„CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST

DOCTORAL SCHOOL

MEDICINE

CLINICAL AND EVOLUTIONARY PARTICULARITIES OF ENT PATHOLOGIES IN PATIENTS WITH ACUTE INFECTIOUS DISEASES

- ABSTRAT OF DOCTORAL THESIS -

Ph.D. Coordinator:
Assoc. Prof. Dr. HAINĂROȘIE RĂZVAN

Doctoral candidate:
PLEȘCA VLAD-ȘTEFAN

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Summary of the Doctoral Thesis

" CLINICAL AND EVOLUTIONARY CHARACTERISTICS OF ENT PATHOLOGIES IN PATIENTS WITH ACUTE INFECTIOUS DISEASES"

The doctoral thesis is composed of two parts:

1. The general part, consisting of two chapters, presents general information about acute otic and sinus pathologies and the involvement of various infectious agents that can cause these conditions or modulate their progression.
2. Personal contributions, representing the results of three studies conducted during the doctoral research.

General Presentation

Chapter 1. Defining characteristics of ENT pathologies

In the first chapter, I briefly highlighted the main areas of study in otorhinolaryngology (ENT) and cervicofacial surgery (CFS), emphasizing the importance of studying pathologies in this medical specialty. Special emphasis was placed on presenting the classification of acute otitis.[1] I addressed the most important and recent data regarding the pathophysiological mechanisms and therapeutic management of these conditions. Similarly, I presented data on acute rhinosinusitis, considering the latest classifications [2], diagnostic methods and therapeutic strategies. Additionally, I presented the evolutionary stages of the development of the paranasal sinuses to provide a better understanding of the conditions analyzed. [3]

Chapter 2. Particularities of ENT pathologies in the context of acute infectious diseases

In this chapter, I analyzed the importance of monitoring and maintaining the health of the nose, throat, and ears, as these regions play a role in mediating defense functions against pathogens. I discussed the impact of acute infectious diseases in the ENT sphere and the major challenges posed by these conditions due to the wide spectrum of clinical presentations they generate. I presented brief, updated information about influenza virus

and SARS-CoV-2 infections, clearly, concisely, and up to date illustrating the ENT complications they can cause, either directly or indirectly by altering the immune response. Among bacterial infections with a major impact on the ENT sphere, I detailed the impact of *Streptococcus pneumoniae* infection.[4] I presented recent data on the epidemiology, clinical features, and management of pneumococcal infections in the ENT sphere. At the same time, I highlighted the importance of vaccination in the prevention of acute otitis and sinusitis. Additionally, I considered it useful to present ENT conditions (acute otitis/acute sinusitis) in a specific group of individuals, namely people living with HIV. I highlighted the most common forms of ENT conditions in this population group and summarized recommendations for their management, emphasizing the role of the multidisciplinary team. Finally, I addressed the importance of telemedicine, artificial intelligence, and personalized management in treating ENT pathologies. [5–7]

Personal Contributions

Chapter 3. Aim, Objectives, and General Study Planning

The primary aim of the current doctoral thesis was to extensively identify and characterize the clinical and evolutionary particularities of patients hospitalized with acute otitis and acute sinusitis in an infectious diseases' hospital, with the goal of improving the management of patients evaluated and cared for outside of ENT centers.

The objectives derived from the main aim of the study are:

- O1.Demographic characterization of the population hospitalized with acute otitis and/or acute sinusitis in an infectious diseases' hospital;
- O2.Identification of the types of otitis and sinusitis among hospitalized patients;
- O3.Identification of the clinical and evolutionary particularities of acute otitis/acute sinusitis in the paediatric population;
- O4.Identification of the clinical and evolutionary particularities of acute otitis/acute sinusitis in the adult population;
- O5.Characterization of the epidemiological and etiological context of otic and sinus involvement;
- O6.Quantification of the clinical and evolutionary impact of influenza virus infections in the development of acute otitis/acute sinusitis;

- O7.Identification of the particularities of acute otitis/acute sinusitis in immunocompromised hosts with HIV infection.

To achieve the aim and objectives, three studies were conducted as follows:

- Objectives O1, O2, O3, O4, and O5 were achieved through Study 1, titled "Incidence and particularities of acute otitis and sinusitis in hospitalized patients."
- Objective O6 was achieved through Study 3, titled "Impact of influenza virus infections on the development of acute otitis and sinusitis – clinical and evolutionary aspects."
- Objective O7 was achieved through Study 2, titled "Hospitalization of HIV-infected patients for acute sinusitis and otitis."

The specific methodologies for each study are detailed in the corresponding chapters. All studies were conducted at the National Institute of Infectious Diseases (INBI) "Prof. Dr. Matei Balș" in Bucharest. INBI "Prof. Dr. Matei Balș" is one of the most prestigious medical institutions in Romania, specializing in the diagnosis, treatment, and research of infectious diseases.

Chapter 4. Study 1 – Incidence and Particularities of Acute Otitis and Sinusitis in Hospitalized Patients

We conducted a retrospective study among cases hospitalized at the National Institute of Infectious Diseases "Prof. Dr. Matei Balș" that were diagnosed with acute otitis (AO) and/or acute sinusitis (AS) during the period from January 2018 to December 2023.

All consecutive hospitalized cases with a primary or secondary diagnosis of AO or AS during the analysed period were eligible for inclusion in the analysis. Patient identification was performed using ICD-10 diagnostic codes. For acute otitis, codes H60, H62, H65, H66, and H67, with all their subtypes, were used. For acute sinusitis, codes J01.0, J01.1, J01.2, J01.3, J01.4, J01.8, and J01.9 were used.

The inclusion criteria were a primary/secondary diagnosis of AO and/or AS according to ICD-10 codes, otic and/or sinus involvement evaluated by an ENT specialist

and documented in the patient's file, and complete data in the observation sheets. Patients' records were assessed based on ENT consultation and discharge summary, confirming their inclusion in the study as well as the type of otic and/or sinus involvement.

We classified cases of AO into four categories: acute external otitis (AEO), acute congestive otitis media (ACoOM), acute serous otitis media (ASeOM), and acute purulent otitis media (APuOM). Similarly, cases of AS were classified into four categories: acute maxillary sinusitis (AMS), acute ethmoidal sinusitis (AES), acute sphenoidal sinusitis (ASS), and acute frontal sinusitis (AFS). For each patient, we collected demographic data, medical history, clinical data, laboratory investigation results, imaging investigation results, etiological context, evolution during hospitalization, and duration of hospitalization.

Patients were divided into seven age categories: infants (0 – 12 months), toddlers (13 – 35 months), preschoolers (3 – 4 years), school-aged children (5 – 13 years), adolescents (14 – 17 years), adults (18 – 64 years), and elderly (65 years and older).

Statistical analysis was performed using SPSS IBM software version 25.

Results

4.1. General analysis of the cohort

- We identified a total of 2211 eligible cases that were included in the final analysis, with a predominance of male patients (52.6%). Overall, among the paediatric population, cases were predominantly male, while in the adult population, cases were predominantly female.
- Paediatric cases predominated (63.5%), and most patients were hospitalized during the pre-pandemic period (2018-2019, 71.1%).
- The overall incidence of acute otitis cases was 56.6%, while the incidence of acute sinusitis cases was 51.2%.
- Among patients with acute otitis, cases of acute congestive otitis media predominated (51.9%), followed by cases of acute purulent otitis media (26.7%) and acute serous otitis media (17.2%). The incidence of acute external otitis was 2.6%. In the majority of cases, unilateral otic involvement was identified (70.0%).
- Among patients with acute sinusitis, 89.6% had maxillary sinus involvement, 31.6% had ethmoidal sinus involvement, 18.3% had frontal sinus involvement, and 5.6% had sphenoidal sinus involvement.

- Acute sinusitis was more frequent in female patients compared to acute otitis, which was more frequent in male patients ($p < 0.001$).
- Overall, cases of acute otitis were significantly more frequent in the paediatric population, whereas cases of acute sinusitis were significantly more frequent in the adult population ($p < 0.001$).
- Overall, the length of hospitalization did not differ between patients with acute otitis and those with acute sinusitis; however, concurrent dual involvement (otic and sinus) increased the median length of hospitalization by 2 days, from 5 to 7 days.
- In the paediatric population, obesity was one of the main comorbidities for both acute otitis cases (18.5%) and acute sinusitis cases (38.7%).

4.2. Characteristics of acute otitis in the pediatric population

- A total of 1118 paediatric cases with acute otitis were included in the final analysis.
- Male patients predominated (59.0%), and nearly half of the cases were toddlers (49.4%). Infants accounted for 10.6% of the cases. [8]
- The median age of the pediatric cohort with acute otitis was 2.4 years (IQR: 1.5, 4.0 years).
- The clinical presentation of children diagnosed with acute otitis was dominated by fever (88.7%), cough (57.5%), and nasal congestion (53.0%).
- In infants, the presence of nasal congestion was significantly associated with otic involvement compared to other age groups ($p = 0.001$), while otalgia ($p < 0.001$) and headache ($p < 0.001$) were significantly more frequent among school-aged children and adolescents compared to other pediatric age groups.
- Acute congestive otitis media was the most common type of otic involvement in children (53.3%). Nearly one-third of the children (27.6%) were diagnosed with acute purulent otitis media, and 18.1% of the cases were classified as acute serous otitis media. Only 1% of the children were diagnosed with acute external otitis (AEO).
- Otalgia was significantly more common in children diagnosed with acute purulent otitis media (55.3%) and those with acute external otitis (81.8%, $p < 0.001$), while odynophagia was more frequent in patients with acute serous otitis media and acute congestive otitis media ($p < 0.001$).

- Acute purulent otitis media in the pediatric population was associated with elevated levels of leukocytes ($p < 0.001$), neutrophils ($p = 0.001$), and markers of the inflammatory syndrome (fibrinogen, $p = 0.002$; ESR, $p = 0.019$; and CRP, $p = 0.003$).
- The median age was higher for patients with acute external otitis compared to other types of acute otitis (4.5 years [IQR: 1.2, 7.3 years]).
- In 555 cases (49.8%), a viral infection was detected concurrently with the episode of acute otitis. The most common infections were with influenza viruses (20.5%), followed by SARS-CoV-2 (5.8%) and adenovirus (4.9%). A total of 38 children with acute otitis were diagnosed with measles. *Streptococcus pneumoniae* was isolated from otic secretion culture in 31 out of 49 cases of acute purulent otitis, and in the remaining 18 cases, streptococcal isolation was performed after the spontaneous perforation of the tympanic membrane.

4.3. Characteristics of acute sinusitis in the pediatric population

- A total of 351 cases of acute sinusitis were included in the analysis.
- Male cases predominated (56.7%), and the majority (61.5%) were among school-aged children (5 – 13 years, 61.5%). No cases were identified in infants, and only 28 cases (8.0%) were in toddlers (1-2 years). The median age was 8.75 years (IQR: 5.75, 12.1 years).
- Cases of acute maxillary sinusitis predominated (320, 91.2%), followed by acute ethmoidal sinusitis (87, 24.8%), acute frontal sinusitis (52, 14.8%), and only 9 cases (2.6%) of acute sphenoidal sinusitis.
- The clinical presentation of children with acute sinusitis was dominated by fever (86%), cough (48.1%), nasal obstruction (47.6%), and headache (45.9%).
- Headache was significantly more frequent in older children, school-aged children, and adolescents compared to toddlers and preschoolers ($p < 0.001$).
- We did not identify any changes in the clinical presentation or laboratory parameters that were significantly associated with the type of sinus involved. Additionally, the duration of hospitalization was similar regardless of the affected sinus region.
- Influenza viruses were most frequently associated with acute sinus involvement. Streptococcus pneumoniae was identified as the etiological agent in 4.3% of cases. In 2.8% of cases each, sinus involvement occurred in the context of measles and chickenpox.

4.4. Characteristics of acute otitis in the adult population

- A total of 133 adult cases of otitis were included in the study.
- Female cases predominated (54.9%). The median age was 43 years (IQR: 30, 57 years). The distribution of cases was inversely proportional to age, with only 27 elderly patients diagnosed with acute otitis over the six years analysed.
- The presence of at least one chronic disease was high, at 62.4% of cases.
- Fever (75.2%), cough (75.2%), and otalgia (43.6%) were the most frequent symptoms in the clinical presentation of adults with acute otitis.
- Acute congestive otitis media was the most frequently diagnosed (53/133, 39.8%), followed by acute purulent otitis media (46/133, 34.6%), and acute external otitis (21/133, 15.8%). The fewest cases were of acute serous otitis media (13/133, 9.8%).
- The presence of nasal obstruction increased the risk of acute serous otitis media by 6.1 times (OR=6.1) compared to other types of otitis (p=0.002), while the presence of cough increased the risk of acute congestive otitis media by 2.3 times (OR=2.3) compared to other types of otitis (p=0.021).
- Among viral etiologic agents associated with otic involvement in adults, SARS-CoV-2 was identified in 27 cases (23.3%), and influenza viruses in 18 cases (13.5%). *Streptococcus pneumoniae* was isolated in culture in 11 cases (8.3%), all of which were acute purulent otitis media.
- Acute purulent otitis media required a significantly longer duration of hospitalization compared to other types of otitis (median of 10.5 days, $p<0.001$). Additionally, elderly patients, over 65 years old, required 5 days longer hospitalization compared to those under 65 years (13 days vs. 8 days, p=0.005).

4.5. Characteristics of acute sinusitis in the adult population

- A total of 729 cases of acute sinusitis were included in the analysis.
- Female cases predominated (57.8%), and the majority were in the adult population under 65 years old (86.3%), with a median age of 40 years (IQR: 30, 53.5 years).
- The clinical presentation was dominated by fever (79.7%) and headache (63.2%).
- The maxillary sinuses were the most frequently involved in 81.0% of cases, followed by the ethmoidal sinuses (34.8%), frontal sinuses (20.0%), and sphenoidal sinuses (7.0%).

In most cases, only one type of sinus was involved (56.9%), and the incidence of pansinusitis was low at only 1%.

- Acute ethmoidal sinusitis was identified at younger ages compared to acute maxillary sinusitis (39 years vs. 53 years, $p < 0.001$).
- The median duration of hospitalization was similar regardless of the type of acute sinusitis or the number of sinuses involved.

Chapter 5. Study 2 – Hospitalization of known HIV-Infected patients for acute sinusitis and otitis

HIV infection continues to be a significant challenge worldwide, with a considerable impact both at the individual level and on public health. Despite effective antiretroviral therapies, a high number of new cases are diagnosed annually, [9] and many patients are hospitalized for AIDS-defining illnesses, as well as non-AIDS events or other acute or chronic diseases. [10–12]

Published data to date show an incidence of up to 90% of ENT manifestations in people living with HIV.[13] In Romania, the impact of ENT conditions on patients living with HIV has not yet been systematically quantified. It is well known that Romanian patients infected with HIV exhibit a high frequency of various chronic conditions, contributing to the complexity of their medical management. Additionally, many of these individuals require hospitalization either due to the exacerbation of chronic diseases or in response to various acute infectious episodes. This situation underscores the urgent need to address the healthcare of these patients in a more integrated manner, including heightened attention to the prompt diagnosis and treatment of ENT conditions, which can significantly influence their quality of life and prognosis. A better understanding of how ENT conditions affect patients with HIV could lead to improved prevention and treatment strategies, thereby reducing the frequency and severity of hospitalizations.

We conducted an analysis among individuals living with HIV who were hospitalized at the National Institute of Infectious Diseases "Prof. Dr. Matei Balș" in Bucharest. The study focused on HIV patients admitted with acute sinus or otic pathologies (as a primary or secondary diagnosis) from January 2018 to December 2023. The National Institute of Infectious Diseases "Prof. Dr. Matei Balș" in Bucharest coordinates the national management of HIV-infected patients.

In the analysis, we included individuals living with HIV who were hospitalized at the National Institute of Infectious Diseases "Prof. Dr. Matei Balș" in Bucharest during the study period for acute infectious pathology (with symptom onset no later than seven days prior to hospitalization) and were diagnosed by an ENT specialist with acute otitis (AO) and/or acute sinusitis (AS).

Patient identification was carried out using ICD-10 diagnostic codes. For otitis, codes H60, H62, H65, H66, and H67 with all their subtypes were used. For sinusitis, codes J01.0, J01.1, J01.2, J01.3, J01.4, J01.8, and J01.9 were used, and for HIV infection, codes B20, B21, B22, B23.0, B24, Z11.4, Z20.6, and Z83.0 were utilized.

The inclusion criteria were: a primary/secondary diagnosis of AO and/or AS according to ICD-10 codes, otic and/or sinus involvement evaluated by an ENT specialist and documented in the patient's file, and complete data in the observation sheets. Patients' records were assessed based on ENT consultation and discharge summary, confirming their inclusion in the study as well as the type of otic and/or sinus involvement.

We classified cases of AO into four categories: acute external otitis (AEO), acute congestive otitis media (ACoOM), acute serous otitis media (ASeOM), and acute purulent otitis media (APuOM). Similarly, cases of AS were classified into four categories: acute maxillary sinusitis (AMS), acute ethmoidal sinusitis (AES), acute sphenoidal sinusitis (ASS), and acute frontal sinusitis (AFS).

For each patient, we collected demographic data, clinical data (signs and symptoms), laboratory parameter results (complete blood count, biochemistry, inflammatory syndrome), imaging evaluation results, HIV infection stage, antiretroviral treatment, etiological context, evolution, complications, and duration of hospitalization.

Patients were divided into three age categories: children (< 18 years), adults (18 – 64 years), and elderly (> 65 years).

Statistical analysis was performed using SPSS IBM software version 25.

Results

- A total of 179 cases of patients living with HIV were identified as being hospitalized with diagnoses of acute otitis and/or acute sinusitis.[14]
- Cases of acute sinusitis had a significantly higher incidence compared to cases of acute otitis (83.1% vs. 22.9%).
- Female patients predominated (58.1%), with a median age of 32.5 years (IQR: 29.5, 42.3 years).

- Most HIV patients were in stage C3 (n = 103, 57.5%), followed by stage B2 (n = 23, 12.8%) and stage C2 (n = 16, 8.9%).
- The incidence of sinus involvement in HIV patients was similar to that in the general population (see conclusions from Study 1): maxillary sinuses (94.0%), ethmoidal sinuses (31.5%), frontal sinuses (21.5%), and sphenoidal sinuses (1.3%).
- Similarly, the types of otic involvement in people living with HIV were similar to the general population (see conclusions from Study 1), with a higher percentage of acute purulent otitis media and acute external otitis: acute congestive otitis media - 34.1%, acute purulent otitis media - 31.7%, acute serous otitis media - 19.5%, and acute external otitis - 14.7%.
- HIV infection stage, sex, or the presence of associated chronic pathologies did not predispose to infection of a specific paranasal sinus or a specific subtype of acute otitis ($p > 0.05$ for each case).
- We identified that the median age of patients with acute maxillary sinusitis was significantly lower than that of other types of acute sinusitis (32.9 years vs. 43.7 years, $p=0.043$). Similarly, cases of acute congestive otitis media were identified in younger patients (28.2 years vs. 43.7 years, $p = 0.007$). Otic involvement in the form of acute external otitis was detected in patients with a higher median age compared to other types of otitis (49.5 years vs. 30 years, $p = 0.001$).
- There were no significant differences in the frequency of acute otitis or acute sinusitis concerning CD4 lymphocyte levels or adherence to or type of antiretroviral treatment.
- The clinical presentation was dominated by fever (65.9%), nasal congestion (63.7%), and headache (58.7%). Patients with acute sinusitis more frequently presented symptoms such as nasal congestion ($p<0.001$) or headache ($p=0.001$) and had underlying septal deviation ($p = 0.018$) or inferior turbinate hypertrophy ($p=0.023$), while patients with acute otitis most frequently presented otalgia as the main symptom ($p<0.001$).
- We identified a higher median duration of hospitalization for those diagnosed with acute otitis (8.5 days) compared to patients hospitalized for acute sinusitis (7 days, $p=0.016$).

Chapter 6. Study 3 – Impact of influenza virus infections on the development of acute otitis and sinusitis – clinical and evolutionary aspects

Although influenza is a disease that benefits from specific prophylaxis through vaccination as well as effective antiviral treatment, it remains one of the most significant viral infections in humans. The number of influenza cases is high each year, with many requiring hospitalization, particularly due to complications. Among these complications, acute otitis (AO) and acute sinusitis (AS) hold an important place [15,16] having a significant impact on patients' quality of life and, at the same time, generating additional costs for healthcare systems. In a recent study on a pediatric cohort under 14 years of age with influenza, AO ranked first among complications, followed by pneumonia and sinusitis. [17,18] Bacterial superinfections, especially those colonizing the nasopharynx, are responsible for the occurrence of acute otitis and/or sinusitis in influenza patients. *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae* are frequently implicated as bacterial agents complicating influenza. [17]

We conducted a study among hospitalized cases of influenza that presented with complications of acute otitis or acute sinusitis during the period from January 2018 to December 2023. All cases included in the analysis were hospitalized at the National Institute of Infectious Diseases (INBI) "Prof. Dr. Matei Balș".

We included in the analysis all consecutive cases of influenza (both pediatric and adult populations) where the presence of influenza viruses was documented by RT-PCR (monoplex or multiplex) and where acute otitis and/or acute sinusitis complications were identified by an ENT specialist during hospitalization. Cases diagnosed with influenza through rapid antigen detection tests, those with incomplete data in the information system or patient records, and those where other viral co-infections were identified by multiplex RT-PCR or rapid antigen detection tests were excluded.

Cases were identified in the information system based on the specific ICD-10 codes for influenza virus infections: J10, J11. For otitis, the codes H60, H62, H65, H66, and H67 with all their subtypes were used, and for sinusitis, the codes J01.0, J01.1, J01.2, J01.3, J01.4, J01.8, and J01.9 were used. All cases were verified for meeting the inclusion criteria. For each eligible case, the following data were collected from patient records.

We classified cases of acute otitis (AO) into four categories: acute external otitis (AEO), acute congestive otitis media (ACoOM), acute serous otitis media (ASeOM), and acute otitis media (AOM). Similarly, cases of acute sinusitis (AS) were classified into five categories: acute maxillary sinusitis (AMS), acute ethmoidal sinusitis (AES), acute

sphenoidal sinusitis (ASS), acute frontal sinusitis (AFS), and acute unclassified sinusitis (AUS).

For each patient, we collected demographic data, data on signs and symptoms, laboratory investigation results, imaging evaluation results, etiological context, and duration of hospitalization.

Patients were divided into three age categories: children (< 18 years), adults (18 – 64 years), and elderly (> 65 years).

Statistical analysis was performed using SPSS IBM software version 25.

Results

- A total of 1571 cases of influenza confirmed by RT-PCR were hospitalized during the analysed period. The cumulative incidence of otitis and sinusitis was 20.6% (324 cases), with 233 cases (71.9%) diagnosed with acute otitis and 122 (37.7%) with acute sinusitis. Among these, 31 cases (9.4%) had dual otitis-sinusitis involvement.[19]
- The median age was 4.0 years (IQR: 2.1, 11.4), with a predominance of pediatric cases (80.6%), and only 9 cases occurring in the elderly (2.8%).
- Acute sinusitis was significantly more frequent in adults compared to cases of acute otitis, thus the median ages between sinus and otic involvement differed significantly, 28.2 years vs. 2.7 years ($p<0.001$).
- Influenza type A viruses were identified most frequently in 67.2% of patients, with no significant differences between otic or sinus involvement ($p=0.486$).
- The clinical presentation was dominated by influenza-specific symptoms, fever (97.2%), cough (80.2%), and nasal congestion (65.4%). Otalgia was significantly more frequent in patients with acute otitis (53.5%, $p<0.001$), headache was more frequent in those with acute sinusitis (50.5%, $p<0.001$), while nasal congestion was more common in patients with dual otitis and sinusitis involvement (90.3%, $p=0.009$).
- No significant changes in blood tests were identified, except for a more frequent decrease in lymphocyte count in those with acute sinusitis (86.7%, $p<0.001$) and an increase in monocyte count in those with acute otitis (31.0%, $p<0.001$).
- The median duration of hospitalization was 4 days (IQR: 3, 6 days) and increased by one day in those with dual otitis and sinusitis involvement (5 days (IQR: 3, 7 days), $p=0.314$). The presence of chronic diseases or age did not influence the duration of hospitalization in any of the analysed groups ($p>0.05$ for each).

- More than half of the acute otitis cases were of the congestive type (56.7%), and most often the involvement was unilateral (70.8%). Acute maxillary sinusitis was the most frequent among sinus involvement (79.5%). In 28 cases (23.0%), involvement of two different sinuses was documented, and in 3 cases (2.5%), involvement of three different sinuses was documented.
- Influenza B infection increased the risk of acute congestive otitis media by 2.1 times ($p=0.020$, OR=2.1), while influenza A viruses increased the risk of acute maxillary sinusitis by 2.7 times ($p=0.029$, OR=2.7).
- There were no differences in the duration of hospitalization based on the type of influenza or the type of otitis or sinusitis ($p>0.05$ for all).

Final Conclusions and Personal Contributions

I conducted three studies that highlighted significant epidemiological, clinical, and evolutionary aspects among paediatric and adult patients hospitalized for acute otitis and/or acute sinusitis outside of a specialized ENT care centre. The obtained results significantly complement the specialized literature, providing a comprehensive view of the impact of these pathologies within our country's population. From each chapter, I published the results in Web of Science-indexed journals to disseminate the obtained data, aiming to enhance medical knowledge, clinical practice, public health decisions, and to open opportunities for new research directions.

The results presented in each chapter are of interest to current medical practice. The data provided by the studies conducted in this doctoral thesis can be utilized for:

- Identifying risk groups and adapting treatments, as the study's conclusions indicate a higher incidence of acute otitis in the paediatric population and acute sinusitis in adults, also highlighting differences between sexes. Acute otitis predominates in young male children, while sinusitis is more frequent in adults and females. This information allows physicians to be more vigilant and to tailor diagnostic and treatment strategies based on the patient's age and sex.
- Personalizing care based on the clinical presentation and type of acute otitis or acute sinusitis, as the studies detail the types of otitis and sinusitis and the predominant symptoms associated with each type, providing a solid basis for personalized treatment. For example, patients with acute purulent otitis media, who require longer hospitalization, should be carefully identified, and appropriate management should be applied to reduce hospitalization durations and potential complications.
- Closely monitoring patients with upper respiratory tract viral infections, as we identified a direct link with otic and sinus involvement, especially in the paediatric population. Additionally, the conclusions regarding the increased incidence of acute otitis and sinusitis in patients with influenza and the identification of specific pathogens such as *Streptococcus pneumoniae* are essential for developing effective therapeutic regimens. This includes the appropriate use of antibiotics to avoid microbial resistance and ensure effective treatment. The study also highlights the importance of vaccination against influenza and Streptococcus pneumoniae to reduce the incidence of ENT complications.

- Closely monitoring individuals living with HIV, as our findings indicate a higher incidence of sinusitis compared to otitis in this population. The study's conclusions emphasize the need for specific and integrated management for immunocompromised patients. This involves monitoring these patients and adopting preventive measures to reduce the risk of complications. Integrating these conclusions into clinical guidelines can significantly improve the quality of life for these patients and reduce the duration and severity of hospitalizations.
- Developing prevention strategies and reducing hospitalization duration, as identifying factors that prolong hospitalization, such as concurrent otic and sinus involvement, helps in creating early and effective intervention strategies. These strategies can include combined treatments and appropriate monitoring for patients with dual involvement, thereby reducing recovery time and optimizing medical resources. Additionally, educating patients about early signs and symptoms can contribute to reducing hospitalization duration and preventing complications.
- Raising awareness about the importance of early diagnosis and treatment, as the conclusions emphasize the need for early and accurate diagnosis, especially in pediatric patients, to avoid complications and reduce hospitalization duration. Implementing ENT screening programs and rapid diagnosis in hospitals and clinics can significantly improve treatment outcomes and prevent the severe progression of otitis and sinusitis.

The conclusions of this work open multiple avenues for future research. Among these are:

- Analysing the evolution of patients with otitis and sinusitis over a longer period could provide additional information about long-term complications and the efficacy of administered treatments. This type of study could help develop long-term treatment protocols and improve prevention strategies.
- Investigations into the costs associated with the hospitalization and treatment of acute otitis and sinusitis could provide important insights for optimizing resources in the healthcare system. Such studies could also highlight the importance of prevention and early treatment in reducing medical costs.
- Research into the efficacy of new antibiotics, antivirals, and other innovative treatments for managing otitis and sinusitis could significantly improve treatment outcomes.

Clinical studies evaluating new technologies, such as rapid diagnostics through molecular biology techniques, could expedite the diagnostic and treatment processes.

- Developing novel diagnostic methods for acute otitis, such as utilizing digital endoscopy with diagnostic capabilities for various types of otic pathologies through large language models, which can achieve high diagnostic accuracy and monitor the progression of otic diseases in real-time.
- Future research could further explore the role of vaccination, particularly against influenza viruses and other respiratory pathogens, in preventing otitis and sinusitis. The effectiveness of vaccination programs could be assessed by monitoring the incidence of these conditions in vaccinated populations compared to unvaccinated ones.

Implementing these research directions can significantly enhance patient care for ENT conditions and optimize healthcare resources, while also providing new insights for the development of more effective treatments and preventive strategies.

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1. GERMS, 14(1), 2024, IF – 1.7: **Pleșca VȘ**, Marinescu AG, Voiosu C, Drăgănescu AC, Streinu-Cercel A, Vilaia A, Hainărosie R, Pleșca DA, Săndulescu O. Occurrence of acute otitis and sinusitis in patients hospitalized for influenza. GERMS. 2024;14(1):38-44. doi: 10.18683/germs.2024.1416

2. Journal of Clinical Medicine, 13(11), IF – 3: **Pleșca, V.S.**; Miron, V.D.; Marinescu, A.G.; Drăgănescu, A.C.; Pleșca, A.D.; Săndulescu, O.; Voiosu, C.; Hainărosie, R.; Streinu-Cercel, A. Hospitalizations for Acute Otitis and Sinusitis in Patients Living with HIV: A Retrospective Analysis of a Tertiary Center in Romania. J. Clin. Med. 2024, 13,3346. https://doi.org/10.3390/jcm13113346

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