's homeostasis⁽³⁰⁾. The phenomena in comparison to the Fe anions in oxidative phosphorylation suggest that ETC-mediated ROS generation from mitoflashes originates from the proton-gating process, wherein the gating pore's depolarization cut-off ionizes the hydrolysis chain for ROS production catalyzed by the PMF^(13, 27, 29, 31). The mitochondrion is considered an energy-producing organelle that generates ROS and heat as byproducts of oxidative phosphorylation⁽¹⁰⁾.

c) *Sebaceous Pathway in Upstream Mitochondria*

While HDL-C mediates RCT, LDL-C is internalized into cells through LDL receptor (LDLR)-mediated endocytosis, an important source for steroidogenesis^(10, 32). The LDL is degraded frequently in lysosomes, and its cholesterol is released for use in the synthesis of membranes, steroid hormones, and bile acids⁽³³⁾. Coated pits in discrete regions of the surface membrane where receptors cluster, invaginate into the cell to form endocytic vesicles, enclosed by extracellular ligand; the LDL receptor enters the cell together with LDL, after which it recycles to the surface, strongly up-regulated by estrogen in pituitary somatotrophic GH₃ cells^(33, 34). Indirect evidence shows that ezrin phosphorylation to phosphoezrin is involved in the receptor-mediated endocytotic process, corroborating with the mitochondrial pathway analysis in section 2.2^(34, 35).

Lipoproteins primarily manifest in plasma forms during endocytosis. Macropinocytosis is not only actively involved in the uptake of Ip(a) , but it also represents an important endocytic uptake mechanism for native LDL in macrophages during atherogenesis^(36, 37). A relational chart among clathrin-mediated endocytosis, clathrin-independent endocytosis, macropinocytosis, and transcytosis is seen in Figure 1⁽³⁷⁾.

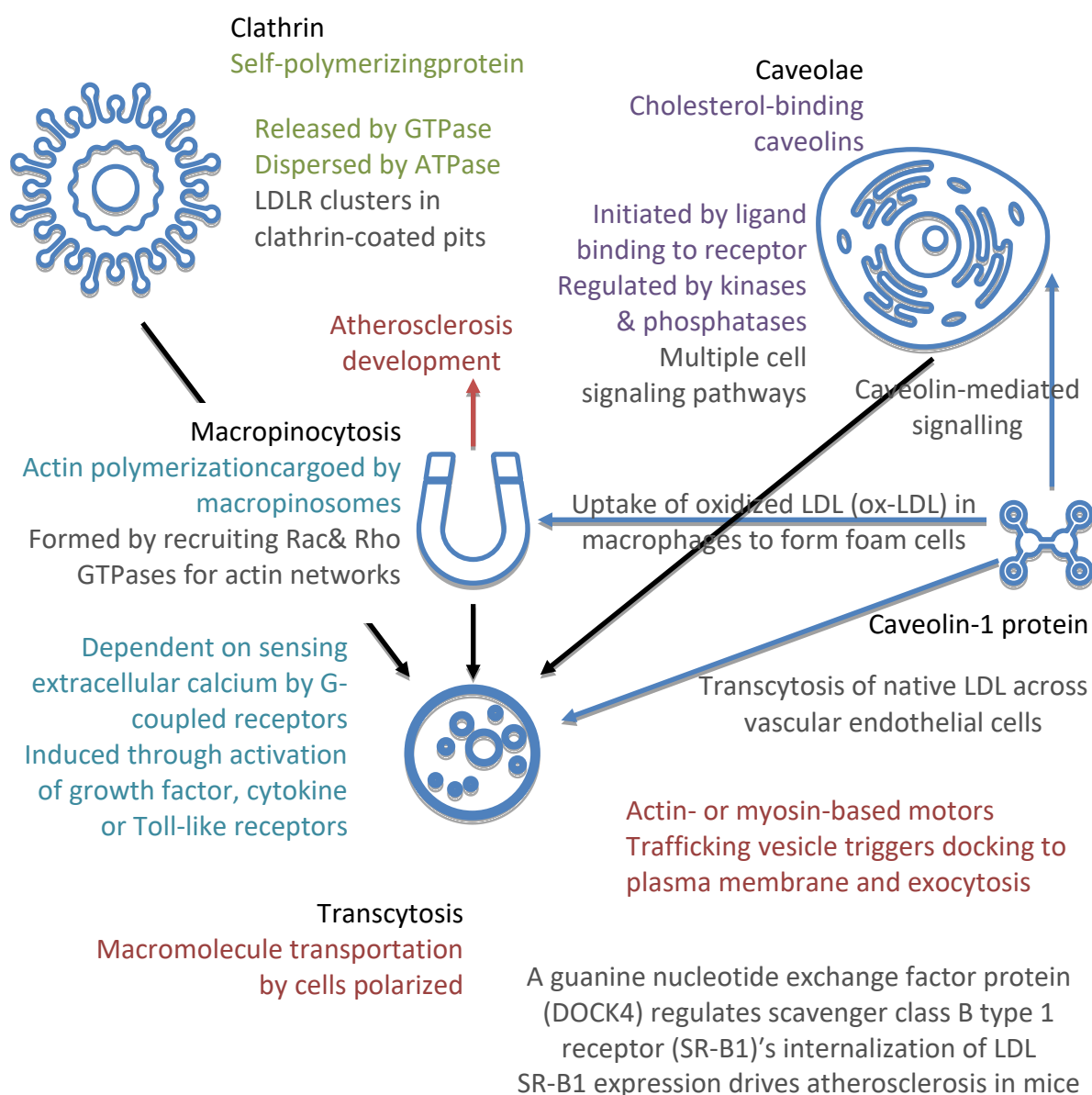


Figure 1: Main Endocytosis Forms of LDL-Related Lipoproteins and Atherosclerosis Development in the Endocytotic Chains.

Dynamin both Catalyzes Mature Clathrin-Coated Vesicle Releases and Promotes Membrane Fission in Release of Caveolin-Coated Vesicles. SR-B1 Receptor is Traditionally Thought of as an HDL Receptor.

While caveolin-1 protein is mainly responsible for ox-LDL in endocytosis, possibly contributed by the ATP dispersion effects, macropinocytosis, initiated by extracellular calcium, is mainly responsible for Lp(a) uptake by intracellular engulfment of cargoes and Lp(a) cell surface binding⁽³⁶⁾. No direct evidence in the archival research is obtained on macrophage infection by SARS-CoV-2, albeit the calcium channel infection path and amelioration of Lp(a)-induced atherosclerotic burden by selective serotonin reuptake inhibitors (SSRIs) suggest a plausible correlative risk during the innate immune response^(36, 38, 39). Further in vitro experiments are needed to determine the concise pathological

depths beyond the autophagy-lysosome pathway, especially concerning the confounding variables of electronegative LDL (L5) and ApoE⁽⁴⁰⁻⁴²⁾.

d) Reverse Cholesterol Transport In Sebaceous Immune Chains

RCT links hematology with lipid metabolism by autophagy and the autophagy-lysosome pathway. The three main lipid metabolism pathways are exogenous, endogenous, and RCT, with the last crucial for homeostasis⁽⁴³⁾. SARS-CoVs' immune escape capabilities concentrate on the autophagy-lysosome pathway, by hijacking autophagy initiation to form

unique double-membrane vesicles (DMVs) and by hijacking host cell endoplasmic reticulum associated degradation (ERAD) machinery ⁽⁴²⁾. The risen HDL-C indicator to the decreased prognosis of SARS-CoV-2 severe and critical cases, therefore, is relatively significant if macrophage infection potentials are eliminated ⁽⁸⁾.

Lipolysis is critical in SARS-CoV-2 vaccines' lethal adverse symptoms, besides carcinogenesis. Since macropinocytosis is induced through activation of growth factor, cytokine, or Toll-like receptors, carcinogenesis is mainly contributed by DMVs' formation ^(37, 42). With its blocking of autophagy, namely RCT, epithelial homeostasis is broken in the exogenous pathway for lipid metabolism mediated by epidermal growth factor (EGF) ^(43, 44). It is therefore hypothesized that rapid acidification is not the cause / precondition, but the effect of SARS-CoV-2 infection from the cholesterol cell locking, resulting in host cell lysis ^(43, 45, 46). The subsequent pathway blocked is the mitochondrial ATP synthesis ⁽⁴³⁾. This is why even when SARS-CoV-2 vaccines targeted the S1 protein's binding to angiotensin-converting enzyme 2 (ACE2), myocardial adverse events still happen with the S2's influence ⁽⁴⁷⁾.

Even if there's no direct SARS-CoV macrophage infection, macrophages' functions in the subsidiary caveolin-1 protein's intracellular lipid metabolism are still compromised seen in Figure 1. Lipid-poor ApoA-I, secreted by the liver and intestines, is lipidated in the circulation via cholesterol efflux by transporters located in peripheral tissues and macrophages, generating mature HDLs, which are hydrolyzed or returned to circulation for relipidation ⁽⁴³⁾. The upstream ROS and steroidogenesis are blocked, resulting in endocrine and neurological symptoms after SARS-CoV-2 vaccination. Macrophage apoptosis from host cell lysis creates further risks of atherosclerosis and secondary necrosis ⁽⁴³⁾.

e) Autophagy Induction and the Upstream ROS

The RCT's mitochondria-protective functions are reflected in HDL. Lipid peroxides in oxLDL stimulate ROS formation and impair oxygen consumption at Complexes I, II/III, and IV of the respiratory chain, resulting in mitochondrial dysfunction ⁽¹⁰⁾. Antioxidization by hydrolyzing cholesteryl esters and phospholipids in oxidized lipoproteins functions via the HDL-associated protein Paraoxonase 1 (PON1); the lysosphingolipid Sphingosine 1-Phosphate (S1P) of HDL, synthesized in hematopoietic and endothelial cells, induces Reperfusion Injury Salvage Kinase (RISK) and Survivor Activating Factor Enhancement (SAFE) pathways, with the STAT3-mediated attenuation of mitochondrial injury ⁽¹⁰⁾. The symbiotic upstream ROS dynamics amongst mitochondria, ATP, and melanin are thus interlinked by macroautophagy in sebaceous immunobiology ^(10, 48).

ATP signaling is mediated by binding to purinergic receptors type P2, expressed by human keratinocytes, Langerhans cells, and fibroblasts ⁽⁴⁸⁾. The P2X receptor family consists of seven different ligand-gated ion channels that elicit the flow of cations (Na^+ , K^+ , and Ca^{+2}) when activated by extracellular ATP; P2Y₁ and P2Y₂ receptors are expressed by proliferating keratinocytes in the basal layer of the epidermis, and keratinocyte cell numbers in vitro can be increased by low concentrations of ATP, uridine 5'-triphosphate, and adenosine 5'-diphosphate (ADP) ⁽⁴⁸⁾. Further detailed research in the correlations to clathrin-independent endocytosis may shed new light on the complexities in sebaceous immunobiology, including PMF's roles in Complex I & III ROS production currently concentrated on iron-sulfur clusters ^(13, 31, 37, 48).

Extra-adrenal and extra gonadal steroidogenesis is critical for upstream signaling of sebaceous immunobiology. Toll-like receptors are the key element in innate sebaceous immunology, compared to the T cell and B cell adaptive immunity ⁽⁴⁹⁾. While vitamin D levels' photochemical synthesis by the absorption of UVB energy by 7-dehydrocholesterol in the epidermis can be hydrolyzed at positions other than C25 by CYP11A1 in steroidogenic organs, the assumption on the reverse correlation between the activity of the cutaneous pigmentary system and vitamin D production is widely accepted by experts in the field of vitamin D ⁽⁵⁰⁾. Extra-adrenal and extra gonadal steroidogenesis take place where CYP11A1 is expressed, such as in both breast tumors and surrounding normal breast tissue, in the human gut and colon cancer cells, and in the heart, skin and cells of the immune system, with pathways that commence from cholesterol ⁽⁴⁹⁾. The hypothalamic-pituitary-adrenal (HPA) axis in the psychiatric focus of suicidology regulates local steroidogenic activity by phenotypes ⁽⁴⁹⁾.

The HPA axis, therefore, can also be influenced by mitochondrial ROS dynamics in the heart. The two major endogenous ROS sources across the endocytotic spectra, i.e., oxidative phosphorylation and proton gradient across mitochondrial membrane potential, correlate to cardiac polarity and depolarization ⁽³¹⁾. Myocardial infarction might occur by ischemia conversion of ATP to ADP and adenosine monophosphate (AMP), impacting cyclic AMP (cAMP) and damaging innate immunity ^(31, 51).

III. RESULT

Albeit further research and review are needed to determine the endocrine dysfunctions caused by SARS-CoV infections, the causal infection path from Ip(a) is inferentially falsified in the study. Lipoprotein indicators in COVID-19 severity are phenomenological to ROS damages in the sebaceous immunobiological chain. The plausibility elimination of the steroidogenesis

pathway has narrowed down the neuronal infection paths to stem cell migration pathways for the unvaccinated, and stem cell and leukocytes for the vaccinated.

IV. CONCLUSIONS

Ischemia-induced AMP homeostasis dysregulation is the key lethal element in COVID-19 vaccination poisoning. With the viral infection potentials on human embryonic stem cells, COVID-19 vaccination diffuses viral concentration while increasing its productive infection capacities^(47, 52, 53). Not only the coercive mandates on COVID-19 vaccination and tracking need to be lifted, but also it is medically recommended against COVID-19 vaccination.

Stem-targeting H₂O₂ may treat stem cell infection by apoptosis, given the clearance on intact upstream sebaceous pathways and AMP homeostasis⁽⁵²⁾. Apart from the concentration on SARS-CoV-2 therapeutic explorations, the review has roughly mapped sebaceous immunobiology in relation to the earth's environment. Further research study on the centromeres' roles will be published separately.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

DATA AVAILABILITY

No data associated with the review.

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Artificial Intelligence (AI) in Family Medicine– A Summary

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Abstract- This bibliographic review evaluates Artificial Intelligence (AI) theory's applications in the field of Family Medicine. Globally billions of people suffer from multiple health related issues throughout their lives including diseases of the heart, lungs, kidney, diabetes, and many forms of cancer. Diagnosis, remedy, and prevention of these disorders are multifaceted, and machine/computer based investigative tools for doctors are immediately needed to augment their decision-making. This study includes various applications of AI/machine learning (AI/ML) procedures in family medicine and its various sub-specialties. AI/ML-centered medicine offers better solutions over standard family medicine covering birth through end of life care. These include treatments for adolescents, geriatrics, disorders of pain and sleep, and sports injuries. However, several implementation hurdles for AI in clinical family medicine persist.

Keywords: *AI and machine learning in family medicine, AI and machine learning in geriatrics, AI and machine learning in disorders of pain and sleep, AI and machine learning in sports injuries.*

GJMR-C Classification: NLM Code: W 26.5



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Artificial Intelligence (AI) in Family Medicine— A Summary

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Abstract- This bibliographic review evaluates Artificial Intelligence (AI) theory's applications in the field of Family Medicine. Globally billions of people suffer from multiple health related issues throughout their lives including diseases of the heart, lungs, kidney, diabetes, and many forms of cancer. Diagnosis, remedy, and prevention of these disorders are multifaceted, and machine/computer based investigative tools for doctors are immediately needed to augment their decision-making. This study includes various applications of AI/machine learning (AI/ML) procedures in family medicine and its various sub-specialties. AI/ML-centered medicine offers better solutions over standard family medicine covering birth through end of life care. These include treatments for adolescents, geriatrics, disorders of pain and sleep, and sports injuries. However, several implementation hurdles for AI in clinical family medicine persist.

Keywords: AI and machine learning in family medicine, AI and machine learning in geriatrics, AI and machine learning in disorders of pain and sleep, AI and machine learning in sports injuries.

I. INTRODUCTION

The main objective of this paper is to appraise applications of Artificial Intelligence (AI) and Machine Learning (ML) in the field of family medicine. Since 1990s there has been major advancements in the use of AI to images based fields of medicine (e.g. radiology, pathology, and ophthalmology,...).¹

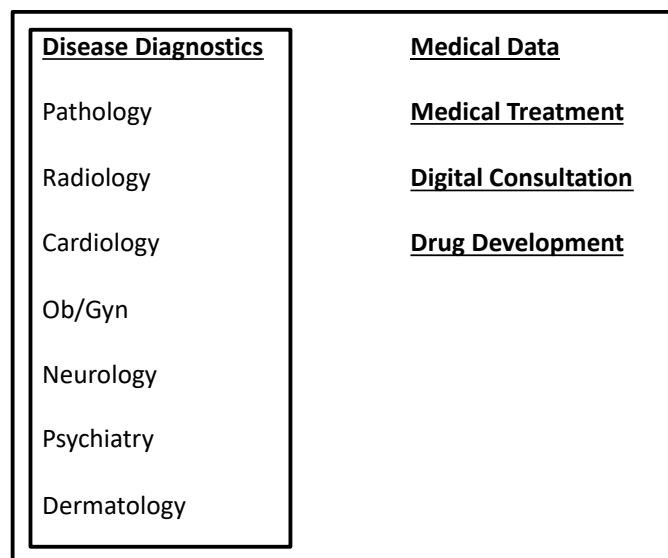


Figure 1: AI in medicine¹

In the field of Family Medicine, AI has applications in disease diagnostics and prevention in numerous subspecialties (Figure 2).

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Age Groups	Subspecialties	Objectives
Birth to Death	Geriatrics Hospice and Palliative Medicine Sports Medicine Sleep Disorder Pain Management	Disease/Disorder - Prevention - Diagnostics

Figure 2: AI in Family Medicine

In this article, first we reviewed AI-based family medicine research in various clinical situations that are included in Figure 2. Secondly, different ethical and social issues of Artificial Intelligence, for use in various family medicine presentations, are discussed.

II. ARTIFICIAL INTELLIGENCE OR AI

Artificial Intelligence or AI is an intelligence that is artificial and not natural. AI is established on several statistical ideologies in which an observation is 'learned' by a computer or a machine. The understanding of the observation by a machine gets smarter as more learning by the machine takes place. After an appropriate extent of this training, Artificial Intelligence, as a human being, becomes suitable for crafting decisions. In this section the main AI terms and ML-based algorithms are described.

a) AI Fundamentals

In this section, essential AI terms are concisely reviewed.²

Machine learning (ML) methodology brings statistical modeling and a machine (computer) together in order to learn from available information. Machine Learning is categorized into 'supervised' and 'unsupervised' learning.

- i. *Supervised learning technique* constructs a forecast model based on known output and input data values. The model is then applied to forecast new output for a specified new input information. Supervised learning is applicable for both i) a 'classification' model for output classifications (e.g., a patient has cancer or patient is cancer-free based on an MRI image) and ii) a 'regression' model for a continuous output variable (e.g., patient's cholesterol level).
- ii. *Unsupervised learning technique* is applicable when there is no output prediction variable present and input data is not labeled. This approach groups data together, to comprehend the intrinsic structure of the data, based on their resemblances (e.g., clustering patterns in a sample of patients with an illness that could lead to new drug therapy).

- iii. *Semi-supervised learning* is a fusion of 'Supervised' and 'Unsupervised' learning methodologies.

Artificial Neural Networks or ANNs accomplishes an output forecast that results from several independent parts of calculations and weightings. ANN, analogous to a network of neuron inside a brain, has a set of artificially layered/connected neurons to transfer information across the network.

b) ML Algorithms

Supervised Machine Learning contains the splitting of the accessible information into both 'training' and 'examination' sets for authentication of the algorithm. In this type of machine learning, the following algorithms are broadly employed:

- a) *Regression*: For machine learning, both 'linear regression' (use of least squares regression line between 'the cause' or independent variables and 'the effect' or dependent variables), and 'logistic regression' (applied for binary conclusions of 'yes or no,' or 'no illness or illness' with classifications of either categorical or continuous) techniques are frequently used and are built on data types.
- b) *Decision Tree (DT)*: The decision tree-based algorithm includes a set of procedures that describe the route from 'the root' to 'the leaves'.
- c) *Naive Bayes*: Naïve Bayes algorithm hypothesizes that the characters under evaluation are independent of each other.
- d) *Support Vector Machine (SVM)*: The SVM-based machine learning algorithm discovers a nonlinear association and classifies data by relating a hyperplane that best differentiates the presence of two collections.
- e) *k-Nearest Neighbor (k-NN)*: This ML algorithm is used for data classification of nonparametric grouping. The 'k', is the square root of the number of occurrences and its isolation from a pre-selected point.
- f) *Random Forest (RF)*: Random Forest based ML algorithm, prevents 'overfitting' and is an effective tool for a precise appraisal of classifiers. However,

these algorithms are less capable than the SVM and k-NN based methods.

- g) *Convolutional Neural Networks (CNNs)*: 'Convolution' is a system of a mathematical function on two functions that produces a third function. CNNs learn by several duplications of both 'analyzing' and 'weighting' the patterns it identifies in the pictures.

III. AI IN FAMILY MEDICINE

Family medicine professionals' work includes the diagnosis or identification of a disease followed by its prognosis (or a prediction of the course of the disease including the treatment and outcomes), and if needed, referring patients to appropriate specialists, providing care to patients with empathy, and documenting the data. Globally, over the past few years, AI is being evaluated for its application in family medicine.

In 2018, Blease et al. conducted a cross sectional survey of 1,474 General Practitioners (GPs) in the United Kingdom about the computerization and the future of primary care. About half (720) of the GPs replied to this survey. Majority out of them responded that AI will unlikely be able to replace doctors for diagnosing patients (68%), devising custom-made treatment strategies (61%), referring patients to specialists (61%), and providing compassionate care (94%).

However, about half of the family physicians (53%), who answered the survey, believed that technology can completely replace doctors for the purposes of prognostics of a disease. Also, a significant majority of the respondents (80%) believed that AI will be able to replace doctors for the purposes of medical documentation.³

Summerton et al., in 2019, observed that clinical information obtained from patients in family practice is ill-defined. This is where AI's language processing techniques can provide the tools to analyze unstructured data from patients' records. AI, per the authors, being a focused technology has on surface inconsistency with the comprehensive nature of family medicine. The authors believe that AI can assist in the projecting value of symptoms which is explicit knowledge. However, according to them, tacit knowledge such as how to obtain a patient's confidence is where AI may fall short.⁴

In 2021, Baser et al. evaluated the artificial intelligence related anxiety of family physicians in Turkey. The sample size for the study included 402 family physicians. Even though most doctors have no formal training on AI based applications, their anxiety levels were low. The authors therefore concluded that a structured AI based training program for applications in family practice can contribute as a decision support system and can enhance patient safety.⁵

Darcel et al. in 2023 studied the obstacles that Canadian patients (n=22), health providers (n=21), and health leaders (n=5) recognize with respect to applying AI in primary care based medicine. Major obstacles in implementing AI included (a) readiness of system and data, (b) the possibility for inequity and bias, and (c) the rules of AI. For each of these categories respondents were concerned about trust in the AI technology itself or in the health provider applying it.⁶

In 2020, Liaw et al.'s study concluded that AI based tools are not disposed for realization yet. There are significant consequences for confidentiality, misuse, and overtreatment with applying AI. In order for AI to be widely used in family medicine, the family practice physicians need to partake in appropriate plan, strategy, research, and delivery approaches. The authors also stressed that personal connections are more important than computer based tools.⁷

a) *AI in Diabetes Detection in Family Medicine*

Globally diabetes affects hundreds of millions of people. In the US the count is around 40M, with approximately 1.4M people diagnosed with the disease annually, and causes more than 100,000 deaths per year. The disease costs annually around \$340B which includes \$240B in medical costs and \$100B in loss in productivity. An early detection and timely medical treatment of various types of diabetes (type 1, type 2, and gestational) is therefore important.

Wei et al.'s work in 2010 utilized electronic clinical notes from Mayo Clinic and combined 'Natural Language Processing' (NLP), 'ML,' and 'Ontology' to automatically associate it to patients. Their AI model attained an F- score larger than 0.95 for both type 2 diabetes mellitus and control groups when utilizing all identified concept units (semantic type-Disease or Syndrome) as characters.⁸

Shankaracharya et al.'s research in 2012, from India, used the health reports of 1,415 hospitalized patients that were classified as either 'diabetic' or 'non-diabetic'. A new ML algorithm, named "mixture of expert," was used by the authors for training based on 1,104 patients' diabetic state, while 311 patients' data was kept for authentication of the algorithm. The model produced excellent sensitivity (99.5%), specificity (99.07%), and total classification accuracy (99.36%) for classifying 'pre-diabetic,' 'diabetic,' and 'non-diabetic' individuals.⁹

b) *AI in Heart Disease Detection in family medicine*

Annually, heart disease causes about 700K deaths in the US. To reduce these deaths, an early detection and treatment of the disease is therefore critical.

In 2020, Choi et al. evaluated 'AI-Clinical Decision Support System' (AI-CDSS) for assisting doctors in diagnosing of heart failure which is a difficult task. The AI-CDSS model included a combination of

'expert-driven' and 'ML- driven' methods to advance the knowledge base for the diagnosis of heart failure. The model utilized a retrospective unit of 1,198 patients (training: n=600 and testing: n=598) with and without heart failure for the AI-CDSS model development and evaluation of its performance. The concordance rate, which is the probability that a pair of individuals will both have a certain characteristic (given that one of the pair has the characteristic), between 'AI-CDSS model' and 'heart specialists' was 98%, while that between 'heart specialists' and 'non-heart specialists' was 76%. Thus, AI-CDSS may be helpful to the 'non-heart specialists', such as family physicians for the heart failure diagnosis when the heart specialists are not available.¹⁰

c) *AI in Cancer Detection in Family Medicine*

In the US, cancer causes more than 600K deaths annually. To reduce these deaths, an early detection and treatment of the disease is therefore important.

Hamilton et al. in 2013 noticed that diagnostic delay for cancer appeared to have contributed to about 5,000 to 10,000 additional deaths annually in the UK. Risk assessment tools (RATs) for selecting patient for evaluation of lung and colorectal cancer diagnoses were established to help GPs. The study included 614 GPs who were provided RATs for 2,593 patients with either respiratory (n=1,160) or bowel (n=1,433) related symptoms. In comparison with the preceding six months, 292 additional X-rays produced 47 more diagnoses for lung cancer. Similarly an additional 270 colonoscopies yielded identification of 10 more cancers. Thus the application of RATs based AI produced enhanced diagnostic activity in primary care for additional diagnoses of cancer.¹¹

In 2019, in England an AI based novel diagnostic tool 'C the Signs' that assists in cancer detection was given to 1,000+ GP practices. The AI tool supported in GP consultation for a) advising on what to investigate, and b) referrals the patient may require. In east England, a pilot run of 'C the Signs' demonstrated an amplified cancer detection rate of 6.4% versus 0.21% in non-pilot practices.¹²

d) *AI in Depression in Family Medicine*

Feeling unhappy, having low interest in normal activities, and further comparable symptoms for at least two weeks all can be the signs and symptoms of depression.

Kurian et al.'s work during 2005 and 2006 focused on a clinical trial of primary care facilities in Texas to assess a computerized decision support system (CDSS) which included 55 patients with major depressive disorder (MDD). The physicians utilized CDSS to treat 32 patients while the remainder 23 patients received usual care. The CDSS employed patients saw a appreciably superior symptom decrease, based on the 17-item Hamilton Depression Rating Scale

or HDRS(17), versus patients that received the usual care with a p-value < 0.001.¹³

In 2021, Tanguay-Sela et al.'s research assessed Aifred, a CDSS which utilizes AI to help doctors in choosing treatments for patients with MDD, established on patient characteristics. Twenty physicians (residents in either psychiatry or family medicine) in this study, each had three clinical communications with patients depicting mild, moderate, and severe incidents of MDD. These physicians had availability of the CDSS for their treatment choices. Overall 60% of them professed that the CDSS is a valuable tool in their process of treatment-finalization, with family medicine doctors recognizing the highest utility. In addition, they found the AI tool to be suitable in reviewing treatment choices with patients.¹⁴

e) *AI in Attention Deficit Hyperactivity Disorder (ADHD)*

A person with attention deficit hyperactivity disorder (ADHD) illness has variations in the development of brain and brain activity from a typical brain, which disrupts attention, and the ability to sit motionless. It is important to diagnose patients with signs of ADHD as soon as possible to provide them with efficient treatment.

During 2019-2020, Loskutova et al.'s research analyzed a web-based 'American Academy of Family Physician AdultADHD Toolkit' comprised of tools to help in the identification, management, and healing of adults with symptoms of ADHD. The study included evaluation of 97 primary care and behavioral health care specialists' usage of the Toolkit for the duration of 17 weeks. Various statistical analyses showed that the Toolkit enhanced health care professional's knowledge versus baseline in areas for treatment effects, outcomes, existing ADHD resources with p-value < 0.05 for each. Eighty seven percent of participants acknowledged that the Toolkit tackled most of their needs involved in identification, management, and treatment of ADHD for adults.¹⁵

f) *AI in Mood Disorders in Family Medicine*

Type of primary care patients troubles of mood include a) major and minor depression, b) anxiety disorders, c) dysthymia, and d) bipolar spectrum disorders. These mood disorders result in increased morbidity and deaths. Their early detection and treatment is therefore important.

Nemesure et al.'s work in 2021 focused on utilizing AI to assist primary care professionals in early detection of GAD (Generalized Anxiety Disorder) and MDD (Major Depressive Disorder). The authors applied a new ML pipeline approach which included deep learning to 're-analyze' Electronic health records (EHRs) based information from an observational study of 4,184 undergraduate students undertaking a health screening including a psychiatric (GAD and MDD) evaluation. The model was trained, excluding psychiatric data, with 59 'biomedical' and 'demographic' characters from the

health appraisal, and a set of engineered characters were used for model training. This trained AI model applied to test data yielded 0.73 Area Under Curve (AUC) value, 0.66 sensitivity, and 0.7 specificity for GAD (AUC of 0.67, sensitivity of 0.55, and specificity of 0.7 for MDD).¹⁶

IV. AI IN SPECIALTIES OF FAMILY MEDICINE

a) *AI in Geriatrics*

Geriatrics, the practice of care for older adults, is an important subspecialty of family medicine which focuses on the aging process. Aging in blood and nervous systems can accelerate a person's probability to experience medical complications. Improving the quality of life in elderly population is therefore important.

In 2021 Petrauskas et al.'s research acknowledged that the assessment of a geriatric patient is a time consuming procedure as it comprises of an assortment of questionnaires with some times biased and erroneous patient answers. The authors considered the 'explainable artificial intelligence' (XAI) centered CDSS to evaluate diet-associated elements and to define the possibility of patient's health threats linked with syndromes of a) malnutrition, b) dehydration, c) eating disorders in dementia, and d) oropharyngeal dysphagia. 83 geriatric patients from Lithuania, with diverse nutritional related health circumstances, were analyzed for the four syndromes based on CDSS, and they were compared with the judgements of the doctors attained using standard evaluation approaches. The proposed CDSS proficiently diagnosed diet associated geriatric syndromes with great accuracy of a) malnutrition: 88%, b) dehydration: 87%, c) eating disorders in dementia: 90%, and d) oropharyngeal dysphagia: 88%.¹⁷

Vaiyapuri et al.'s work, in 2021, focused on the monitoring of elderly living in smart homes for accidents such as falls. The authors devised an 'Internet of Things' (IoT) supported fall recognition model utilizing 'optimal deep convolutional neural network' (ODCNN) for smart homes where IoT devices can be used to detect and then capture falls. The falls typically can result in death due to subsequent complications. The model's classifier distinguished between 'fall' and 'non-fall' incidents. If a 'fall' incident is detected, then the smartphone directs an alert to the closest hospital. The model resulted in an accuracy over 99% for both the numerous cameras fall and the UR (University of Rzeszow) fall recognition data.¹⁸

b) *AI in Hospice and Palliative Medicine*

Hospice care is 'comfort upkeep' deprived of healing intent, while palliative comfort care is comfort care that can have curative intent. A family physician with specialty in hospice and palliative medicine delivers care to mitigate the distress felt by patients with 'life-limiting' ailments.

In 2018, Avati et al. explored challenges posed in enhancing access to palliative care as physicians over-appraise patient prospects and there is a lack of supporting staff. The authors using ML and patients' EHR data trained Deep Neural Network in order to forecast death of patients during the succeeding 3 to 12 months. This forecast was updated on a daily basis based on the AI model and was utilized as a decision maker for categorizing patients who could benefit from the palliative care, as the care resource availability is limited. The authors demonstrated AI's application in palliative medicine.¹⁹

Wang et al., in 2019, developed a deep learning algorithm using longitudinal EHRs in order to forecast death risk as a proxy sign for classifying patients with dementia; this is a group who could benefit from palliative care.

This retrospective cohort study included six-month, twelve-month, and 24-month death forecast models which utilized patient demographic information and themes created from clinical notes from a health care delivery system in Boston, Massachusetts. The study included 26,921 patients (60.4% women, mean age, 74.6 years). The models were trained using data from 24,229 patients with a mean age of 74.8 years (60.4% women.) The remaining 2,692 patients' data with the mean age of 75 years (60.6% women) was used for evaluation. The six-month model achieved AUC of 0.978, the 12-month model with 0.956, and the 24-month with 0.943. Their algorithm based on a) patient demographic information and b) clinical notes demonstrated encouraging results in forecasting death among patients with dementia in distinctive time periods.²⁰

c) *AI in Sports Medicine*

A family physicians with expertise in sports medicine focuses in identifying and remedying injuries associated due to sports and exercise. This specialist also helps people with ailments that may have consequences on their well-being and physical performance.

In 2021, Rigamonti et al.'s research focused on fictitious sports injuries analysis using an AI algorithm. The five cases of acute and subacute sport-related injuries were crafted: a) concussion, b) ankle sprain, c) muscle pain, d) chronic knee instability, and d) tennis elbow. The indications of these occasions were submitted into a 'chatbot-guided' app and its results were associated to the pre-defined injuries. The app asked between 25 and 36 questions, requesting photos to explain the issue faced per patient for each of these cases. The cases of a) a mild concussion, b) an ankle sprain, c) a muscle pain in the thigh, and e) the condition of the chronic epicondylitis were all correctly diagnosed individually. However, for a chronic ACL instability the algorithm did not conclude the chronic

characteristic of the pathology but provided a recommendation to see a doctor for further evaluation. The model thus provided an excellent tool, which either diagnoses correctly or provides correct referral to see a medical specialist.²¹

Novatchkov et al.'s, in 2013, evaluated the potential of AI in weight training based on 15 participants performing 3-5 sets (10-12 repetitions) on a leg press machine. The authors utilized pattern recognition procedures for the assessment of exercises performed on training machines. The machines were incorporated with sensors to measure both force and displacement, which were then used to calculate velocity and time periods. These factors as an input to ML methodologies resulted in an automatic evaluation of the workout procedure producing individuals with suitable feedback. The authors' AI model yielded good performance in automating performance evaluation on weight training equipment and giving prompt advice to sportsman/sportswoman.²²

In 2019, Bloomfield et al.'s study focused on assessing patients going through 'total knee arthroplasty' with data acquired from wearable sensors. The authors utilized ML approach to analyze the data to provide and categorize patients into pertinent groups. 68 patients finished instrumented 'timed-up-and-go' examinations pre-operation and also at after two, six, and twelve week post-operation. Wearable sensors based system isolated 55 items for evaluation and an AI algorithm divided patients into differing categories centered on the derived characters. The 68 patients were split into two groups of 46 and 22 with appreciably distinctive test end times of 12.6 seconds and 21.6 seconds respectively with $p\text{-value} < 0.001$. At 12 week post-operation evaluation, 64% of first group enhanced their function, while 63% of the second group showed pre-operative function. The authors demonstrated that wearable sensors can be integrated with functional examinations during medical visits and that ML can deconstruct multifaceted configurations to disclose clinically pertinent factors.²³

d) *AI in Sleep Disorders*

A family physician with an expertise in sleep disorders diagnose and manage medical conditions that arise during sleep, that interrupt sleep, or that are disturbed by interruptions in the 'wake-sleep' cycle. This specialist is proficient in the evaluation and analysis of polysomnography and administration of a 'sleep laboratory.'

In 2020, Goldstein et al.'s work summarized a position statement on application of AI in treatment of sleep disorders. The authors foresee that AI's early application in the sleep medicine facility is the 'assisted scoring' of sleep and related incidents through 'PolySomnoGraphy' or PSG. They recommend possible medical use cases that excel the 'sleep laboratory' and

are projected to expand our knowledge of sleep disorders, and therefore improve patients' health by advancing their sleep care.²⁴

Onyema et al.'s research in 2022 focused on AI modeling of sleep apnea disorder. The data represented 18 patients with apnea syndrome. The AI model demonstrated a substantial association between ECG-BP, ECG-EEG, and EEG-BP. The authors determined that the long-term interaction amongst physiological indicators can assist doctors to appreciate the hazards linked with these interactions and aid in detection of obstructive sleep apnea early.²⁵

e) *AI in Pain Management*

A family physician with a specialization in pain medicine identifies and treats people suffering with acute or chronic pain, or pain related to illness.

In 2021, McGrath et al. work evaluated how in the future AI technology can be integrated in the field of anesthetics. The authors were concerned about how the deep learning models, being built on closed processes, do not offer insights into the connection between input and output data. They worry about if the model were to create "strange" answers in unexpected operating situations. The physicians, in application of anesthetics, do require complete control and therefore will need rule based system.²⁶

Piette et al., in 2022, evaluated if 'AI' propelled 'Cognitive Behavioral Therapy for chronic pain' or if 'AI-CBT-CP' amplified its efficacy due to patient collaborations. The authors utilized 168 patients based 11,133 'AI-CBT-CP' interactions collected over 10 weeks every week. For each patient, the AI model by optimizing a reward function based on a patient's pain related information, chose from three treatments: a) a 15 minute live therapy, b) 45 minute live therapy, and c) asynchronous therapist feedback utilizing an 'interactive voice response' or IVR call. The reward scores jumped from 0.29 at the start to 0.46 during the 100th week with $p\text{-value} = 0.002$. The authors demonstrated that 'AI-CBT-CP' can acquire from experience what medical management modalities work well to enhance patient results and at the same time preserving doctor's time.²⁷

In 2021, Salekin et al.'s research focused on AI model to enhance pain management after surgery in neonatal intensive care units (NICU) including minimizing complications. The authors claimed a proactive approach of pain avoidance/minimization intended at precluding harm to newborns from either post-surgical pain or withdrawal due to opioids. Their AI model was built on vital signs, body and facial motions, and incidences of crying to predict 'time-to-pain' inception subsequent to post-surgical sedation. This prediction would allow a time period preceding the pain inception for easing with either non-narcotic medicines or non-medicinal mediations.²⁸

V. CHALLENGES AND OPPORTUNITIES FOR AI IN FAMILY MEDICINE

There are many obstacles in implementing AI in family medicine which include (a) a readiness of system and data, (b) the possibility for inequity and bias, and (c) the rules of AI. A majority of people do not trust in AI technology, including some of the health providers, as personal connections are more important than computer based tools. Additionally there are major consequences for confidentiality and misuse with utilization of AI. AI by itself could not replace human empathy. In order for AI to be extensively used in family medicine, the family practice physicians need to participate in appropriate plan, strategy, research, and delivery approaches with the technology. Consequently, collaborations between Machine Learning and family practice experts can be effective in both diagnosis and treatment. AI-based technology strengthen family physician's proficiency and improve patient care, while decreasing treatment costs. However, AI-based diagnosis in family medicine is still not commonly used in clinical practices due to the presence of many legal, privacy, and ethical matters.

VI. CONCLUSION

AI has the power to magnify clinical efficiency due to its inclination to manage an enormous quantity of data appropriate for automation. However, personal connections are more important than computer based tools. Therefore, in order for AI to be commonly used in family medicine, the family medicine professionals need to partake in its implementation planning, strategy, research, and distribution methods. AI is not going to replace family medicine physicians; instead it can assist family medicine doctors with intuitions that can streamline healing management. AI with the prospective to advance the accuracy of diagnosing different ailments can assist family medicine physicians in delivering appropriate disease recognition and its consequent treatment.

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GJMR-C Classification: NLM: QY 39



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Biochemical, Cytological and Microbiological Profile of Cerebrospinal Fluids Analyzed at Thedouala General Hospital Laboratory

Baldagai Ndeva ^α, NdaMefo'o Jean Pierre ^σ, Yaba Dana Basil ^ρ & Adiogo Dieudonné ^ω

Abstract- Introduction: To investigate whether biochemical, cytological, and microbiological examinations of CSF could predict infection, thus facilitating therapeutic decision-making at the Douala General Hospital laboratory, a retrospective, cross-sectional, and descriptive study was conducted. Our study population included the biological records of patients who underwent biochemical, cytological and microbiological analysis of cerebrospinal fluid analyzed at the Douala General Hospital laboratory between January 1; 2010, and December 31; 2016, 6years period.

Method: The sampling technique we used was based on the exhaustive consecutive recruitment of all cerebrospinal fluid results analyzed at the Douala General Hospital laboratory that met the inclusion criteria.

Results: Our results showed that 2,097 CSF of the analyzed patients were retained over the period defined by our study. The CSF collected in most cases concerned the pediatric population, 26.47%. The male sex was predominant, with 43.14% of the patients and a sex ratio of 1.1. The number of CSF received per year varies, with a peak in 2014 (18%) of the population with a low in 2012 (12.5%). 87% of the samples received in the laboratory were from inpatients, or 101.61%. Of the data collected, 56.86% were from pediatrics and 26.36% from internal medicine. Most of CSF samples had a clear appearance, 64.82%, followed by hemorrhagic models. One population had 72% low glycorrhaply, with hyperproteinorrhaply in 43.8% of cases. A rate of 65.45% of the data had a leukocyte profile. Among the fungal flora, 65% were dominated by *Cryptococcus neoformans*. As for the bacterial flora, *Streptococcus pneumoniae* represented 98.4%, followed by gram-negative bacteria in 27.8%. In the search for signs of CSF decapitation by initial antibiotic therapy, 0.67% had positive soluble antigens.

Conclusion: Cytological biochemical and microbiological examination of cerebrospinal fluid (CSF) is an emergency, as recovery often depends on early diagnosis. The chemical examination of CSF can help in the diagnosis in some cases; in particular the biochemical and cytological results allow to invalidate or confirm the results of the culture.

Keywords: cerebrospinal fluid, biochemistry, cytology, microbiology, laboratory.

I. INTRODUCTION

Cerebrospinal fluid (CSF) is a clear biological fluid in which the brain and spinal cord are immersed. It is contained in the meninges, more precisely in the subarachnoid space [1]. It circulates in the four cerebral ventricles inside the brain. It is synthesized mainly in the choroid plexus, but also, in the capillaries of the spinal and peri-brain subarachnoid space.

CSF comprises water, protein, glucose, and ions [2]. It usually is sterile and produced from plasma constituents by filtration and active secretion. CSF must provide the central nervous system (CNS) with a constant physicochemical environment to maintain its functions. Its composition is different from that of plasma, although it is close to it [1,3].

However, this composition can be modified in many circumstances associated with neurological disorders. Thus, in the course of pathologies of the meninges and the encephalon, whether infectious, inflammatory, tumoral or immunological, biochemical (glucose, albumin, protein, chlorine) and cytological modifications are observed, as well as the presence of microorganisms (bacteria, viruses, fungal agents, parasites). The analysis of cerebrospinal fluid, which is based on the evaluation of changes in the homeostasis of the environment, is therefore essential for a precise diagnosis of these pathologies.

Conditions affecting the central nervous system are very often life-threatening. This is why CSF examination is carried out in health facilities at different levels of the health pyramid in an emergency context for better patient management, and pathologies associated with changes in this fluid are recognized as the fifth cause of hospitalization and the third cause of infant mortality in Yaoundé, Cameroon [4,5].

CSF examination has several orientations, including the diagnosis of certainty of infectious meningitis, which may be bacterial, viral, parasitic, mycological, or immunological in nature. The quality of care and the patient's prognosis in terms of mortality and morbidity depend on the promptness with which a reliable result is returned to the clinician. To reduce the

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time taken to deliver results, specific tests have been developed to compensate for the expected time taken to deliver results (agglutination tests for *Streptococcus*, *Haemophilus*, and *Neisseria*).

The changing profile of germs and patients with meningitis and immunocompromised patients has led to significant epidemiological variations and thus requires new paradigms. Little data is available on the evolution of the cerebrospinal fluid of patients and the interactions between the different parameters.

As not all test parameters are available at the same time, we proposed to investigate the existence of links between data that can be obtained very quickly and pathogen culture data⁹ to be able to offer reliable diagnostic guidance at an early stage.

The objective of this work is to study the biochemical, cytological, and microbiological profile of cerebrospinal fluids analyzed at the Douala General Hospital. Specifically, the aim is to (a) describe the demographic characteristics of the patients in whom cerebrospinal fluid was analyzed, (b) analyse the cytological, microbiological, and biochemical characteristics of the cerebrospinal fluids, (c) determine the frequency of germs and (d) identify the sensitivity profile of the pathogens to antibiotics.

II. MATERIALS AND METHODS

The study was retrospective, cross-sectional, and descriptive, was conducted at the Douala General Hospital (DGH) in the medical biology laboratory department.

It is a public hospital at the top of the health pyramid in Cameroon, whose missions include the provision of care, research, and teaching. It has 12 departments grouped into hospital and medical-technical.

The work was carried out at the laboratory service, the LBM of the Douala General Hospital, which has eight analysis units. Our study was conducted from 02 January; 2017 to 31 May; 2017 and focused on cerebrospinal fluid analyzed at the laboratory of the Douala General Hospital from 1^{er} January 2010 to 31 December, 2016, i.e. a period of 6 years. The study population consisted of the records of patients who received cerebrospinal fluid analysis at the DGH laboratory during our study period. We included in our study all CSF of patients registered and analyzed at the medical biology laboratory of the Douala General Hospital, during the period defined by our research. Very hemorrhagic samples, coagulated samples, and cerebrospinal fluids qualified as insufficient by the laboratory were excluded from our study.

The sampling technique we used was based on exhaustive consecutive recruitment of all cerebrospinal fluid results analyzed at the Douala General Hospital laboratory meeting the inclusion criteria. The recruitment

was systematic, consecutive, and complete over our study period.

For data collection, we used (a) the register of the laboratory's reception unit from which we obtained information on age, sex and, department of origin; (b) the register of entries and results of the bacteriology unit; (c) the register of results of the current analysis of the biochemistry unit; (d) the data sheets for data collection.

The data collection was done thanks to a pre-established data collection form; it provides information on demographic, cytological, and biochemical data grouped as follows.

- The identification of the patient and the service of origin of the patient's CSF;
- The cytological appearance of the CSF;
- The results of the bacteriological examination;
- Biochemical test results.
- Results of the antibiogram.

The data collection was based on the reception registers where we extracted the patients' information on the date; patient's name; prescriber; collector; carrier; quotation; and invoice number.

Only the date of the day, Age, sex, origin of service, type of analysis, and identification number were retained for this item.

✚ The registers of the bacteriology unit in which the following headings were found: date, names, department, order number, age, sex, examination requested, and results.

The data collected were CSF appearance, WBC count, and WBC count when the number of elements was more significant than five per 3 mm, red blood cells, yeast, bacterial flora, culture, and isolated germs.

The element count was performed on a Malassez cell and observed under a light microscope with an objective of 40. This was a count of the elements (leukocytes, red blood cells, parasites) present in the CSF, and the result was expressed in parts per mm³.

- Cryptococcus testing in the CSF was performed by the India ink test
- The soluble Ag test was carried out by the immunoelectrophoresis technique using the SLIDEX meningitis-kit five from BIOMERIEUX

✚ The biochemistry records were subdivided by date, name, age, sex, parameter, results, and department.

The main variables to be surveyed were the following:

- Proteinorachy expressed in g /L;
- Glucorachy in g/L ;
- chlorurorachy in mmol/

The following assays were used in this study:

- The determination of proteinopathy was carried out by the endpoint colorimetric method with pyrogallol

red combined with sodium molybdate on the semi-manual VISUAL® spectrophotometer from BIOMERIEUX.

- The determination of chlorine was carried out by the potentiometric method described by Nernst, on Roche Cobas C311.
- The determination of glucose in CSF was performed by the hexokinase enzymatic method on Cobas C311 at a wavelength λ of 340 nm.

Thus, all the information collected in the three registers was transcribed on a data sheet which is individual for each patient and has an identification number.

III. RESULTS

All data were recorded and anonymized for analysis using Microsoft Office EXCEL 2010.

The analysis was done using Statistical Package for Social Science (SPSS) version 20 and Stata 11, and their confidentiality was ensured by replacing names with codes.

The chi-square test (or Fisher's exact test) was used for qualitative variables (mean, proportion), and the student's t-test or the Wilcoxon or Mann-Whitney U-test for quantitative variables (mean)

We have retained the value of P below 5% as statistically significant.

During our study, we identified 2121 CSFs of patients who were analyzed at the medical biology laboratory of the GDH. We included 2097 (Figure 1)

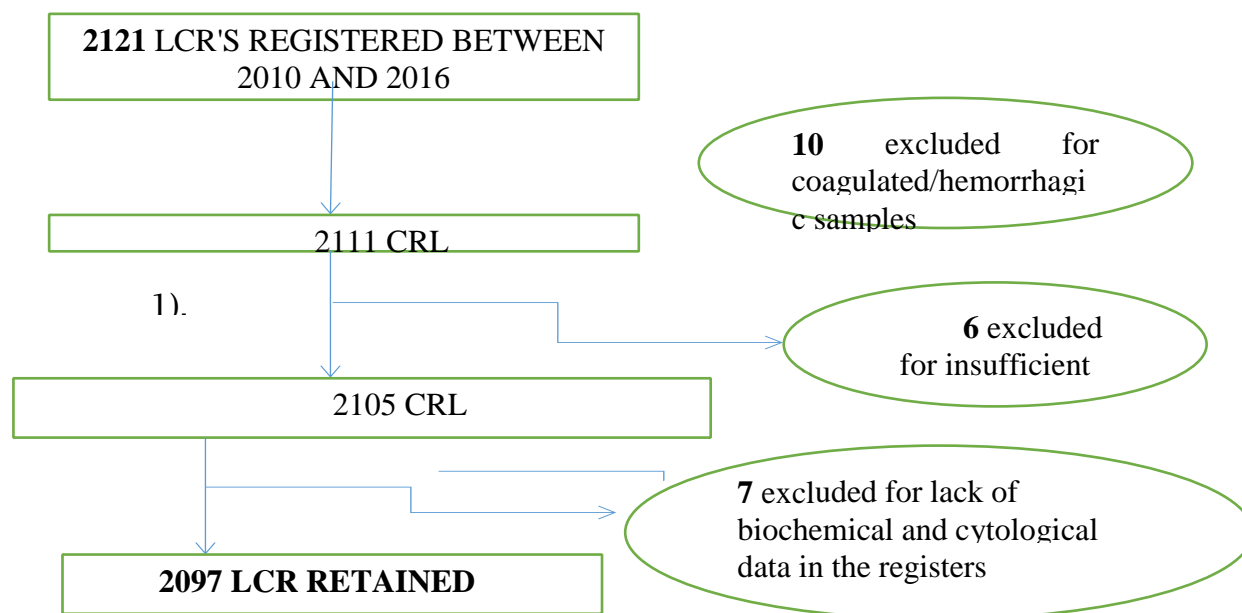


Figure 1: CSF patient recruitment scheme

1. Description of demographic characteristics

CSF distribution of patients by gender

Regarding the distribution of the CSF of the patients according to sex, figure 2 shows that 17.59% of the population did not have information on sex. We note that 43.14% of the population is male, with a sex ratio of 1.1 in favor of males.

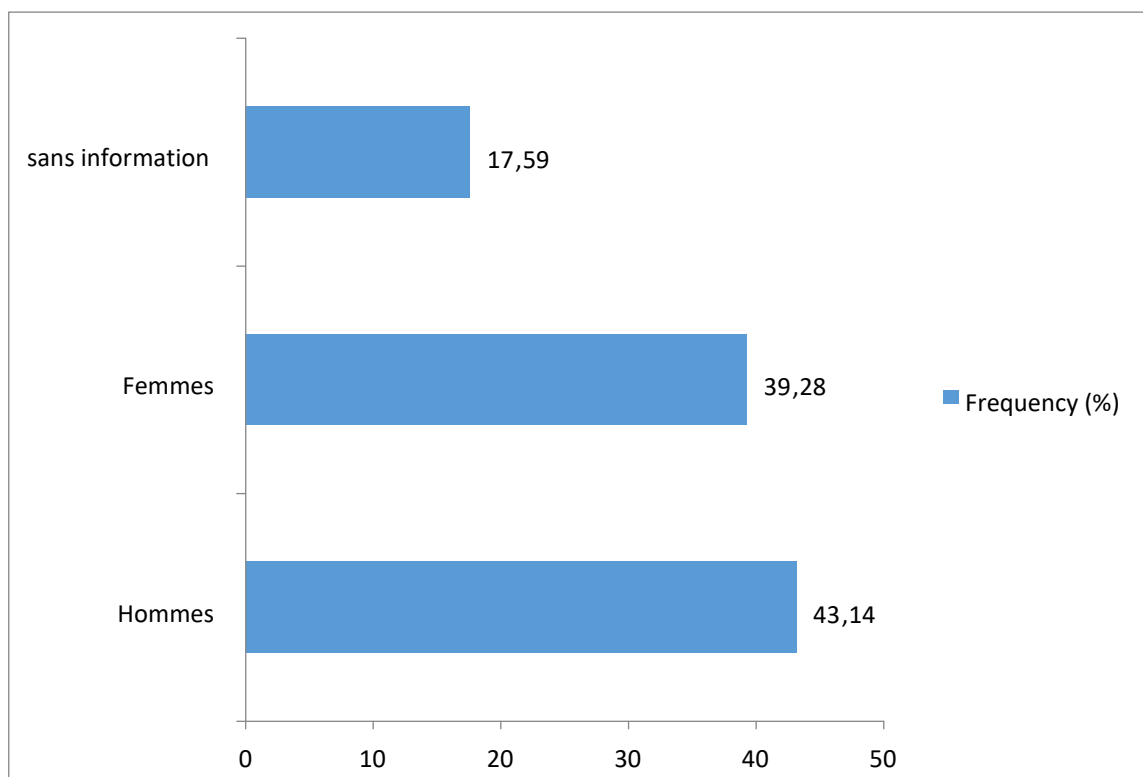


Figure 2: Distribution of CSF according to gender

CSF distribution of patients according to Age

Figure 3 shows that 26.7% of the study population did not have any information on the patient's age, and the subjects in the age group above 15 years were the most represented at 29.7%.

However, most of the study population had a pediatric age of 43.59%.

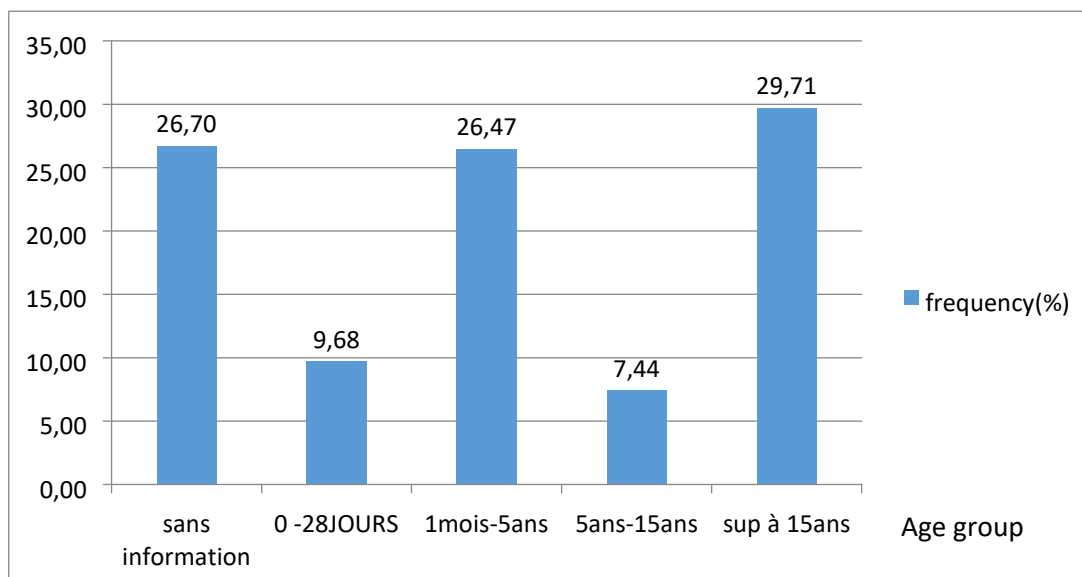


Figure 3: CSF distribution of patients according to Age

Number of CRLs per year

Figure 4 shows that the frequency of CRLs analyzed at the HGD varies according to the year. The lowest analysis rate was observed in 2010. We keep a

peak in 2014 (18%) of the population and a regression in 2012 (12.5%) and 2016.

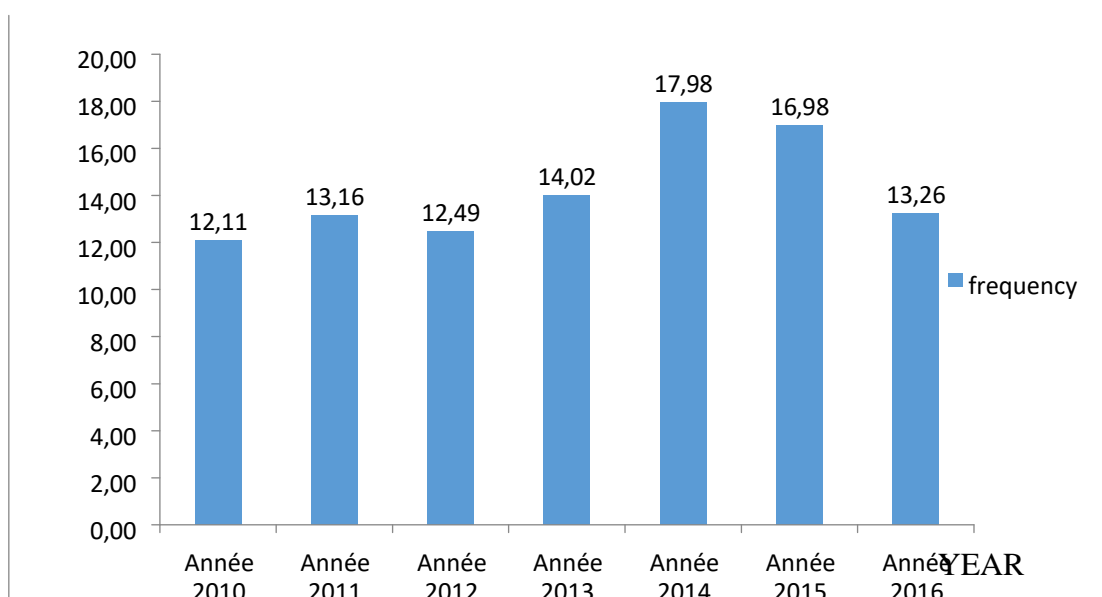


Figure 4: Distribution of CRLs by year

2. Origin of CSF

Figure 5 shows that 87.6% of the samples received in the laboratory came from patients in the DGH, and 10.44% had no information about the source of the CSF.

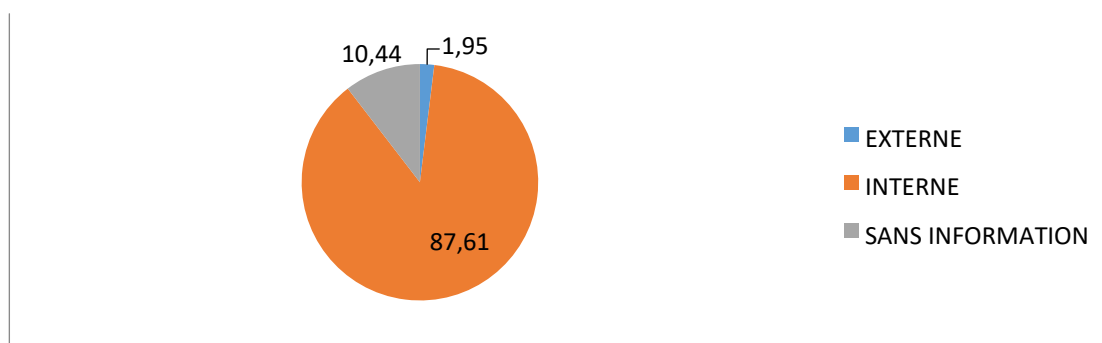


Figure 5: Distribution of CSF by patient type

Distribution of CRLs according to the services of origin

The distribution of patients' CSF according to the different departments shows that the highest rate, 43.8%, is represented by patients from the pediatric department, indicating that the most affected subjects are children. In second place comes the internal medicine department, with a rate of 26.36%, followed by the neonatology department, with a rate of 9.06% (Figure 6).

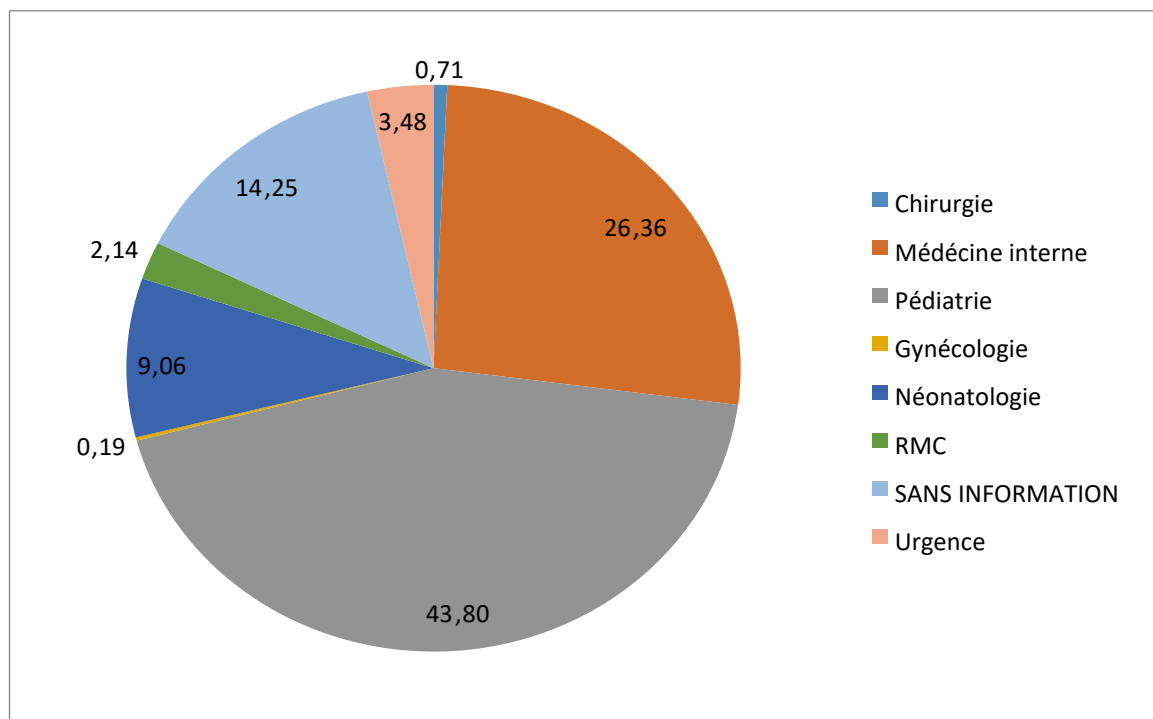


Figure 6: Distribution of CSFs by originating service

3. Biological characteristics of CSF

CSF appearance

The CSF analyzed was 65% clear, followed by hemorrhagic 15%, cloudy 8%, and xanthochromic 7%.

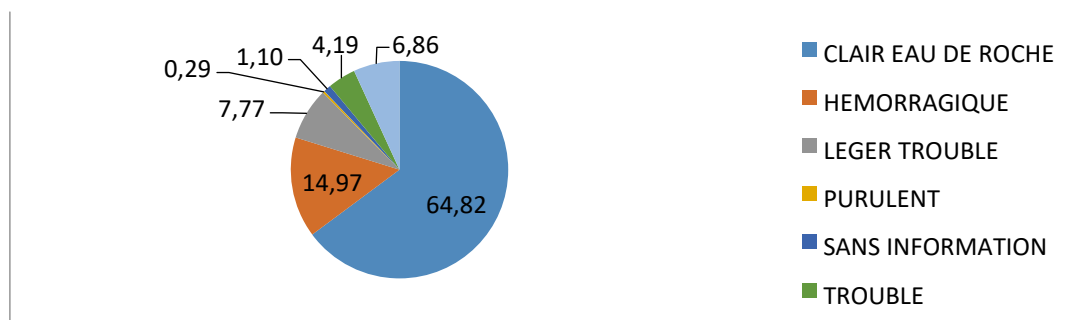


Figure 7: Distribution of CSF appearance

4. Biochemical characteristics

Distribution of CSF according to glycorrhapgy

Table 1 shows that 20.78% had hypoglycorrhapgy, while 79.2% had normal glycorrhapgy.

The mean value was 0.63. The minimum value was 0.14, and the maximum value was 0.65.

Table 1: Distribution of glycorrhapgy in patients

Glycorrhapgy	Workforce	Frequency (%)	Average	Standard deviation
< 0.45 G/L*	435	20,78	0,21	0,14
0.45 - 0.50 G/L**.	1297	61,82	0,6	0,18
> 0.50 G/L	365	17,40	1,23	0,65
Total	2097	100,00		

*hypoglycorrhapgy; **Normoglycorrhapgy

Distribution of CSF according to proteinopathy

According to Table 2, we observed hyperproteinopathy in 43.8% of the cases, i.e., 0.76 of

the overall average proteinopathy. The minimum value was 0.067 and, the maximum was 3.43.

Table 2: Distribution of CSF analyzed according to proteinopathy

Proteinopathy	Workforce	Frequency (%)	Average value	Standard deviation
< 0.20 G/L*.	510	24,36	0,11	0,067
	668	31,84	0,33	
	919	43,80	1,45	
Total	2097	100,00		
0.20 - 0.45 G/L**.				0,086
> 0.45 G/L***				3,43

*hypoproteinopathy; **normoproteinopathy; ***hyperproteinopathy

Distribution of CSF according to chlorurorachy

Regarding the distribution of CSF according to chlorurorachy, 31.50% of the study population showed a decrease in chlorurorachy, as shown in Table 3.

Table 3: Distribution of CSF according to chlorurorachy

Chlorurorachia	staff	frequency
No response	2	0,10%
< 120 mmol/L*.	1098	31,50%
120-130 mmol/L	982	46,80%
> 130 mmol/L	15	0,70%
TOTAL	2097	100%

*Hypochlorurorachia; ** Normochlorurachia

5. Characteristics cytological.

Distribution of the CSF population according to the leukocyte profile

We note from Table 4 that 22.16% of CSF analyzed had more than five elements.

Table 4: Distribution of CSF according to leukocyte profile

Leukocyte value	Number of employees(n)	Frequency (%)	average value	Type deviation
< 5 elements /mm3	1632	77,84	0,65	1,764
> 5 elements /mm3	553	22,16	441,63	1,28
Total	2097	100,00		

5.1 Distribution of the CSF population according to the presence of red blood cells

We observed red blood cells in 18.83% of the liquids collected and sent to the laboratory; 81.17% did not contain red blood cells (figure 8).

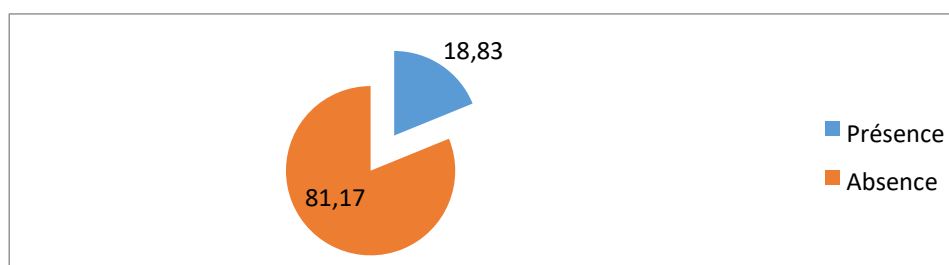


Figure 8: Distribution according to the presence of red blood cells

6. Characteristic microbiological

Table 5 shows that from 2010 to 2016, 96 germs were isolated from the CSF received, i.e., a proportion of 31.6% of positive cultures.

We note a significantly higher frequency in 2015 (6.16%), i.e., 22 germs were isolated, followed by 2013 (6.12%) and 2010 (5.12%); 2012 was the year in which fewer germs were isolated (2.67%).

Table 5: Distribution of positive CSF cultures by year

Number of CRLs/year	Number of employees(n)	Number of CRLs/year	% CSF positive
Year 2010	13	254	5,12
Year 2011	8	275	2,9
Year 2012	7	262	2,67
Year 2013	18	294	6,12
Year 2014	15	377	3,97
Year 2015	22	357	6,16
Year 2016	13	278	4,67
TOTAL	96	2097	4,57

Distribution of isolated species

According to Table 6, the types of germs isolated were fungal and bacterial, and no viral germs were isolated.

The fungal flora was dominated by the *cryptococcus neoformans* germ, i.e., 63.54%.

The bacterial flora represented 35.42% dominated by gram-positive cocci, including *Streptococcus pneumonia* (17.71%) and 13.04%, gram-negative bacteria.

Table 6: Strains isolated from CSF

Type of germs isolated	Number of employees(n)	Frequency (%)
<i>Candida albicans</i>	1	1,04
<i>Cryptococcus neoformans</i>	61	63 ,54
<i>Enterobacter</i>	2	2,08
<i>Escherichia coli</i>	2	2,08
<i>Haemophilus influenzae</i>	1	1,04
<i>Klebsiela</i> sp	2	2,08
<i>Listeria monocytogenes</i>	1	1,04
<i>Neisseria meningitidis A</i>	1	1,04
<i>Neisseria meningitidis B</i>	3	3,13
<i>Pseudomonas sp</i>	2	2,08
<i>Staphylococcus aureus</i>	2	2,08
<i>Streptococcus agalactiae</i>	1	1,04
<i>Streptococcus pneumoniae</i>	17	17 ,71
Total	96	100,00

The search for soluble antigens in the CSF was positive in 14 cases (0.67%), and the majority of tests (99.14%) were negative (Table 7).

Table 7: Distribution of CSF analyzed by soluble antigen result

	Number of employees(n)	Frequency (%)
Negative	2080	99,14
Positive	14	0,67
No information	3	0,19
Grand total	2097	100,00

Distribution according to soluble antigens

Table 8 shows that of the soluble antigens identified, 10 (0.48%) were associated with *Streptococcus pneumoniae*, followed by *Neisseria meningitidis* (0.15%).

Table 8: Germs identified after soluble antigen test

Germs identified after soluble antigen test	Number of employees(n)	Frequency (%)
<i>Haemophilus influenzae</i>	1	0,05
<i>Neisseria meningitidis A</i>	1	0,05
<i>Neisseria meningitidis B</i>	2	0,10
<i>Streptococcus pneumoniae</i>	10	0,48
<i>Sterile CSF</i>	2078	99,5
<i>No information</i>	6	0,29
Total	2097	100,00

Distribution according to flora type

Of the fungal agents encountered, a total of 62 were identified, with a predominance for *Cryptococcus neocons*, followed by *Candida Albicans* (Table 9).

Table 9: Distribution of CSF analyzed according to the yeast isolated

Distribution according to the yeast isolated	Number of employees(n)	Frequency (%)
<i>Candida Albans</i>	1	0,05
<i>Cryptococcus neoformans</i>	61	2,91
<i>Not observed</i>	2032	96,85
<i>No information</i>	3	0,19
Grand total	2097	100,00

Table 10 shows that the bacterial culture isolated 0.86% of gram-positive cocci, followed by gram negative bacilli (0.38%). This shows a low population of GC negatives and a higher population of BGN.

Table 10: Distribution of CSF analyzed according to bacterial flora

Distribution according to bacterial flora	Number of employees(n)	Frequency (%)
BG -*	10	0,38
CBG -**	2	0,14
CG -***	4	0,28
CG +****	20	0,86
Nobs*****	2058	98,38
No information	3	0,19
Grand total	2097	100,00

BG -*: gram-negative bacilli; CBG -**: gram-negative cocci; CG -***: gram-negative cocci CG +**** gram-positive cocci; Nobs*****: Not observed

Distribution of germs isolated by age group

Concerning the distribution of isolated germs by age group of the population, we note, according to Table 11, that the age group above 15 years is the most

dominant, with 10.93% of positive CSF, followed by the pediatric population. The 5 to 15-year-old people had 3.6% positive CSF. The 0 to 5-year-old people had a positivity rate of 2%.

Table 11: Distribution of germs isolated by age group

Age groups	Number of employees(n)	Isolated germs	Frequency (%)
0-28 days	291	5	2,06
1 month - 5 years	556	11	1,98
5-15 years old	195	7	3,62
over 15 years	622	69	10,93
No information	560	4	0,5
Total	2097	96	4,58

Regarding the distribution according to age and species, Table 12 shows that the 0 to 28-year-old population shows a wide dispersion of the isolated

germs. In the population from 1 month to 5 years and up to 15 years, a predominance of *streptococcus pneumonia* observed.

Table 12: Age and species distribution

Type of germs isolated	0-28 days	1 month-5 years	5-15 years	Sup 15years	Without information
<i>Candida albicans</i>	0	0	0	1	0
<i>Cryptococcus neoformans</i>	0	0	0	61	0
<i>Enterobacter</i>	1	1	0	0	0
<i>Escherichia coli</i>	1	0	0	1	0
<i>Haemophilus influenzae</i>	0	1	0	0	0
<i>Klebsiella</i>	0	1	1	0	0
<i>Listeria monocytogenes</i>	0	0	0	1	0
<i>Neisseria meningitidis A</i>	1	0	0	0	0

<i>Neisseria meningitidis B</i>	1	1	1	0	0
<i>Pseudomonas sp</i>	0	0	0	2	0
<i>Staphylococcus aureus</i>	0	1	1	0	0
<i>Streptococcus agalactiae</i>	1	0	0	0	0
<i>Streptococcus pneumoniae</i>	0	6	4	4	3
Total	5	11	7	69	4

Table 13 shows that the germs separated were more frequent in female subjects.

Table 13: Distribution of germs separated by gender

Overall distribution of infected CSF by gender	Number	Number of employees(n)	Frequency (%)
Male	904	41	4,53
Women	824	44	5,34
without information	369	11	2,98
Total	2097	96	

a. *Susceptibility profile of isolated BGN to anti-infective agents* According to figures 8 and 9, we observe a predominant sensitivity to the carbapenem family of molecules concerning gram-negative bacilli (BGN), with in particular 17.31% for imipenem, and 9.62% for meropenem Followed by the fluoroquinolone family with

respect to the sensitivity of the germs isolated to anti-infectives.

On the other hand, figure 9 shows that the resistance rate to BGN molecules of the beta-lactam family is increasing, with a rate of 12.5% for ticarcillin, followed by sulphonamides. 6,62%

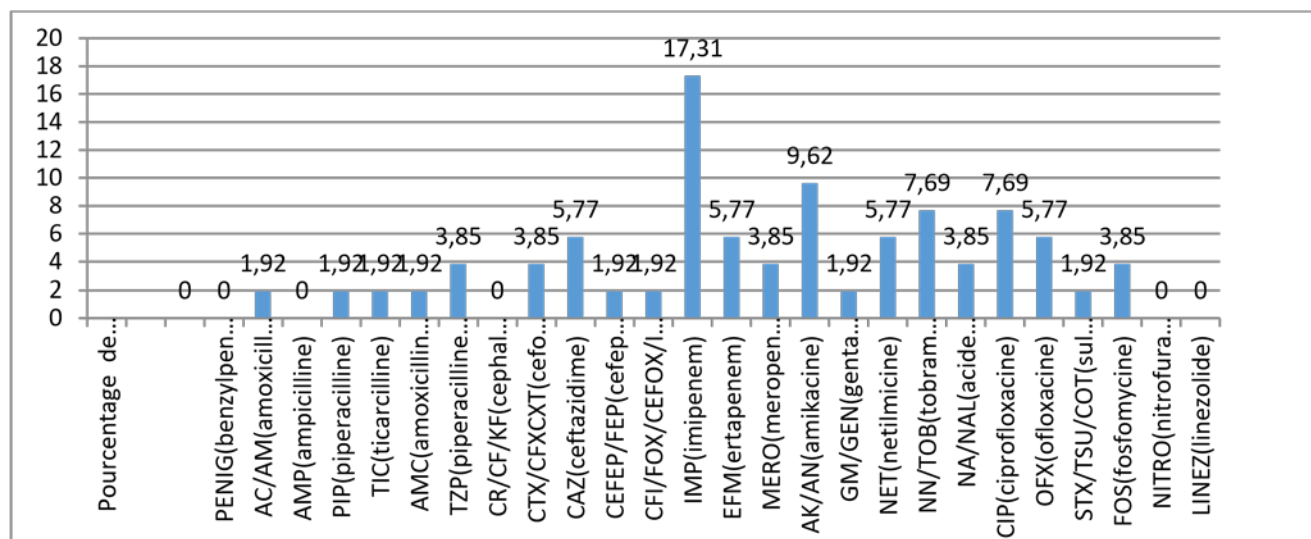


Figure 8: Susceptibility profile of BGN to anti-infective agents

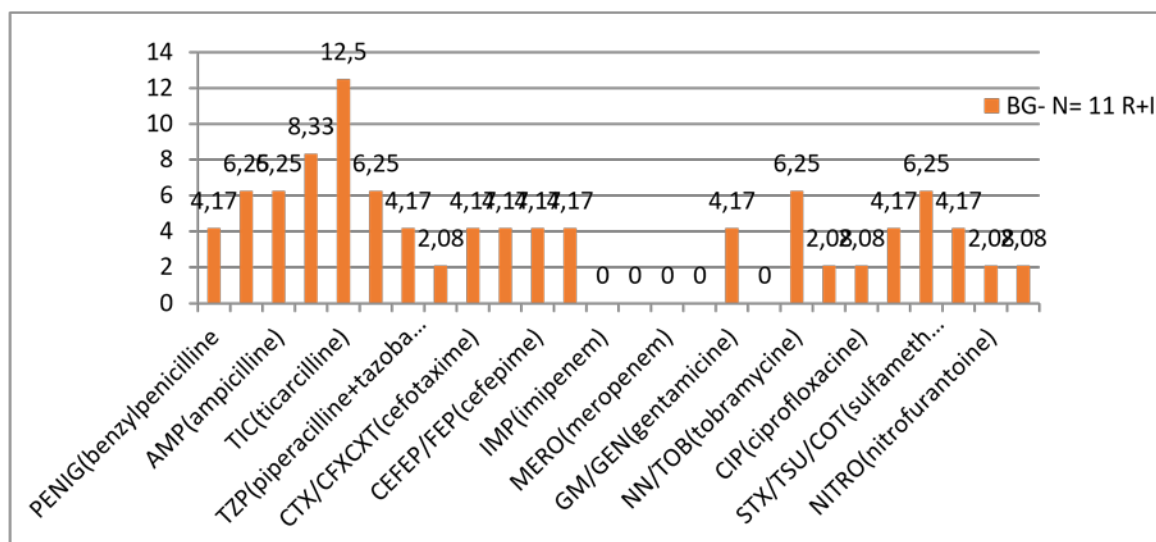
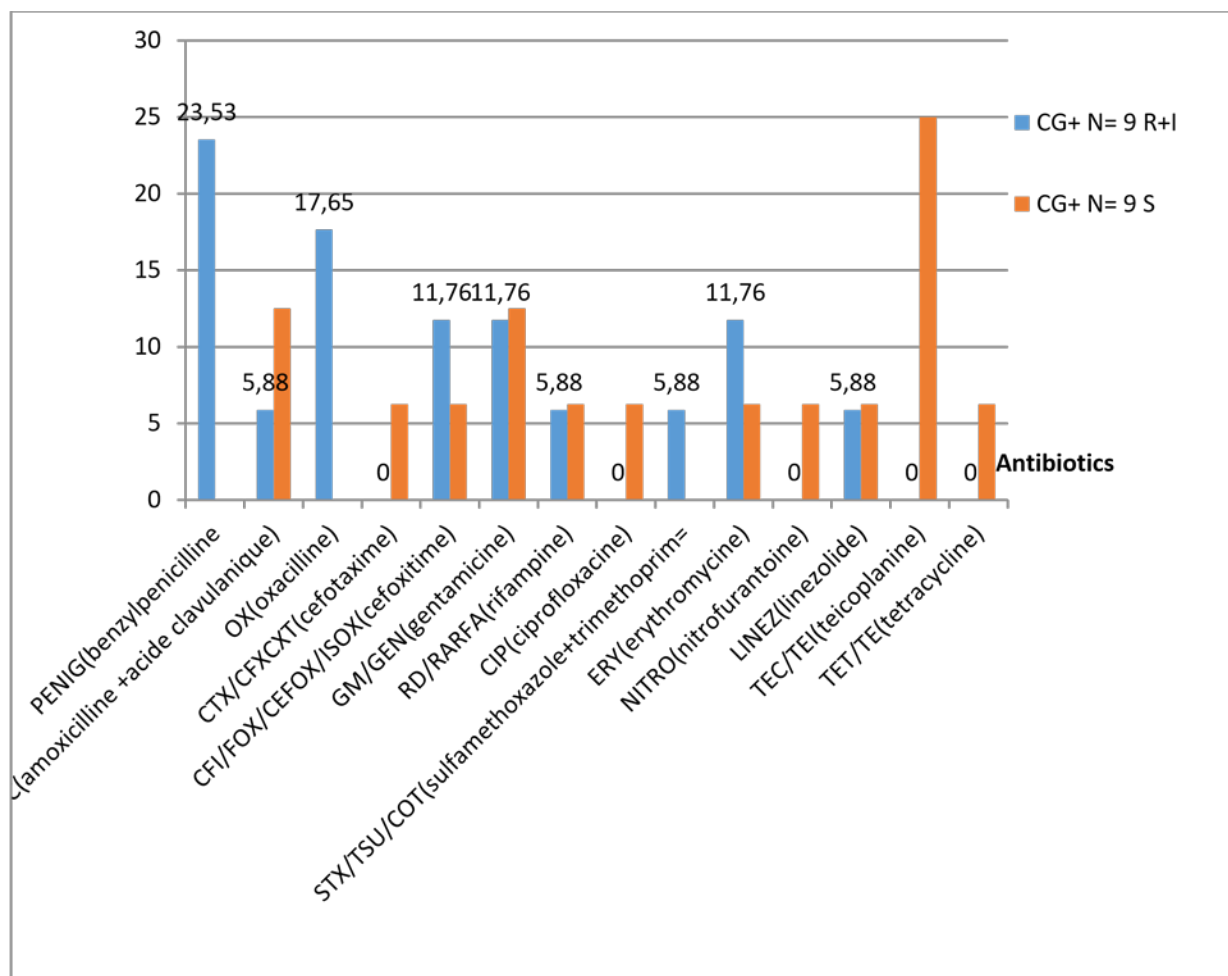


Figure 9: Resistance profile of BGN to anti-infective agents

BGN: gram-negative bacillus; N: number; R+I: resistant/intermediate

Figure 10 shows that penicillins for peniG and first-generation cephalosporins show marked resistance to the molecules tested. However, the glycopeptides

show a better sensitivity of 25% for teicoplanin, followed by C3G.



CG+: gram-positive cocci; S: sensitive

Figure 10: Antibiotic susceptibility and resistance profile for GC+.

7. Associations

a. Cellular profile according to germs

Enterobacteriaceae infections showed the highest average leukocyte count (5054-7125), followed

by streptococci (1906-3100); Neisseria showed a low cell count, according to Figure 11.

The germ cell profile shows a statistically significant relationship with $p = 0.0001$

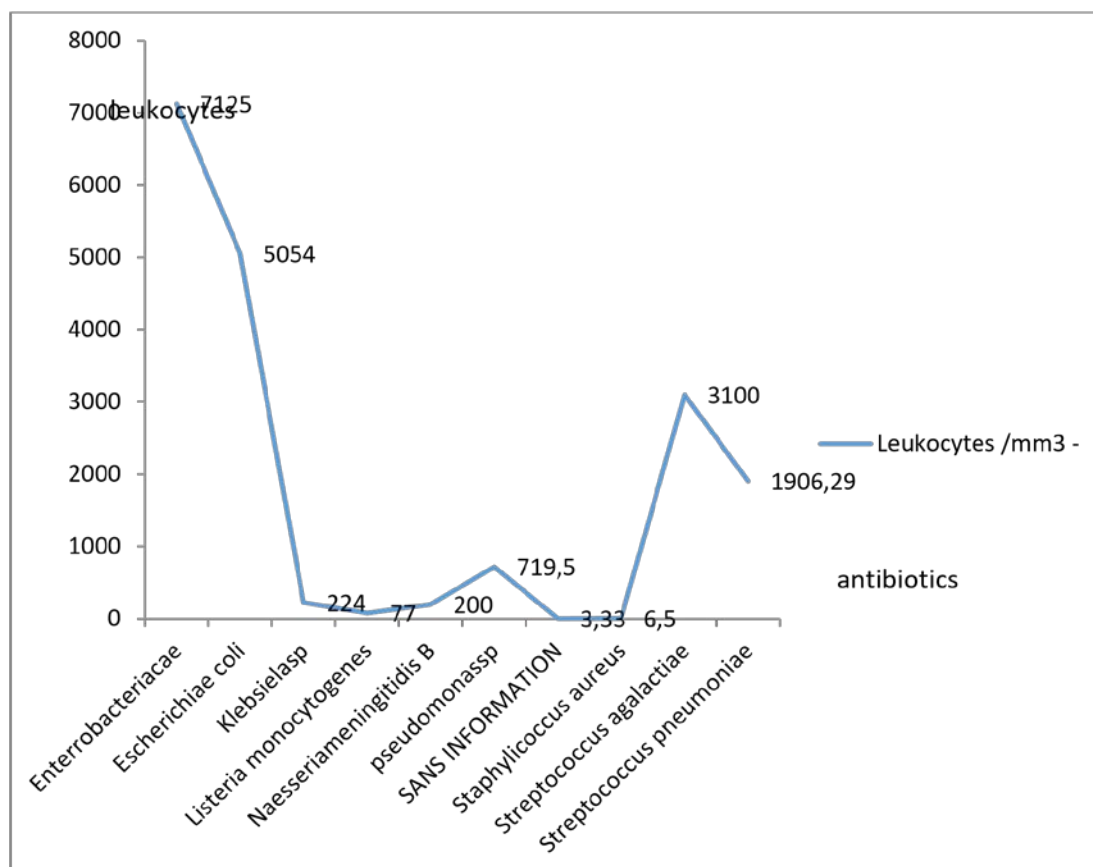


Figure 11: Average leukocyte values according to germs

b. Biochemical profile according to the germs

In Figure 12, we observe that the proteinopathy is high in enterobacteria infections (1.64-2.19g/L), followed by streptococci (2.31-2.34g/L). This implies that enterobacteria have a long evolution and a late management.

For Neisseria and Listeria, proteinopathy was not detectable, which may be related to early diagnosis. This justifies the non-significance of the P-value, $p = 0.8465$ for the results obtained.

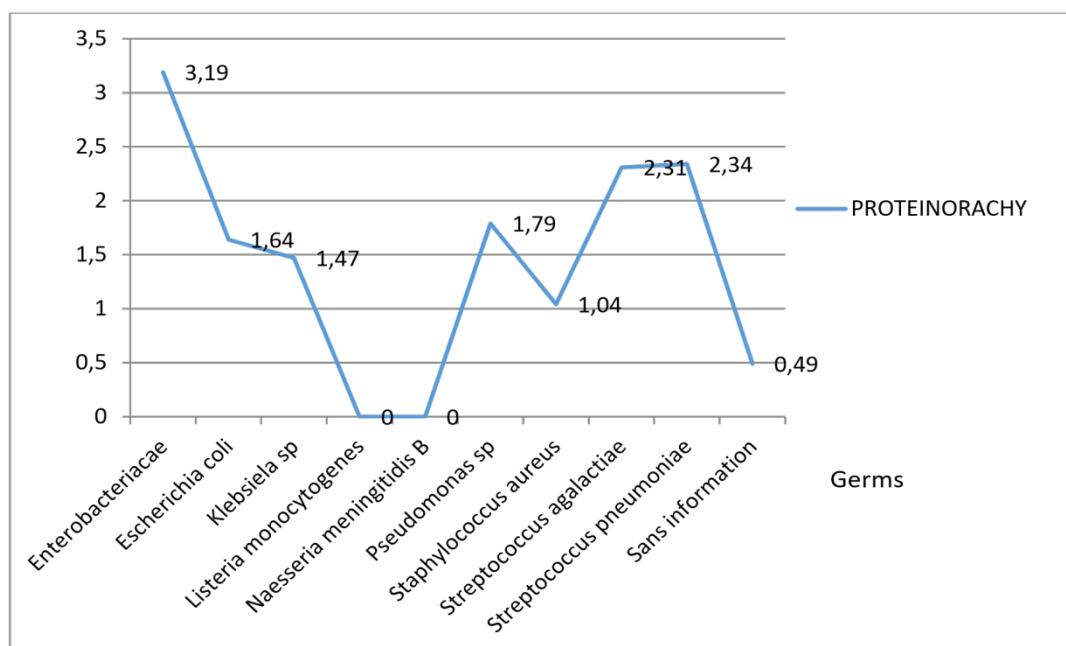


Figure 12: Average number of germs isolated as a function of proteinopathy

Figure 13 shows that glycorrhaphy is low in the vast majority of cases. It is customary in cases of identification of *Klebsiella*, *streptococcus aureus* With a highly significant P-value $p = 0.0156$.

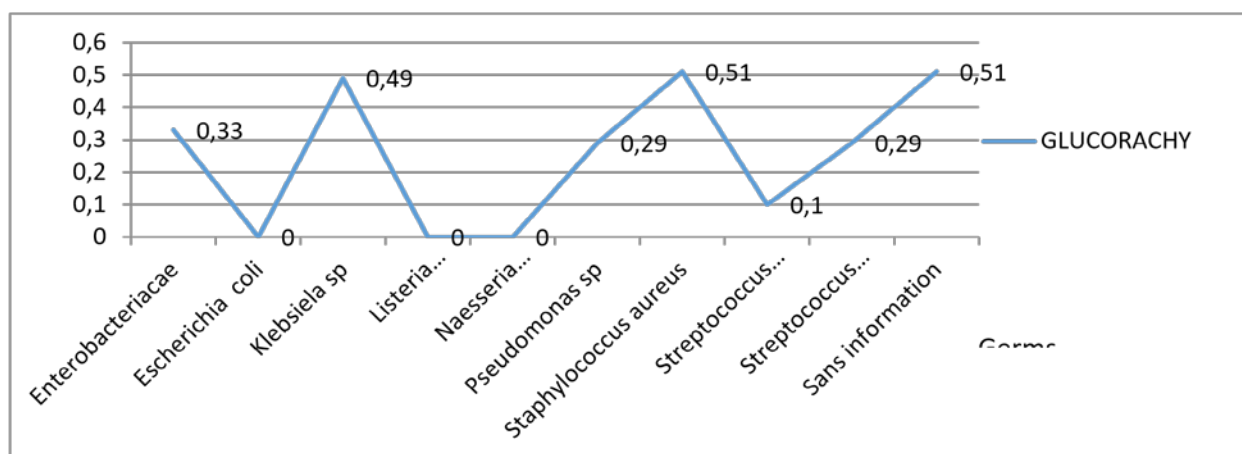


Figure 13: Average number of germs isolated as a function of glycorrhaphy

During bacterial infection, the cell profile is granulocytic with a high cell count (2148 cells on average), a proteinopathy greater than 1.85g /l, and a low glucorachy (table 13).

During fungal infections, the cellularity is low, with an average of 80 elements per mm³, the proteinopathy is high, and the blood glucose level is less than 0.84g/l

Table 13: Relationship between pathogen type-cell distribution and biochemical parameters

	Leukocytes of NP* Elts**/mm 3	Protein g /l	Glucose g/l
Bacteria	2148,95	1,85	0,26
Fungi	80,21	0,84	0,63
Remaining	97,76	0,84	0,62

PN: polynuclear; Elts: elements

IV. DISCUSSION

Our study population was predominantly male, with a frequency of 43.14% against 39.28% for the female sex, i.e., a sex ratio of 1.1. However, gender is not a risk factor for neuromeningeal diseases.

Concerning the distribution of CSF according to sex, 17.59% of the population did not have information on sex, and 26.7% of the study population did not have information on patient's age. The work of De Fondat et al. in 2006 in France showed that between 5 and 20% of the samples transmitted could be non-compliant and that transcription or labeling errors were frequent [26].

During our study, we observed that 26.7% of the CSF analyses were performed on children aged 1-5 years. At the same time, we could establish that 43.8% of the CSF analyzed came from the pediatric ward. Indeed, this could be explained by the fact that in current practice, lumbar puncture is prescribed in emergencies to rule out the risk of meningitis, whose complications can occur in neonatology [26].

In second place were CSF samples from the internal medicine department, with a rate of 15.68%. This could be explained by the fact that this department is specialized in the management of infectious pathologies such as HIV-AIDS, tuberculosis, neuromeningeal cryptococcosis, or lymphoproliferative homeopathy.

Microbiological examination of the CSF

• Macroscopic examination of the CSF

The macroscopic examination is the first step in the analysis of a CSF, as the appearance of the CSF is characteristic of the type of germ involved.

During our study, we noted that 65% of the CSF analyzed was clear, 15% was hemorrhagic, 8% was cloudy, and 7% was xanthochromic.

A clear CSF may or may not be suggestive of illness. In the case of disease, the germs involved may be bacteria such as *Listeria monocytogenes*, *Mycobacterium tuberculosis*. Fungi with *Cryptococcus neocons*, enteroviruses in viral cases, or parasites [27].

The hemorrhagic appearance may be associated with trauma, hemorrhagic illness, vascular abnormality, and deficit in sampling quality [28,29]. However, reports of macroscopic appearance are variable and depend on the visibility of observers [30].

• Biological data

In our study, we had 20.78% of glycorachy below the reference value, taking into account that glycorachy represents 60% of blood glucose, hypoglycemia can also be reflected by; a hypoglycorachy [31]. The occurrence of hypoglycorrhagia could result in a bacterial infection.

High proteinopathy of neonates with a higher proteinopathy value than the reference value of 43.8%.

From the data used, 22.16% had CSF with more than five cells per mm³ of the hemorrhagic CSF will increase the number of cells per mm³.

Also, 65.45% of the population had a lymphocyte-like leukocyte profile, thus pointing to a viral origin condition with normal mean glycorachy and high proteinopathy up to 0.84g/l, low chlorurorachy.

Of the predominantly granulocytic fluids, the glycorrhaphy was 0.63 on average, which could be explained by early treatment combined with late collection and therapeutic glucose intake.

The mean proteinopathy is around 1.68g/l. It is higher than in the lymphocyte profiles.

• Prevalence of germs

The cell count allowed differentiation between a bacterial and viral profile. A significant predominance of polynuclear cells is usually observed in bacterial identifications, whereas it is lymphocytic in viral conditions. From the culture results, it is observed that the majority of CSFs were negative, with a rate of 97.23%, while positive cultures represented only 2.77%. In the search for signs of decapitation by initial antibiotic therapy, 0.67% (14) was positive. This is related to antibiotic therapy administered before lumbar puncture.

• Research on the frequency of germs

A total of 96 pathogens were identified. A proportion of 65% of 62 fungi overwhelmed by cryptococci 98.4%. Bacterial germs were dominated by the isolation of *Streptococcus pneumoniae* species at 47%, followed by gram-negative bacteria at 27.8%.

The isolation of cryptococci in the internal medicine department is explained by the many immunocompromised patients.

Pneumococcus was found to be the primary bacterial infectious agent, which is expected (32.5%), group B streptococcus (5.8%), and Haemophilus influenza (3.2%). These results are contradictory with studies conducted by Levy et al. in France, where group B streptococcus predominates in patients over 28 days and under two months of age (49.4%) and pneumococcus in children aged 2 to 12 months (45.2%) [32].

The low presence of meningococci is explained by the fact that we are not in the meningococcal meningitis belt and the compulsory vaccination program primarily for the pediatric population [32].

• Cellular profile of glucose as a function of germs

Bacterial infections will be associated with polynuclear hyperleukocytosis with hypoglycorachia and hyperproteinemia.

While fungal infections we obtained from our results a less frank hypoglycorrhaphy, which is related to the inflammatory reaction expected in these types of patients, the other pathogens are opportunists, not true pyrogens.

• Germ profile

Enterobacteriaceae represented high cellularity, low glycorrhaphy, and high proteinopathy, which is contradictory to the literature data, as they are non-pyogenic germs; this type of reaction may be associated with a delay due to management.

Staphylococci, which are pyrogens, are associated with high cellularity, hypoglycorrhaphy, and high proteinorrhaphy profiles in agreement with expected data from the literature. For *Neisseria* and *Listeria*, the proteinopathy was undetectable, which might be related to a high diagnostic precocity.

The sensitivity profile of the germs could not be discussed due to the small number of strains isolated per species. This does not allow an opinion to be formed.

V. CONCLUSION

Analysis of cerebrospinal fluids received at the Douala General Hospital shows a low frequency of pathogen isolation and, among the pathogens isolated, a predominance of fungal agents of the genus *Cryptococcus*. With regard to bacterial agents, *Streptococcus pneumoniae* was the most represented pathogen.

Bacterial infections were associated with hypercellularity, hypoglycorachia, and hyperproteinorrachia.

For fungal agents, the number of cells was lower with normal glycorrhaphy and a low elevation of the proteinorrhaphy.

From the above, it might be possible to predict the microbiological result from the biochemical and cytological parameters with good correlation.

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- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

- a) A title which should be relevant to the theme of the paper.
- b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
- c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
- d) An introduction, giving fundamental background objectives.
- e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
- f) Results which should be presented concisely by well-designed tables and figures.
- g) Suitable statistical data should also be given.
- h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

- i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
- j) There should be brief acknowledgments.
- k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.



FORMAT STRUCTURE

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, "What words would a source have to include to be truly valuable in a research paper?" Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.



Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

PREPARATION OF ELETRONIC FIGURES FOR PUBLICATION

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

TIPS FOR WRITING A GOOD QUALITY MEDICAL RESEARCH PAPER

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.



6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.



20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium through which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

INFORMAL GUIDELINES OF RESEARCH PAPER WRITING

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.



Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.



The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.



Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."



Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

THE ADMINISTRATION RULES

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

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Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.



CRITERION FOR GRADING A RESEARCH PAPER (COMPILATION)
BY GLOBAL JOURNALS

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	A-B	C-D	E-F
<i>Abstract</i>	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
<i>Introduction</i>	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
<i>Methods and Procedures</i>	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
<i>Result</i>	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
<i>Discussion</i>	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
<i>References</i>	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring



INDEX

A	S
Assortment · 22	Sebacous · 8, 9, 10, 12, 13, 14, 15
C	
Causative · 6	
Coercive · 14	
Confounding · 11	
Covalently · 9	
D	
Disseminated · 1	
E	
Engulfment · 11	
F	
Fatality · 6	
Fictitious · 23	
H	
Hepatic · 3, 5, 9	
Hibernation · 8	
I	
Inception · 24	
P	
Persistent · 1	
R	
Relapse · 1, 3	
Relipidation · 12	



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