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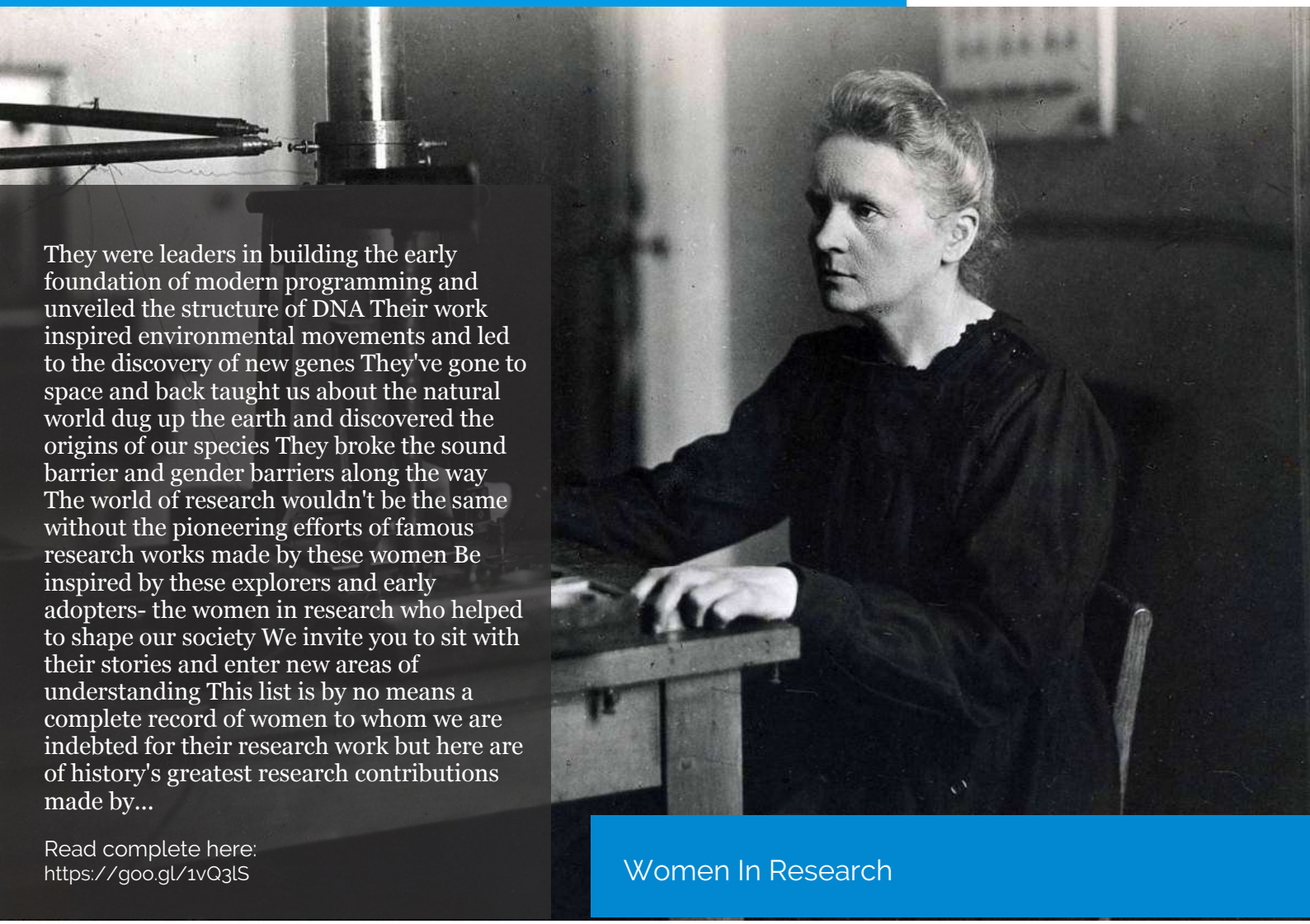

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# Exploring the Interplay of AHD, TB, and Cryptococcal Antigen in Nasarawa State

*Olufunmilola Abodunde, Folake Isona, Oluwasola Oni, Chinwe Umeozulu, Kayode Joseph, Faith Audu, Hafsat Usman, Adeniyi Ojuope, Temitope Olayemi & Esther Loyin*

## ABSTRACT

This study explored the existing relationships between Advanced HIV Disease (AHD), Tuberculosis (TB), and Cryptococcal Antigen (CrAg) among People Living with HIV (PLHIV) in Nasarawa State, Nigeria. This was achieved by investigating the relationship and prevalence of TB and CrAg among individuals diagnosed with AHD in Nasarawa State; and by assessing the distribution and association of demographic characteristics of the study population with TB and Cryptococcal Antigen. This study employed a cross-sectional survey design, sampling respondents across different demographics at the same time. The study sample were individuals who are currently receiving antiretroviral treatment from our healthcare facilities in Nasarawa State, Nigeria. Results showed that TB and CrAg has low prevalence among the study population, however, compared to a larger population, this will be a serious concern. The study also suggest that the demographic information of the study population had no significant relationship on the development or presence of TB or CrAg, however, the study was able to establish that PLHIVs who had AHD were mostly women (59.8%) in the State. Recommendations were made based on the study findings and the study concluded that the existing relationships among the study variables were not impacted significantly by either age or gender of the population.

*Keywords:* advanced HIV disease (AHD), cryptococcal antigen (CrAg), people living with HIV (PLHIV), human immunodeficiency virus (HIV).

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*Keywords:* advanced HIV disease (AHD), cryptococcal antigen (CrAg), people living with HIV (PLHIV), human immunodeficiency virus (HIV).

## I. INTRODUCTION

The challenge of HIV disease continues to pose a global threat despite measures and interventions to contain the spread of the infection. Primarily, the HIV virus once contracted can be managed to mitigate potential effects on the immune system of the carrier (Meloni et al., 2020; Oku et al., 2014). This is achievable when the individual carrier (herein referred to as 'patient' or 'study population' in this report) adheres strictly to the drug regimen. For the efforts made in the HIV interventions programs from Organisations such as USAID, WHO, PEPFAR, etc, to be effective to both manage and prevent transmission of the disease, adherence to medications and the use of contraceptives have been encouraged globally, with adequate awareness creation (Abou Ghayda et al., 2020; Drain et al., 2020; Meloni et al., 2020; Oku et al., 2014; Yombi & Mertes, 2018).

However, some persons who either do not adhere to their medication, or did not ascertain their HIV status until their immune system becomes incapable of handling the commobids of the viral disease, may become liable to the advanced stage of the disease, otherwise known as Advanced HIV Disease (AHD).

Common diseases that often occur in AHD patients are Tuberculosis and Cryptococcal meningitis (Dabla et al., 2015; Oladele et al., 2023). Tuberculosis (TB) is an infectious disease which is solely caused by the presence of bacterium 'Mycobacterium tuberculosis' (Boulware et al., 2021; Oladele et al., 2023). TB is transmitted through airborne particles, called droplet nuclei, and primarily affects the lungs but can also impact other body parts (De Cock et al., 1992; Lawn et al., 2011). It is recognised as one of

the leading infectious killer diseases worldwide (Boulware et al., 2021; Dabla et al., 2015; Oladele et al., 2023; WHO, 2023; 2002). The relationship between TB and AHD is that AHD is a level of HIV presence in the human system where the immune system has been highly compromised (CD4 < 200 cells/uL) An individual with a highly compromised immune system stands a higher risk of contracting TB infection (Balachandra et al., 2020; Dabla et al., 2015; De Cock et al., 1992).

Cryptococcal Meningitis is another disease that AHD carriers stand a high chance of being infected with (Balogun et al., 2016). Cryptococcal Antigen, specifically the cryptococcal polysaccharide antigen (CrAg), is a core component associated with the fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii (Balogun et al., 2016; De Cock et al., 1992). The detection of Cryptococcal Antigen serves as a diagnostic measure employed to identify the presence of this antigen within the body, primarily in the blood or cerebrospinal fluid (CSF), thereby facilitating the diagnosis of cryptococcal infections (Binnicker et al., 2012; Ezenabike et al., 2020).

These infections predominantly affect the lungs and central nervous system, posing significant risks to individuals with compromised immune systems, notably those infected by Advanced HIV Disease (AHD) (Balogun et al., 2016). It is however important to note that timely identification of the Cryptococcal Antigen plays a pivotal role in its early detection and management, which ultimately enables the prompt initiation of appropriate treatment strategies to mitigate the associated morbidity and mortality (Binnicker et al., 2012; Ezenabike et al., 2020). As an infection that thrives on a compromised immune system, individuals with AHD are at higher risk of this fungal infection (WHO 2002; De Cock et al., 1992).

The co-occurrence of Advanced HIV Disease (AHD), Tuberculosis (TB), and Cryptococcal Antigen presents a profound and multifaceted health challenge. This is because AHD is a stage of HIV infection where the individual's immune system has been compromised, hence the increased tendencies for other health complications and opportunistic infections (Oladele et al., 2023). Therefore, understanding the intricate interplay and potential relationships between these conditions is imperative for developing comprehensive strategies to mitigate their devastating consequences.

While extensive research has been conducted over the years on each of these conditions individually, the effect of co-infection of TB and CrAg with AHD and the risk it poses to the AHD patient requires further studies. The combination of AHD, TB, and Cryptococcal Antigen creates a complex medical scenario where each condition exacerbates the deleterious effects of the other, thus, creating a synergistic decline in health status and outcomes for affected patients. Although, there has not been a global prevalence report of AHD, as at the last report of WHO (WHO, 2023), however, the concerns about the deleterious opportunistic infections such as TB remains a significant challenge, especially with people living with HIV (WHO, 2023).

The presence of TB and Cryptococcal Antigen infections in PLHIV's intensifies the burden of disease, leading to accelerated disease progression, increased mortality rates, and diminished treatment response (WHO, 2023). The weakened immune system associated with AHD not only heightens susceptibility to TB infection but also hampers the body's ability to control the spread of TB bacteria, resulting in more severe manifestations and heightened transmission risks, as well as high risk of death (WHO, 2023).

This study aims to address the gap in knowledge by examining the interplay of AHD and the other two opportunistic infectious diseases, as well as identifying potential factors that may contribute to their simultaneous occurrence, and the study also examined whether there is any significant relationship between age/sex and TB or CrAg among people who had AHD. By unravelling the intricate connections between these conditions, this research endeavours to provide important insights that can inform the development of tailored interventions, improve diagnostic accuracy, enhance treatment approaches, and

enhance the overall prognosis and quality of life for PLHIV, as well as individuals living with the challenging triad of AHD, TB, and Cryptococcal Antigen.

## II. OBJECTIVES

This study aims to examine the interplay between AHD, TB, and Cryptococcal Antigen (CrAg). To achieve this broad objective, the following specific goals were set:

1. Investigate the relationship and prevalence of TB and CrAg among individuals diagnosed with AHD in Nasarawa State;
2. Assess the distribution and association of demographic characteristics of the study population with TB and Cryptococcal Antigen.

## III. METHODS

### *3.1 Study Design*

This study was a cross-sectional study, collecting specified data across age groups for the purpose of investigating the study variables within the age groups. The study population are the patients newly diagnosed (over the last 12 months)with HIV who have AHD in six health facilities in Nasarawa State. The primary data collected were subjected to rigorous statistical analysis as highlighted in subsequent sections.

### *3.2 Data Source and Collection*

This study utilised data extracted from the Retention and Audit Determination Tool (RADET), the electronic medical records system managed by our organisation, which contain all the medical information of all the PLHIV who are currently receiving Antiretroviral treatment from our facilities. The study population are the patients newly diagnosed (over the last 12 months) with HIV who have AHD in six health facilities in Nasarawa State. The data extraction process was conducted by our Documentation associates who also serve as research assistants, ensuring compliance with data privacy and security regulations. All data were de-identified, with identifiers withheld to maintain patient confidentiality.

## IV. DATA ANALYSIS

The first objective which focused on the relationship and the prevalence rates of TB and CrAg among individuals diagnosed with AHD in Nasarawa State was analysed using both descriptive and inferential statistics. Prevalence rates were presented using frequencies and simple percentages, while the association among the variables were examined using Chi-square. The second objective was aimed at assessing the distribution of demographic characteristics among the study population and examining their association with the presence of TB and Cryptococcal Antigen. The demographic information was analysed using descriptive statistics such as frequencies and simple percentages, while the association between variables were examined using Chi-square.

## V. LIMITATIONS

It is important to acknowledge the limitations of this study, including the retrospective nature of the data and the findings may be specific to the population of individuals with AHD captured in the RADET system, particularly for Nasarawa State, and the generalisation based on the current data may not be applicable to other States within the country where there are cultural or social normative peculiarities. Lastly, confounding factors not accounted for in the analysis could influence the observed associations.

## VI. RESULTS AND DISCUSSIONS

*Objective 1*

The first objective was to investigate the relationship between as well as prevalence rates of TB and Cryptococcal Antigen among individuals diagnosed with AHD in Nasarawa State. We therefore examined the association using the chi-square test, and also calculated the prevalence rates of TB and Cryptococcal Antigen within the population using descriptive statistics, such as percentages and frequencies. Results are presented in Table 1 and 2.

*Table 1:* Descriptive Statistics, Showing the Prevalence of Tuberculosis (TB) and Cryptococcal Antigen (CrAg) Among AHD Patients in Nasarawa State

| Age Category | Sex | TB n (%) | CrAg (%) | Total Sample (n) |
|---|---|---|---|---|
| Adult (20 and above) | Female | 6 (3.3) | 2 (1.1) | 122 |
| | Male | 0 (0) | 0 (0) | 61 |
| Adolescent | Female | 1 (7.7) | 0 (0) | 11 |
| | Male | 0 (0) | 0 (0) | 2 |
| Children | Female | 0 (0) | 0 (0) | 3 |
| | Male | 0 (0) | 0 (0) | 4 |
| Total | Female | 7 (3.4) | 2 (1) | 136 |
| | Male | 0 (0) | 0 (0) | 67 |

The results in Table1 indicate that the prevalence rate of TB and CrAg is significantly low among the AHD population (TB = 3.4%, CrAg = 1%).

However, when added up on a much larger sample (e.g., 10,000), the prevalence rate of 3.4% for TB and 1% for CrAg is a concern as it implies that there are at least 340 and 100 individuals in a population of 10,000 people with AHD who have developed TB and CrAg respectively. Also, the figures indicate that all the individuals who had TB (7) and CrAg (2) were females. To further understand how much these variables associate with each other, a chi-square test was computed, based on the prevalence of AHD and the results are presented in Table 2.

*Table 2:* Chi-Square Statistics Showing the Relationship Between the Prevalence of TB and Cryptococcal Antigen (CrAg) Among Individuals With AHD in Nasarawa State

| | Chi-square | df | p-value |
|---|---|---|---|
| Association | 79.27 | 4 | <.001 |

*Note* DV is Advanced HIV Disease (AHD)*

The chi-square test revealed a significant association between TB and Cryptococcal Antigen among individuals with AHD in Nasarawa State ($\chi^2 = 79.27$, df = 4, $p < .001$). This finding provides comprehensive insight into the relationship between these variables within the specific population of individuals diagnosed with AHD in the state. The observed chi-square value of 79.27 indicates a substantial departure from the expected frequencies under the assumption of independence. This association indicates that TB and Cryptococcal Antigen are not independent conditions among individuals with AHD in Nasarawa State. These results therefore ensure the reliability and validity of the study's findings.

Furthermore, the obtained p-value of less than .001 demonstrates a high level of statistical significance. It indicates that the association between TB and Cryptococcal Antigen is unlikely to be attributed to random chance alone.

Although there is paucity of empirical data on the existing relationship between AHD and opportunistic infections like TB and CrAg, however, this study was able to document evidence that AHD patients who test positive on TB are likely to test positive on CrAg and vice versa. This is in tandem with the findings of Balogun et al (2023) and Rajasingham et al (2019) who reported similar figures (1.6% and 1.4% respectively) of CrAg among immunocompromised PLHIVs. Even though they (Balogun et al., 2023; Rajasingham et al., 2019) did not particularly focus on TB, their documented reviews suggest that TB is strongly associated with CrAg. Also, the prevalence studies available on HIV especially from the World Health Reports did not report any prevalence of CrAg, despite the

emphasis on HIV and opportunistic factors such as TB.

Although our current findings did not indicate any prevalence report on AHD, it documents the prevalence of TB and CrAg as mild among the AHD population within the study area (see Table 1). But in a previous study, we reported AHD prevalence in six healthcare facilities in Nasarawa State to be high (51%) among newly enrolled HIV patients (Umeozulu et al., 2023). This was also corroborated in Auld et al. (2017) and Balogun et al. (2021). This implies that AHD remains a concern, not only for existing patients but also for the newly enrolled. Furthermore, it has been corroborated in literature that there are chances that HIV gets more severe among people living in Sub-Saharan African nations including Nigeria (Balanchandra et al., 2019; Balogun et al., 2016; Meya et al., 2021). Other studies also support our findings that a compromised immune system leaves PLHIV susceptible to opportunistic infections, including TB and CrAg (Balogun et al., 2016; Meya et al., 2021; World Health Statistics, 2023).

*Objective 2*

The second objective of this study aimed to assess the distribution of demographic characteristics among the study population (people with AHD) and also examine their association with the presence of TB and Cryptococcal Antigen.

Specifically, we investigated the demographic characteristics of the population, including age and sex. Furthermore, we explored the relationship between these demographic characteristics and the occurrence of TB and Cryptococcal Antigen in individuals with AHD.

The demographic information was analysed using descriptive statistics such as frequencies and simple percentages, while the association between variables were examined using Chi-square. Results are presented in Tables 3 and 4.

*Table 3:* Descriptive Statistics Showing the Distribution of the Demographic Characteristics of the Population

| Age_Group | Sex | Frequency (n) | Percentage (%) |
|---|---|---|---|
| Adult | Female | 122 | 59.8 |
| | Male | 61 | 29.9 |
| Adolescent | Female | 11 | 5.39 |
| | Male | 2 | 0.98 |
| Children | Female | 3 | 1.47 |
| | Male | 4 | 1.96 |
| Population Total | | 204 | 99.5 |

*Missing System = 1 (0.5%)*

Results in Table 3 indicate that the majority of the AHD population are adult females [122 (59.8%)], which is exactly twice the adult male population (For breakdown of the prevalence, see Table 1).

This implies that AHD is more prevalent among adult females within the study area compared to adult males. Other information on the population presented mild coverage of adolescents, among whom the female gender was still significant, although there were more male children among this population than females. However, to understand whether or not these demographic characteristics are strongly associated with TB and CrAg, a further analysis was computed, as shown in Table 4.

*Table 4:* Chi-Square Statistics Showing the Association between Demographic Characteristics, TB and CrAg Among Individuals with AHD in Nasarawa State

| Relationships | Chi-square | df | p-value |
|---|---|---|---|
| Sex*CrAg | 1.82 | 2 | .403 |
| Sex*TB | 4.51 | 2 | .105 |
| Age_Group*CrAg | 0.76 | 2 | .944 |
| Age_Group*TB | 1.85 | 2 | .763 |

The results in Table 4 shows that the demographic characteristics of an AHD patient has no significant relationship with the presence or development of TB and or CrAg. The association between sex and Cryptococcal Antigen was assessed using Pearson Chi-square test, yielding a non-significant result ($\chi^2 = 1.82$, df = 4, p = .403).

Similarly, the association between sex and TB was not found to be significant ($\chi^2 = 4.51$, df = 4, p = .105). Also, the relationship between age group and Cryptococcal Antigen ($\chi^2 = 0.76$, df = 4, p = .944) as well as the relationship between age group and TB ($\chi^2 = 1.85$, df = 4, p = .763) were examined, and the results showed no significant associations.

These findings indicate that there is no significant association between the demographic characteristics (sex and age group) and the presence of TB or Cryptococcal Antigen among individuals diagnosed with AHD. These results are supported in literature that although a significant proportion of PLHIVs, especially those who are already immunocompromised, are females, gender difference has no significant effect on the presence of TB or CrAg (Akinbami et al., 2012; Laah & Ayiwulu, 2010). Also, studies have ascertained that socio-demographic characteristics of PLHIV does not necessarily determine the presence of TB or CrAg (Akinbami et al., 2012). Therefore, our study has been well supported in literature.

## VII. CONCLUSION

The findings of this study reveal important insights regarding the relationships between tuberculosis (TB), Cryptococcal Antigen (CrAg), and demographic characteristics among individuals diagnosed with advanced HIV disease (AHD) in Nasarawa State, Nigeria. Firstly, the prevalence rates of TB and CrAg were found to be significantly low within the AHD population, but when extrapolated to a larger sample size, the number of affected individuals raises concernsThis highlights the importance of addressing these infections in individuals with AHD to prevent adverse health outcomes.

Secondly, a significant association was identified between TB and CrAg, indicating that these conditions are not independent among individuals with AHD in Nasarawa State. This finding emphasises the need for comprehensive management and treatment strategies that consider both TB and CrAg in this population. Finally, the study established that demographic characteristics (that is, age and sex) had no significant associations with the presence or absence of TB and CrAg among individuals with AHD in Nasarawa State. These results align with previous studies suggesting that socio-demographic factors may not be primary determinants of TB or CrAg occurrence in people living with HIV/AIDS. Further exploration is necessary to identify other contributing factors and understand the complex interplay between these variables.

## VIII. RECOMMENDATIONS

Based on the findings of this study, we suggest the following:

1. *Strengthen TB and Cryptococcal Antigen Screening:* Given the significant association

between TB and CrAg among individuals with AHD, it is crucial to enhance screening efforts for both conditions. Healthcare providers should be trained to routinely test individuals with AHD for TB and CrAg, particularly in high- prevalence areas. This will help in early detection, prompt treatment initiation, and prevention of complications.

2. *Integrated Treatment Approaches:* Considering the association between TB and CrAg, it is recommended to adopt an integrated approach to the management of individuals with AHD. Collaboration between tuberculosis control programs and HIV/AIDS clinics should be strengthened to ensure coordinated care. This may involve establishing joint clinics, developing shared treatment protocols, and facilitating seamless referral systems.
3. *Expansion of Prevalence Studies:* The prevalence of AHD, TB, and CrAg should be further explored through larger-scale studies. It is recommended to conduct comprehensive prevalence studies involving a diverse population of individuals with AHD, including both newly diagnosed and existing patients. This will provide a more accurate understanding of the burden of these conditions and inform public health interventions.
4. *Awareness and Education Programs:* Public health campaigns should be developed to raise awareness about AHD, TB, and CrAg among healthcare providers, individuals living with HIV/AIDS, and the general population. These campaigns should focus on promoting early detection, reducing stigma, and educating individuals about the importance of adherence to treatment and regular follow-up care.

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# Casting a Path to Improved Outcomes: The Crucial Role of Total Contact Corrective Casts in Charcot Neuroarthropathy Treatment

*Itzel Caldiño Lozada, Axel Carvajal, Felipe Martínez Escalante & Jannel Santana Canto*

## ABSTRACT

*Introduction:* Charcot's neuroarthropathy is a degenerative disease with an important inflammatory component. It is a multifactorial pathology, but a higher prevalence has been observed in diabetic neuropathy. There are several stages and it can occur in all joints, those of the foot and ankle segment are the most functionally and structurally affected; the deformities are closely related to load causing ulcers and these amputations. Treatment is based on modifying the natural history of the disease and reducing the risk of amputation, following the Charcot treatment algorithm that uses the Caldiño method. This method bases the treatment on total contact corrective casts(TCCC) as conservative and preoperative treatment in cases of instability and deformities for a period of approximately 3 months.

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# Casting a Path to Improved Outcomes: The Crucial Role of Total Contact Corrective Casts in Charcot Neuroarthropathy Treatment

Itzel Caldiño Lozada[α], Axel Carvajal[σ], Felipe Martínez Escalante[ρ] & Jannel Santana Canto[ω]


## SUMMARY

*Introduction: Charcot's neuroarthropathy is a degenerative disease with an important inflammatory component; it is multifactorial, but a higher prevalence has been observed in diabetic neuropathy. There are several stages and it can occur in every joint of the body, those of the foot and ankle segment are the most functionally and structurally affected; the deformities are closely related to load causing ulcers and sometimes ending in amputations. Treatment is based on modifying the natural history of the disease and reducing the risk of amputation. The Caldiño method is a Charcot treatment algorithm which consists on applying serial total contact corrective casts (TCCC) as a nonsurgical or pre surgical treatment in cases of instability and deformities of the foot and ankle for a period of approximately 3 months.*

*Objective: To demonstrate the importance of the use of total contact corrective cast (TCCC) as essential element in the treatment of Charcot arthropathy, the application technique and present the casuistry of patients under the use of the Caldiño Method in the hospital during a period of 20 years.*

*Material and methods: Retrospective review of the casuistry of the Orthopedics Hospital in the foot and ankle service from 2003 to 2023 of patients diagnosed with Charcot neuroarthropathy who were treated under the Caldiño Method for the application of TCCC. A total of 412 medical records of patients seen during this period were identified.*

*Results: 401 patients with a mean age of 59.5 were included, 68.3% (274 p) were males; the most affected foot was the left (63%). Type 2 diabetes predominated in 85% of the cases,. 54% of the cases were diagnosed at stage 2 Eichenholtz On average 3 casts were applied, 3.5% of patients presented with minor complications and in 21% the TCCC was used as pre-surgical treatment.*

*During Follow-up we evaluated the need for reapplication of TCCC or the need for partial support orthosis to achieve an adequate gait.*

*Discussion: The TCCC is a key procedure in the treatment of patients with neuropathic arthropathy if used in a timely manner, as it maintains an aligned foot, free of contact pressure deformities during the unloading stage of treatment. In patients with significant and unstable deformities that require surgical treatment, the use of pre surgical TCCC showed good bone preservation, small bone resections during surgery or the possibility of performing minimally invasive surgeries.*

*Conclusions: In our experience, the use of total contact corrective casts following the Caldiño method is an essential procedure for treating patients with long-standing diabetic neuropathy and advanced stages of Charcot neuroarthropathy.*


## I. INTRODUCTION

Charcot's Neuroarthropathy is a degenerative disease with an important inflammatory component, which responds to load, resulting in articular dislocations and bone fragmentation. Various stages were described by Eichenholtz and its modification allows us to give the appropriate treatment to each one (1-3). The topographic description described by Sanders allows us to perform different forms of immobilization and surgical treatment (4).

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Secondary to the epidemiological transition, the etiology of neuropathic arthropathy has changed from being due to infectious diseases (leprosy, later syphilis) to chronic degenerative metabolic diseases. Diabetes is currently the leading cause of Charcot neuroarthropathy. The National Health and Nutrition Survey (ENSANUT 2022) estimates that the prevalence in Mexico of alterations in glucose metabolism is 22.1%, diagnosed diabetes 12.6% and undiagnosed 5.8% (5,6). Worldwide, the prevalence of diabetic neuropathy is estimated at 26% (7) and Charcot neuroarthropathy at 0.8 to 7.5% (8). Alcoholism has been associated as another cause whose national prevalence is 20.6% in adolescents and 55.5% in adults (9). The natural history of the disease has taught us that it is a multifactorial disease, and its treatment must be multidisciplinary.

Neuroarthropathy can occur in all joints, those of the foot and ankle segment are the most functionally and structurally affected; the deformities are closely related to load causing ulcers and sometimes the need for amputation. The Caldiño method is a Charcot treatment algorithm which consists of applying serial total contact corrective casts (TCCC) as a nonsurgical or pre surgical treatment in cases of instability and deformities of the foot and ankle for a period of approximately 3 months.

The TCCC brings together the treatment concepts dictated by several specialists treating other diseases, Khan and Brand unloaded the affected foot for the treatment of foot pathology related to leprosy, Lozano Platonoff used a cast to treat plantar ulcers and weight unloading, Ponseti uses serial casts in order to achieve peritalar alignment. (1, 2, 12-16).

The TCCC is a suropodalic cast that balances extrinsic forces with a neutral ankle, which is placed taking care of the double helix of the foot, favoring its longitudinal and transverse arches and covering the toes, whose objectives are to achieve a plantigrade foot, anatomically congruent, compatible with standing and walking (10) by avoiding support, reducing edema, forced immobilization of the affected segment, improving the autonomic system, balancing the extrinsic and intrinsic forces of the foot, correcting deformities, closing wounds, aligning the extremity that allows less aggressive corrections and mainly to preserve as much bone as possible when preparing the arthrodesis. This is placed one week after diagnosis and prior use of the Jones bandage.

The description of the technique is exemplified in image 1.

With the patient sitting on the examination table at maximum height, the doctor seated in front of the patient performs the evaluation of the pressure points at the malleolus and sole, looking for skin lesions that suggest areas of greater pressure. Alignment of the limb is observed through gentle maneuvers and reduction of deformities are performed. The skin is adequately lubricated, pressure points are reassessed prior to applying the cast and once the skin is clean and in good condition, a 15 cm cellulose wadding bandage is placed. from distal to proximal in such a way that it covers and protects the toes; a second bandage of cellulose wadding is placed from proximal to distal to achieve partial correction of the deformities. Then a lateral and medial cut is made on the proximal edge of approximately 2 cm, from this point, the placement of the plaster of Paris is started from proximal to distal, leaving the ankle in neutral and reinforcing the correction made when placing the second wadding. It is important to keep an eye on previous crossings at ankle level. The second cast allows us to carry out a greater reduction of the deformities through crossings in the areas that need to be reinforced and the third cast maintains the reduction and covers the toes. The reduction position is maintained during setting. While we smoothen the surface, the areas of reduction of the deformity are molded, the alignment of the hindfoot is monitored and the medial longitudinal arch and the anterior arch of the foot are shaped as far as possible, it is frequent that the first cast does not allow major corrections. Once molded, the cast is smoothed until it has completely set, after 4 weeks it is removed, the foot is cleaned, and the same procedure is carried out every month for a period of 3 months (10).

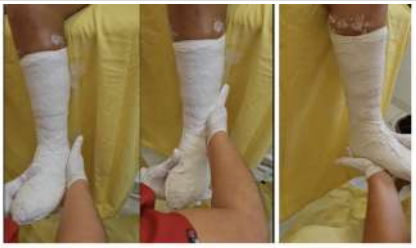
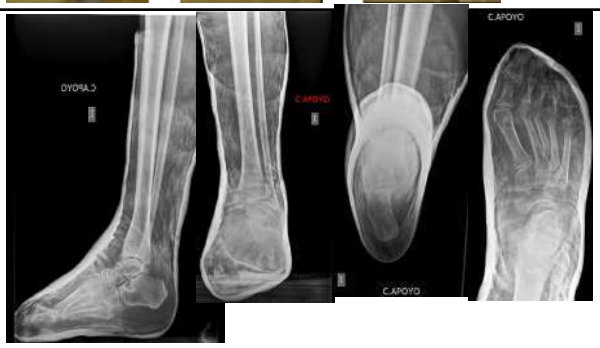
| | |
|---|---|
| Cotton wadding dressing technique |   |
| Placement of second bandage to correct deformity from proximal to distal. Placement of plaster bandage from proximal to distal |   |
| Hindfoot and forefoot alignment maintaining the medial arch |   |
| Smoothing the plaster until it sets. |  |
| Xray |   |

*Figure 1:* Description of the technique used in the Caldiño Method for applying total contact corrective casts (TCCC)

| | |
|---|---|
| Modifications as needed, use of windows if ulcers are present. |    |

Total contact corrective plasters undergo modifications based on the concepts of the Trueta cure to treat infections (17), in case of presenting wounds, areas at risk or ulcers, a cut is made to the plaster (window) in the affected area that allows wound healing techniques and vigilance. It is important to preserve the cover to avoid edema.

*Table 1:* Differences Between Total Contact Plaster and Total Contact Corrective Plaster With the Caldiño Method

| Total contact cast TCC | Characteristic | Total contact corrective cast TCCC |
|---|---|---|
| | | |
| Discharge ulcer closure | Aim | Align deformities and unload weight |
| No | deformity correction | Yes |
| Weekly | Change | Monthly |
| Yes | Windows for healing | Yes |
| Undefined | Use time | 3 months |
| Yes/partial/No | Support | No |
| No | Preoperative use | Yes |
| Infection, ulcers at other sites, bone loss, shortening of the limb. | Complications | Digital lesions due to moisture and periungual pressure in the lesser fingers. |

## II. MATERIAL AND METHODS

A retrospective review of the cases of the Orthopedic Hospital in the foot and ankle service from 2003 to 2023 of patients diagnosed with Charcot neuroarthropathy who were treated under the Caldiño Method (evaluated and authorized by the research committee) for the application of total contact corrective cast.

The objective of the present work is to describe the importance of the use of the total contact corrective cast (TCCC) in the treatment of Charcot´s neuroarthropathy, the application technique and describe the casuistry of patients under the use of the Caldiño Method in the Orthopedics Hospital during a period 20 years.

412 patients with CN attended during this period. Patients with a minimum follow-up of 3 months, with a clinical diagnosis of Charcot Neuroarthropathy (longstanding edema, painless or with mild pain, erythema); history of diabetes,

alcoholism, HIV, liver disease, myelomeningocele sequelae or neurological disorders were included. and radiographic changes (edema in soft tissues, joint diastasis, atypical fractures and fragmentation) who accepted treatment with the Caldiño method. Patients who were not treated with the Caldiño method were excluded.

## III. RESULTS

Of the 412 identified cases, 11 patients who were not treated with the Caldiño method were excluded, leaving a total of 401 patients (Table 2) with a mean age of 46.1 years +/-12 years, the male gender being the most affected in a 68.3% (274 patients); the most affected foot was the left for both sexes (63%). Type 2 diabetes mellitus predominated in 85% of the cases, the average time of evolution of diabetes mellitus was 17.2 years until seeking medical attention for Charcot arthropathy. 54% of the cases were diagnosed with Eichenholtz Stage 2 at their first visit.

On average, 3 plaster casts were placed and there were 14 patients with complications attributed to the total contact corrective cast, which represented 3.5% of the population attended and 84 cases (21%) the total contact corrective plaster was used as pre-surgical preparation.

*Table 2:* Characteristics of the Patients treated under the Caldiño method*

| Age (years)** | 46.1 +/- 12.1 (24-94) |
|---|---|
| Gender | Man |
| Women | |
| 274 (68.3%) | 127 (31.7%) |

* n (%) **Values expressed as mean and standard deviation (range)

Surgical treatment was performed with arthrodesis, different techniques depending on the stage, joints involved and deformity.

Complementary management of post-cast conservative treatment was performed with assisted gait with a walker and long pneumatic boot for one month, use of insoles and comfortable commercial shoes at week 16 on average. The rehabilitation program begins on the day of diagnosis focused on improving mobility and muscle strengthening, strengthening the contralateral limb and glycemic control, as well as psychological and social support. The follow-up of the patient is clinical and is complemented with blood work up and x-rays. Currently, in cases where there is controversy to start loading, a simple magnetic resonance is taken and evaluated with the Balgrist scale. Surgical cases are planned at the second cast change.

## IV. DISCUSSION

TCCC is characterized by deferring support through aligned immobilization as a treatment for neurotraumatic origin where weight bearing in inflamed tissue causes deformities and bone destruction.

Although the literature describes the use of total contact casts for the treatment of diabetic foot with plantar ulcers, not used to deformities corrections like TCCC does. Different authors describe unloading the weight with a total contact cast as the treatment of choice, they complement the treatment with orthoses, insoles, and appropriate footwear. (18-20).

Time of immobilization according to the literature is said to be at least double of what a patient without diabetes would need. In our study time of immobilization was 3 months +/- 2 months, which is consistent with the average reported in the literature in order to go through all fases of the disease. As described Petrova measured C reactive protein, TFN´s and IL6 levels after 3 months of treatment with casts and found lower levels after this time. (21). Virna Zampa use a contrasted MRI determined that the rate of contrast medium uptake occurred during acute inflammatory phase a lasting 3 months. Not all patients can perform it due to the presence of renal disorders, allergies and the high cost. (22) Martin C. Berli describes the use of simple MRI to which the Balgrist scale is applied to predict the immobilization time 3 months or more (23).

Different diagnostic methods have been described, but clinical presentation and physical exploration remain the gold standard for patient follow up and diagnostic.

Cutaneous thermography has been used (2) but in our study we only found it helpful in stages I and II identifying a difference in these stages but normalizes after the firs cast and showed no difference in stages 0 and III.

There is no definite evidence that the use of antiresorptive (alendronate, pamidronate, zoledronate, calcitonin, PTH, denosumab) reduces the immobilization time required (2,12) for this reason it is not included in the Caldiño Method.

According to the statistics obtained, the total contact corrective cast is considered an essential procedure in the treatment of patients with neuroarthropathy, as it allows an aligned foot, free of pressure deformities if used in a timely manner with unloading periods of time. In the case of patients with significant and unstable deformities that require surgical treatment, the use of total contact corrective cast allows for bone preservation, small bone resections or minimally invasive surgeries.

To treat a patient with Charcot's Neuroarthropathy you must take into consideration social and familiar factors to identify risk factors which have led to the actual state of health and to be able to create a support network in the treatment.

## V. CONCLUSION

The total contact corrective cast TCCC is useful in the treatment of Charcot's Arthropathy during its 4 stages, weather it is conservative or pre surgical treatment.

Its objective is to maintain alignment and balance extrinsic and intrinsic forces of the foot to reduce the deformity and obtain a plantigrade foot, in cases where surgery is needed, TCCC favors to conserve bone stock, handle minor deformities and sometimes use minimal invasive techniques.

Every treatment must be complimented by nutritional, rehabilitation, psychological and medical consults to obtain the best results.

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# The Value of Volumetric Computed Tomography Histogram Analysis in the Differential Diagnosis of Mediastinal Lymphoma and Thymoma

*Naciye Sinem Gezer*

## ABSTRACT

*Background:* Thymoma and mediastinal lymphoma are the two most common malignant lesions originating in the anterior mediastinal region. Differentiating between thymoma and mediastinal lymphoma is essential because they require different therapeutic approaches.

*Purpose:* This study aimed to investigate the value of the volumetric computed tomography histogram analysis method in the differential diagnosis of mediastinal lymphoma and thymomas.

*Materials and methods:* From January 2010 to December 2018, 64 patients with histologically confirmed anterior mediastinal tumors underwent thorax CT imaging with intravenous contrast medium for pretreatment evaluation. Thoracic CT examinations were performed using a single spiral acquisition of the entire lung from the apex to the base with subjects in the supine position in a 64-slice CT scanner (Philips Brilliance 64; Philips Medical Systems, Best, The Netherlands). All images were acquired in breath-hold after inspiration with 80-100 *ml of non-ionic iodinated intravenous contrast medium (300 mg iodine/ml) administration.*

*Keywords:* computed tomography, histogram analysis, mediastinal lymphoma, thymoma.

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*Scanning parameters were as follows: voltage 120 kV, current 100 mA, and slice thickness of 0.9 mm. CT histogram measurements were performed by using the licensed imaging analysis software (Myrian; Intrasense, France).*

*Results: Histogram analysis of the lymphoma and thymoma groups showed a significant difference in skewness and kurtosis between the lymphoma and thymoma groups. Lower kurtosis and skewness were observed in thymoma compared with lymphoma. The lymphoma group had a more right-skewed distribution than the thymoma group (p = 0.035)*

*Conclusion: We suggest that the volumetric computed tomography histogram analysis method enables differentiating thymoma from mediastinal lymphoma and thus helps guide the management of the patients.*


*Keywords:* computed tomography, histogram analysis, mediastinal lymphoma, thymoma.

## I. INTRODUCTION

Thymoma and mediastinal lymphoma are the two most common malignant lesions originating in the anterior mediastinal region (1). Differentiating between thymoma and mediastinal lymphoma is essential because they require different therapeutic approaches. While treatment of thymoma cases in the early stages is surgical, in mediastinal lymphomas treatment is chemotherapy and/or radiotherapy (2). Therefore, predicting the pathological classification of thymoma before treatment is highly important for therapeutic decisions. In the assessment of mediastinal tumors, computed tomography (CT) is generally the first-choice modality of diagnostic imaging.

Magnetic resonance imaging (MRI) provides important findings that are diagnostic of disease and facilitates precise assessment of location, a pattern of extension, and anatomical relationship with adjacent structures of the disease (3). Histopathological examination is essential to make a definitive diagnosis.

CT histogram analysis is a new noninvasive and quantitative method by computer-assisted assessment of tumor heterogeneity, which is

related to the distribution and relationship of pixel or voxel gray level attenuation in Hounsfield units (HU) in corresponding CT images. Many previous studies have shown the usefulness of histogram analysis in the diagnosis of various diseases (1,4).

The purpose of this study was to investigate the value of the volumetric computed tomography histogram analysis method in the differential diagnosis of mediastinal lymphoma and thymomas.

## II. MATERIALS AND METHODS

This retrospective clinical study was approved by our institutional review board, and the requirement for informed consent was waived.

From January 2010 to December 2018, 122 patients with histologically confirmed anterior mediastinal tumors underwent thorax CT imaging with intravenous contrast medium for pretreatment evaluation. Among 122 patients, 58 were excluded because of the following criterions: 1) The diagnosis was not thymoma or lymphoma (n=27), 2) The diagnosis was thymic carcinoma and thymic carcinoid (n=10) 3) Patients who previously had a biopsy or were treated for a mediastinal mass (n=4), 4) Thorax CT was taken at another hospital or was performed without a contrasted medium (n=14). 5) The image quality of thorax CT was not adequate for further analysis because of cardiac or respiratory motion artifacts (n=3). Finally, we enrolled 64 patients with thymoma and lymphoma in our study. The thymomas in all 34 patients were proven pathologically after surgical resection and lymphomas in all 30 patients were confirmed histologically after mediastinotomy and video assisted thoracoscopic surgery (VATS).

Ultimately, 34 patients with thymoma (18 men, 16 women, mean age 54 years, range 25–81 years) and 30 patients with lymphoma (15 men, 15 women, mean age 43 years, range 17–79 years) were enrolled in the study.

Thoracic CT examinations were performed using a single spiral acquisition of the entire lung from the apex to the base with subjects in the supine position in a 64-slice CT scanner (Philips Brilliance 64; Philips Medical Systems, Best, The Netherlands). All images were acquired in breath-hold after inspiration with 80-100 ml of non-ionic iodinated intravenous contrast medium (300 mg iodine/ml) administration. Scanning parameters were as follows: voltage 120 kV, current 100 mA, and slice thickness of 0.9 mm.

CT histogram measurements were performed by using the licensed imaging analysis software (Myrian; Intrasense, France). Images that met the criteria were evaluated by two radiologists for volumetric histogram analysis. The analysis was performed by KŞ (2 years of experience) and supervised by NSG (11 years of experience). Both radiologists were blinded with respect to the final diagnosis. The region of interest (ROI) was determined by drawing contours of the mediastinal mass manually slice-by-slice for extraction of the volume of interest (VOI). The VOI generated on axial slices was checked out and corrected, if necessary, on sagittal and coronal reformatted images. The measurement tool was initially set to include a range of pixels from - 100 to + 300 HU. Then, a graph of the percentage of pixel numbers on the y-axis versus the pixel attenuation (HU) number on the x-axis was obtained from the VOI. To investigate longitudinal changes in the mass in detail, the number of pixels in the VOI between -100 HU and 300 HU were calculated at every 20 HU interval and the percentage of each 20 HU density area occupying in the mass between -100 and 300 HU (pixel%) was evaluated for each patient. For statistic analysis, HU numbers on the x-axis were grouped as follows; HU1, between -100 HU and -79 HU; HU2, between -80 HU and -59 HU; HU3, between -60 HU and -39 HU; HU4, between -40 HU and -19 HU; HU5, between -20 HU and -1 HU; HU6, between 0 HU and 19 HU; HU7, between 20 HU and 39 HU; HU8, between 40 HU and 59 HU; HU9, between 60 HU and 79 HU; HU10, between 80 HU and 99 HU; HU11, between 100 HU and 119 HU; HU12, between 120 HU and 139 HU; HU13, between 140 HU and 159 HU; HU14, between 160 HU and 179 HU; HU15, between 180 HU and 199 HU; HU16, between 200 HU and 219 HU; HU17, between 220 HU and

239 HU; HU18, between 240 HU and 259 HU; HU19, between 260 HU and 279 HU; HU20, between 280 HU and 300 HU. The volume of the mediastinal mass and the average HU value for each mediastinal mass were calculated.

Two radiologists also evaluated the CT features of the tumors, including margin, vascular relationship, homogeneity, necrosis, and internal calcification.

### *2.1 Statistical Analysis*

Statistical analyses were performed using a software package SPSS 21.0 ( IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Continuous variables were reported as mean ± standard deviation. Categorical data are given as a percentage (%). Shapiro Wilk's test was used to investigate the suitability of the data for normal distribution. In the comparison of normally distributed groups, independent sample t-test analysis was used for cases with two groups. The Mann-Whitney U test was used for the cases with two groups in the comparison of the groups that did not conform to the normal distribution.

Pearson Chi-Square, Pearson Exact Chi-Square, and Yates Chi-Square analyses were used in the analysis of the created cross tables. A value of $p<0.05$ was accepted as a criterion for statistical significance.

## III. RESULTS

Pathological results were obtained by performing thymectomy in the thymoma group and biopsy with mediastinoscopy or VATS in the lymphoma group. Thymomas and lymphomas are classified according to the World Health Organization classification. The number of Type A, Type B, and Type AB thymomas in the study were 10, 23, and 1 respectively. The pathological compositions of the 30 lymphoma patients included Hodgkin lymphoma (n =11), and Non-Hodgkin lymphoma (n =19).

Sixteen of 34 patients with thymoma (47.1%) and 15 of 30 patients with lymphoma were women (50.0%). There was no significant difference in gender between the thymoma and lymphoma groups ($p = 1.000$).

The mean age was 53.59 ± 14.18 in the thymoma group and 42.70 ± 17.62 in the lymphoma group. The mean age of the lymphoma group (42.70 ± 17.62) was significantly younger than the thymoma group (53.59 ± 14.18 ) ($p = 0.008$). Detailed demographic information and CT findings are summarized in Table 1.

When the margin characteristics were examined, a significant difference was found between the thymoma and lymphoma groups ($p = 0.020$). Thymoma demonstrated multi-lobule margin characteristics while lymphoma had smooth contours.

When the vascular relationship and distribution of patients between the pathology groups were examined, a significant difference was found between the groups ($p<0.001$).

There was no significant difference in homogeneity, necrosis, and calcification of the tumor between the groups ($p>0.05$). The relationship of the tumor with adjacent vascular structures was significantly different between the groups ($p<0.05$).

The mean tumor volume of the lymphoma (331.72 ± 382.19) group was found to be significantly higher than the thymoma (67.40 ± 97.19) group ($p < 0.001$).

Histogram analysis of the lymphoma and thymoma groups showed a significant difference in skewness and kurtosis between the lymphoma and thymoma groups. Lower kurtosis and skewness were observed in thymoma compared with lymphoma. The lymphoma group had a more right-skewed distribution than the thymoma group ($p = 0.035$) (Figure 1). Table 1 shows the results of histogram analysis in thymoma and lymphoma groups.

The mean HU values of the thymoma group (50.30±38.68) and lymphoma group (50.72± 12.14) were not significantly different ($p> 0.05$).

## IV. DISCUSSION

Thymoma and lymphoma are the two most common types of tumors in the anterior mediastinum. Diagnosis is important as it will change the treatment protocol. Although the gold standard is pathology in tissue diagnosis, every surgeon needs to be able to comment with radiological imaging beforehand.

CT is the imaging modality of choice for evaluating thymoma and can help distinguish thymoma from other anterior mediastinal abnormalities (4). In previous studies, the role of CT in the diagnosis of thymoma and mediastinal lymphoma has been discussed, but most studies were focused mainly on qualitatively analyzing the imaging features of the lesions, and few have conducted quantitative analyses (6,7).

The present study aimed to investigate the performance of density histograms (mean HU, skewness, and kurtosis) to differentiate thymoma and lymphoma in patients with a mediastinal mass. Although there we no significant difference in mean HU of the lymphoma and thymoma groups, volumetric CT histogram analysis revealed significant differences in kurtosis and skewness. We suggest that this finding might be associated with the histopathological features of the tumors and their contrast enhancement characteristics. Since lymphoma has enlarged nuclei and hyper-cellularity reducing the extracellular water component, its dense internal structure may alter the percentage of pixels with a higher density (6). In addition, the results of this study may be a consequence of tumor necrosis in thymoma since necrotic tissue would be lower in density and demonstrate less enhancement because of avascularity. Thus, the percentage of hyperattenuating pixels was found to be lower in thymoma. Moreover, it is known that lymphoma often infiltrates into vessel walls (9). This feature may also lead to increased contrast enhancement in lymphoma compared with thymoma and effect density histograms.

It is reported that most malignant lymphomas of the mediastinum occur in younger individuals compared to thymomas (3). The results of our study were in accordance with the literature.

As it is demonstrated in the study of H.Yabuuchi et al., in anterior mediastinal masses, the size of the mass was found to be significantly larger in the lymphoma group in our study (7). Similarly, the mean tumor volume of the lymphoma group was found to be significantly higher than the thymoma group.

The relationship of the tumor with adjacent vascular structures was also investigated and it was found that mediastinal lymphoma surrounds the vessels but does not invade them (4). The results of our study support this finding. In the thymoma group, the vascular invasion was not frequent. Signs of vascular invasion were more frequent in patients with lymphoma mostly surrounding the adjacent vascular structures ($p<0.05$).

Our study has several limitations. First, the calibration of our device is done every four months. However, calibration can be considered a limitation in our work, like all histogram studies.

Many histogram studies in the literature have different CT parameters. Although the image parameters used in our center are the same, obtain of images from different CT scanners is another limitation of the study.

There are studies with histograms in many cancer types, including thymoma and lymphoma. Magnetic resonance imaging system and positron emission tomography were used in the majority of these studies (10,11,12,13,14). These examinations may not be available in many health institutions. Therefore, we found it appropriate to carry out this study with the more easily accessible thorax computed tomography.

Finally, only surgically resected thymomas without presurgical treatment were included. Inoperable thymomas which were in the advanced stage were not included in this study. Future studies with a large sample size are needed to confirm our results.

In conclusion, histogram analysis was performed with contrast-enhanced CT, which was primarily obtained for each patient with an anterior mediastinal mass in this study. Histogram

analysis of the lymphoma and thymoma groups showed significant differences in skewness and kurtosis between the lymphoma and thymoma groups. We suggest that the volumetric computed tomography histogram analysis method enables differentiating thymoma from mediastinal lymphoma and thus helps guide the management of the patients.

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*Table 1:* Demographic and CT Findings, and Histogram Analysis of Thymoma and Lymphoma Groups

| Variables | | Pathology n (%) Mean ± Std. Dev. Median (Q1 – Q3) | | Test Statistics P |
|---|---|---|---|---|
| | | Thymoma (n= 34) | Lymphoma (n= 30) | |
| Age (year) | | 53.59 ± 14.18<br>54.00<br>(42.50-64.25) | 42.70 ± 17.62<br>39.50 (29.25-56.25) | **0.008**$^{t}$ |
| Gender | Female | 16 (47.1%) | 15 (50.0%) | 1.000*** |
| | Male | 18 (52.9%) | 15 (50.0%) | |
| Margin | Smooth | 3 (8.8%) | 9 (30.0%) | **0.020**** |
| | Mild Lobule 3-5 | 3 (8.8%) | 0 (0.0%) | |
| | Multi- lobule >5 | 28 (82.4%) | 21 (70.0%) | |
| Vascular Relationship | Non Invasive | 26 (76.5%) | 8 (26.7%) | **<0.001*** |
| | Invading | 7 (20.6%) | 9 (30.0%) | |
| | Surrounding | 1 (2.9%) | 13 (43.3%) | |
| Homogeneity | Solid -Homogeneous | 11 (32.4%) | 13 (43.3%) | 0.217* |
| | Solid -Heterogeneous | 15 (44.1%) | 7 (23.3%) | |
| | Cystic-Solid Heterogeneous | 8 (23.5%) | 10 (33.3%) | |
| Necrosis | No | 25 (73.5%) | 21 (70.0%) | 0.880** |
| | Yes | 8 (23.5%) | 9 (30.0%) | |
| | Uncertain | 1 (3.0%) | 0 (0.0%) | |
| Calcification | No | 23 (67.6%) | 27 (90.0%) | 0.064*** |
| | Yes | 11 (32.4%) | 3 (10.0%) | |
| Mean Volume | | 67.40 ± 97.19<br>41.89<br>(12.53-101.20) | 331.72 ± 382.19<br>176.83<br>(74.29-487.78) | **<0.001**$^{MW}$ |
| Mean HU | | 50.30 ±3 8.68<br>44.50<br>(34.19-52.99) | 50.72 ± 12.14<br>49.16 (42.47-54.99) | 0.080$^{MW}$ |
| Skewness | | 1.89 ± 0.49<br>2.01 (1.53-2.19) | 2.15 ± 0.47<br>2.22 (1.86-2.45) | **0.035**$^{t}$ |
| Kurtosis | | 2.79 ± 2.18<br>3.02 (1.10-3.98) | 4.01 ± 2.46<br>4.07 (2.36-5.33) | **0.039**$^{t}$ |

**Pearson Chi-Square **Pearson Exact Chi-Square ***Yates Chi-Square t: Independent Samples t Test MW: Mann Whitney U Test*

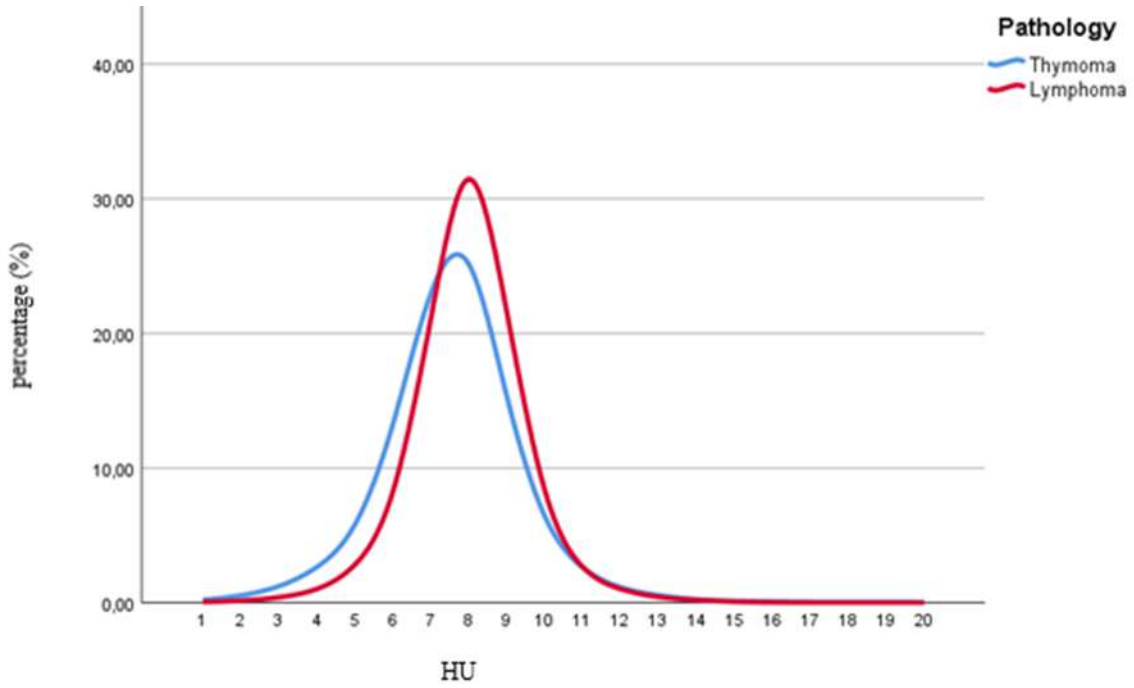


*Figure 1:* Density Histogram of Lymphoma and Thymoma Groups. the Density Histogram Showed the Percentage of the Number of Pixels at Every 20 HU Interval. Blue and Red Curves Represent the Values of Thymoma and Lymphoma, Respectively

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# An Undiagnosed Case of Systemic Lupus Erythematosus Presenting with Diminution of Vision

*Eliya Shrestha, Krishna Gurung, Anju Gurung, Babita Gurung, Hari Maya Gurung & Hari Bikram Adhikari*

## ABSTRACT

Systemic Lupus Erythematosus (SLE) is an autoimmune multisystemic disease which affects many organs which can lead to mortality. A 33-year-old female came with diminution of vision in both eyes for 5 days. Her best corrected visual acuity is 6/12 and 6/60 in right and left eye respectively. Fundus examination showed blurred and elevated disc margin with dilated veins. Macular OCT showed increased macular thickness. MRI brain and orbit were normal. The patient was admitted to hospital for further investigation and treatment. Injection Mannitol 20% 200ml was infused and Tab Acetazolamide was given. The patient complained of severe abdominal pain for which she was referred to physician. On the physical and blood examination she was found to a case of SLE.

*Keywords:* SLE, disc edema.

*Classification:* NLM Code: W1-1065

*Language:* English

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# An Undiagnosed Case of Systemic Lupus Erythematosus Presenting with Diminution of Vision

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## ABSTRACT

*Systemic Lupus Erythematosus (SLE) is an autoimmune multisystemic disease which affects many organs which can lead to mortality. A 33-year-old female came with diminution of vision in both eyes for 5 days. Her best corrected visual acuity is 6/12 and 6/60 in right and left eye respectively. Fundus examination showed blurred and elevated disc margin with dilated veins. Macular OCT showed increased macular thickness. MRI brain and orbit were normal. The patient was admitted to hospital for further investigation and treatment. Injection Mannitol 20% 200ml was infused and Tab Acetazolamide was given. The patient complained of severe abdominal pain for which she was referred to physician. On the physical and blood examination she was found to a case of SLE.*

*Keywords:* SLE, disc edema.

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## I. INTRODUCTION

SLE is an autoimmune multisystem disease which may lead to mortality. The author is presenting a case of bilateral disc edema found to be a case of SLE after systemic investigation. So all cases of disc edema should be investigated thoroughly for detailed evaluation. SLE has been detected in young even in 13 years with neuropsychiatric symptoms(1) especially in female population.

However very few cases has been reported in male patients too(2). Akhil et al reported two male patients presented with generalized body ache and skin involvement. The author is reporting a adult female with neuropsychiatric symptoms.

## II. CASE REPORT

33 years female presented with blurred vision in both eyes for 5 days in both eyes. It was painless gradual onset, progressive in nature but not associated with floaters, flashes or redness. She had difficulty in opening her mouth with generalized body aches and joint pain for the last 7 months. She also complaint of vomiting on ingestion of any food during last 7 months. On ocular examination her uncorrected visual acuity is 6/36 and best corrected is 6/12 in right eye and 6/60 with no improvement in left eye. Her both eyebrows, eyelids, and anterior segment were normal with normal pupillary reflex. Both fundi showed blurred and elevated disc margin with dilated veins. There were cotton wool spots and flame shaped hemorrhage on juxta papillary region and around maculae. Maculae showed dull foveal reflex. The intraocular pressure in right eye is 21 and in left eye is 19. With these findings she is diagnosed with grade IV disc edema in both eyes and differential diagnosis papilledema. MRI brain and orbit showed normal scan. Macular OCT showed increased thickness in macula. With these findings the patient was admitted in ward and diuretic medicine was given intravenously. The patient complaint of abdominal pain so physician consultation was sent. She found to have splenomegaly on abdominal ultrasonography. Further blood investigation revealed hemoglobin 11.5 mg/dl. PCV- 34.5%, platelet-98000 cells/cu mm, urea- 56mg/dl. Autoimmune IFA test showed serum ds DNA positive with dilution of 1:10 primary intensity +1 and endpoint titer 1:10. Serum antinuclear antibodies were positive in primary dilution 1:80, primary intensity of IF 4+, homogenous ANA pattern and endpoint titer 1:640. ABS to extractable nuclear

antigen (ANA BLOT) showed smith antibodies positive, U1 SM/ RNP antibodies positive/SS- A antibodies negative, RO-52 antibodies negative, SS-B antibodies negative, dsDNA strong positive, anti-histone antibodies positive, anti-centromere antibodies negative, SCL-70 IGG antibodies negative, PM-SCL antibodies negative, JO-1 antibodies negative, PCNA antibodies negative, Nucleosome antibodies positive, AMA- M2 Antibodies negative, ribosomal P antibodies positive.

## III. DISCUSSION

SLE with severe disc edema has been reported by Shekhar(1)in 2018. Bettman has reported papilledema in a case of SLE in 1968 associated with asymptomatic intracranial hypertension (3).

The largest multicenter studies were reported by Z. Jin et al in 2021(4). They studied the population attribute factor (PAF) of risk factors of mortality. They found 40.4% death is due to anemia, nonuse of antimalarial drug and hypoalbuminemia. SLE related ocular findings can be found in one-third of cases(5). According to the SLICC criteria for classification of SLE suggest us lupus nephritis alone in presence of at least one of the immunological variables or four criteria with one having a clinical criterion and one immunologic criterion is required to diagnose SLE(6). Neither clinical criteria alone nor positive serological test alone should be considered SLE.

Our patient meets the SLICC criteria for the diagnosis of SLE. Up to 50% of pt with active NP-SLE symptoms may have MRI findings as T2/FLAIR related focal white matter hyperintensities, cortical gray matter lesions, brain atrophy and basilar artery territory infarction(7). However, our case has normal MRI findings.

## IV. CONCLUSION

Systemic lupus erythematosus is a multisytemic autoimmune disease which can present with different sign and symptoms. In this case the case presented with blurring of vision. So, authors emphasize on the detail evaluation of every cases of blurring of vision with disc edema.

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# Overcoming Resistant Infections (Salmonella Tiphymurim) by formulating Antimicrobials (Streptomycin) with Medicinal Synthetic Aluminum Magnesium Silicate {Al4 (SiO4)3 + 3Mg2SiO4 → 2Al2 Mg3 (SiO4)3}

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## ABSTRACT

Enhancing patients` immune responses and antimicrobials` efficacies could overcome Antimicrobial Resistant Infections (AMR). Aluminum-magnesium silicate (AMS) is an approved Nano-stabilizing agent. Stabilizing antimicrobials prolongs time they stay at high-bioavailability and Nano-particles enhance antimicrobials` delivery to effect-targets. Prolonging high-bioavailability time and enhancing delivery to targets improve efficacies of antimicrobials while antioxidants improve immunity of patients. With improved efficacy, antimicrobials` lower dosages achieve desired effects thus avoiding side effects (immune- suppression) from high dosages. Based on these hypotheses, Medicinal synthetic AMS (MSAMS)- Streptomycin (antimicrobial-model) formulation and Vitamin C were used to treat Streptomycin- resistant Salmonella typhimurium infections (AMR-model) in chicks (patient-models).

*Keywords:* antimicrobial resistant infections; 75-% dosages of MSAMS-stabilized medicines; antioxidant-supportive treatments.

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# Overcoming Resistant Infections (*Salmonella Typhimurium*) by Formulating Antimicrobials (Streptomycin) with Medicinal Synthetic Aluminum Magnesium Silicate $\{Al_4(SiO_4)_3 + 3Mg_2SiO_4 \rightarrow 2Al_2Mg_3(SiO_4)_3\}$.

M. C. O. Ezeibe[α], C. C. Ogbu[σ], I. J. Ogbonna[ρ], F. I. Ezeibe[ↀ], C, Alex-Okoroafor[¥], O. Agbakwuru[§], C. A, Akpan[χ], M. E. Sanda[ν], E. Kalu[Θ], N. U. Njoku[ζ] & M. I. Udobi[£]

## ABSTRACT

*Enhancing patients` immune responses and antimicrobials` efficacies could overcome Antimicrobial Resistant Infections (AMR). Aluminum-magnesium silicate (AMS) is an approved Nano-stabilizing agent. Stabilizing antimicrobials prolongs time they stay at high-bioavailability and Nano-particles enhance antimicrobials` delivery to effect-targets. Prolonging high-bioavailability time and enhancing delivery to targets improve efficacies of antimicrobials while antioxidants improve immunity of patients. With improved efficacy, antimicrobials` lower dosages achieve desired effects thus avoiding side effects (immune-suppression) from high dosages. Based on these hypotheses, Medicinal synthetic AMS (MSAMS)-Streptomycin (antimicrobial-model) formulation and Vitamin C were used to treat Streptomycin-resistant Salmonella typhimurium infections (AMR-model) in chicks (patient-models). Streptomycin`s recommended dosage (25 mg/kg) worsened the infection, from -746.86%-reduction to -782.29 %-reduction. Stabilizing Streptomycin with MSAMS at that high dosage worsened the infection further, to -855.43 %-reduction but at 75 % dosage (18.75 mg/kg), stabilizing Streptomycin with MSAMS and supporting the treatment with Vitamin C (through feed) terminated the AMR (100 %-reduction).*

*Keywords:* antimicrobial resistant infections; 75-% dosages of MSAMS-stabilized medicines; antioxidant-supportive treatments.

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## I. INTRODUCTION

Antimicrobial resistance (AMR) is a Global health challenge. Use of antimicrobials as growth promoters in animal farming is a major cause of AMR in humans (Agyare *et al.,* 2018). In poultry, treatment failures due to AMR result in great economic losses. AMR in poultry is also a big risk to human health (Van *et al.,* 2012; Okorie-kanu *et al.,* 2016).

Antimicrobial resistance means loss of sensitivity by microorganisms to drugs which were effective (Sinyangwe *et al.,* 2004). Mechanisms for Antimicrobial resistance include loss of surface specific receptors or transporters for drugs, rapid metabolism of drugs and alteration of specific targets for drugs. There are many reports of increases in resistance involving bacteria of Veterinary and public health importance, including *Salmonella typhimurium,* against commonly used drugs which include Streptomycin (Bortolaia *et al.,* 2016, Nguyen *et al.,* 2017).

Apart from wrong use of antimicrobials in animal farming which causes development of resistance by infections in animals before they are transmitted to human beings, use of high dosages in treating animals leads to high concentrations of residues of the drugs in human foods of animal origin which leads to development of

antimicrobial resistance in humans (Reig and Toldra, 2008, Goetting *et al.*, 2011; Okorie-kanu *et al.,* 2016; Agyare *et al.,* 2018). Despite these public health concerns, antimicrobials are essential in poultry-production. So, effort should be to find treatment-strategies that would prevent and cure AMR.

*Salmonella species* are the most important zoonotic bacterial food-borne pathogens (Addis *et al.,* 2015) being the most frequently isolated bacteria in food-borne disease-outbreaks (Balakrishnan *et al.,* 2018), accounting for around 93.8 million food-borne illnesses and 155,000 deaths per year, worldwide (Heredia and Garcia, 2018). *Salmonella species* have also been associated, with increasing concern for emergence and spread of antimicrobial-resistance (Ejo *et al.,* 2015).

Antibiotic-resistant *Salmonella* infections of both humans and animals are universal concerns, particularly in developing countries (Ejo *et al.,* 2015). Apart from morbidity and mortality which they cause in humans and animals, restrictions to trade and discarding contaminated food due to them are important socioeconomic problems (Tadesse *and* Tessema, 2014*).* Of zoonotic *Salmonella species, S. typhimurium and S. enteritidis are more* common (Dhama *et al.,* 2013; Tadesse and Tessema, 2014; Tegegne, 2019)

Molecules of Aluminum magnesium silicate (AMS), a WHO approved medicine/stabilizing agent, consist of *Nanoparticles* with negative electrical charges on their surfaces and positive charges on their edges (Cristina *et al.*, 2007, Vanderbilt, 2012). Presence of the two charges on AMS *Nanoparticles* makes them to hydrate to form three dimensional colloidal structures in solutions. The colloidal structures stabilize other drugs that are in formulation with AMS (Vanderbilt, 2012). For this effect, AMS is an approved pharmaceutical stabilizing agent.

Meanings for stabilize include protecting a substance from being destroyed. Drug metabolism destroys drugs and renders them no longer effective. So, stabilizing drugs reduces rate at which the body metabolizes (destroys) them so that they remain at high concentrations for extended periods. When drugs remain at high concentrations in blood for longer periods, their effectiveness improves. Also, AMS consists of *Nanoparticles* and *Nanoparticles* enhance delivery of drugs to their effect-targets which also improves efficacy.

Antioxidants (Vitamins A, C and E) reduce oxidative stress and so, protect the immune system to enhance its response to challenges from bacteria, viruses and parasites. The Vitamins are required in small dosages for the immune system to function optimally. Vitamin C supplementation, in particular, has been reported to reduce duration and severity of COVID-19.

It was therefore postulated that treatment strategy of enhancing immunity of patients with antioxidants, enhancing efficacy of antimicrobials by stabilizing them with AMS and reducing side effects of the Antimicrobials by using their lower doses for treatments could terminate treated infections so that none remains to become AMR. Infections that have already become resistant could become curable by same antimicrobials they are resisting.

Nigeria does not have natural deposits of AMS $\{Al_2Mg_3\ (SiO_4)_3\}$ still there are two other solid minerals, Aluminum silicate $\{Al_4\ (SiO_4)_3\}$ and Magnesium silicate $\{Mg_2SiO_4\}$ which are also approved medicines (Galindo and Cereso 2006), found in the country and in many other countries. The two medicines were used to formulate a form of AMS, named, Medicinal synthetic Aluminum magnesium silicate {MSAMS: $Al_4\ (SiO_4)_3 + 3Mg_2SiO_4 \rightarrow 2Al_2Mg_3\ (SiO_4)_3$: Ezeibe, 2012}. To overcome the challenge of AMS, Aluminum silicate and Magnesium silicate being un-absorbable, Dextrose monohydrate was incorporated in MSAMS so that the simple sugar conveys the electrically charged *Nanoparticles* across mucous membranes into blood by the principle of active transport (Murray, 2000) so that antimicrobials stabilized with MSAMS would have systemic effects. A formulation of 10 % MSAMS and 5 % Streptomycin, supported with Vitamin C was used to treat Streptomycin-resistant *Salmonella tiphymurim* infected chicks.

## II. MATERIALS AND METHODS

Eighty (80) broiler-chicks aged 3 weeks (age beyond which *S. typhimurium* may, no longer cause much mortality) which were infected with Streptomycin-resistant *Salmonella typhimurium,* were used for trial of the new drug-formulation and the suggested treatment-strategy. The treatment- groups (20 chicks each) *were:*

Treated with Streptomycin at its 100 %-dosage,
Treated with Streptomycin-MSAMS at Streptomycin`s 100 %-dosage,
Treated with Streptomycin-MSAMS at Streptomycin`s 75 %- dosage + Vitamin C,
Untreated (control).

The treatment lasted 5 days. Before the treatment and on day-3 of the treatment, day-1 post treatment (PT) & day-4 PT, any first two (2) chicks caught on entering pen of each treatment-group were randomly selected, for bile which was used to determine *Salmonella tiphymurim* colony-forming units (CFU). Of bile from each chick, 0.1 ml was added to 0.9 ml of normal saline to get a 1:10 dilution. Again, 0.1 ml of the 1:10 bile dilution was added to 0.9 ml of normal saline to make a 1:100 bile dilution. Finally, 0.05 ml of the 1: 100 bile dilution was plated on MacConkey agar and on SSA agar before incubating at 37˚C for 24 hours. *Salmonella* colonies (X) were counted and expressed as colony-forming units per ml (CFU), using the formula: CFU = x/5 × 10,000. Infection-reduction rate for each group on each day of assessment was calculated as percentage of the mean-CFU before treatment, by which infection of that group reduced (Mean-CFU before treatment – CFU of the group on the day of assessment divided by Mean-CFU before treatment, multiplied by 100). Negative results indicate increase in load of the infection while positive results show reduction in the infection-load. The infection-reduction rates were compared by plotting them as a graph.

## III. RESULTS

Mean colony forming units (CFU) in bile, of the Streptomycin-resistant *Salmonella tiphymurim*-infected chicks before treatment was 8.75. For, the untreated group of chicks the infection-reduction rates were: -482.86 % (increase), -682.86 % (increase) and -716.86 % (increase) for day-3 on the treatment, day-1 PT and day-4 PT. For the group treated at recommended dosage of Streptomycin (25 mg/kg), the CFU-reduction rates for the three days were – 1.83 %(increase), -12.57 % (increase) and -782.29 % (increase) respectively but for the group treated at same recommended dosage of Streptomycin with Streptomycin-MSAMS formulation, the CFU-reduction rates were 14.29 %, 26.40 % and -855.42 % (increase) respectively while for the group treated at 75% of recommended dosage of Streptomycin (18.75mg/kg) with the Streptomycin-MSAMS formulation plus Vitamin C, the reduction rates were 100 %, 100% and 100% respectively (infection-termination). *S. typhimurium* CFUs per/ml of bile of the treated chicks are as presented on Table 1 while their infection reduction rates are as presented on Table 2 while their comparison is as on Figure 1.

*Table 1:* Colony-Forming Units ($\times 10^6$) of Streptomycin-Resistant *Salmonella tiphymurim* in Bile of Chicks Treated With Streptomycin-Medicinal Synthetic Aluminum Magnesium Silicate Formulation and Vitamin C

| Days of treatment | Untreated | | 25mg/kg Strept. | | 25mg/kg Strept-MSAMS | | 18.75mg/kg Strept-MSAMS + Vit. C | |
|---|---|---|---|---|---|---|---|---|
| 3 days on treatment | 51.00 | | 8.91 | | 7.50 | | 0.00 | |
| 1 day post treatment | 68.50 | | 9.85 | | 6.44 | | 0.00 | |
| 4 days post reatment | 74.10 | | 77.20 | | 83.60 | | 0.00 | |

Table 2: Reduction-Rates (%) of Streptomycin-Resistant *Salmonella tiphymurim* Infections, in Chicks Treated With Streptomycin-Medicinal Synthetic Aluminum Magnesium Silicate Formulation and Vitamin C

| Days of treatment: | Untreated | | 25mg/kg Strept. | | 25mg/kg Strept-MSAMS | | 18.75 mg/kg Strept-MSAMS + Vit. C | |
|---|---|---|---|---|---|---|---|---|
| 3 days on treatment | | -482.86 | | -1.83 | | 14.29 | | 100 |
| 1 day post treatment | | -682.86 | | -12.57 | | 26.40 | | 100 |
| 4 days post treatment | | -716.86 | | -782.29 | | -855.42 | | 100 |

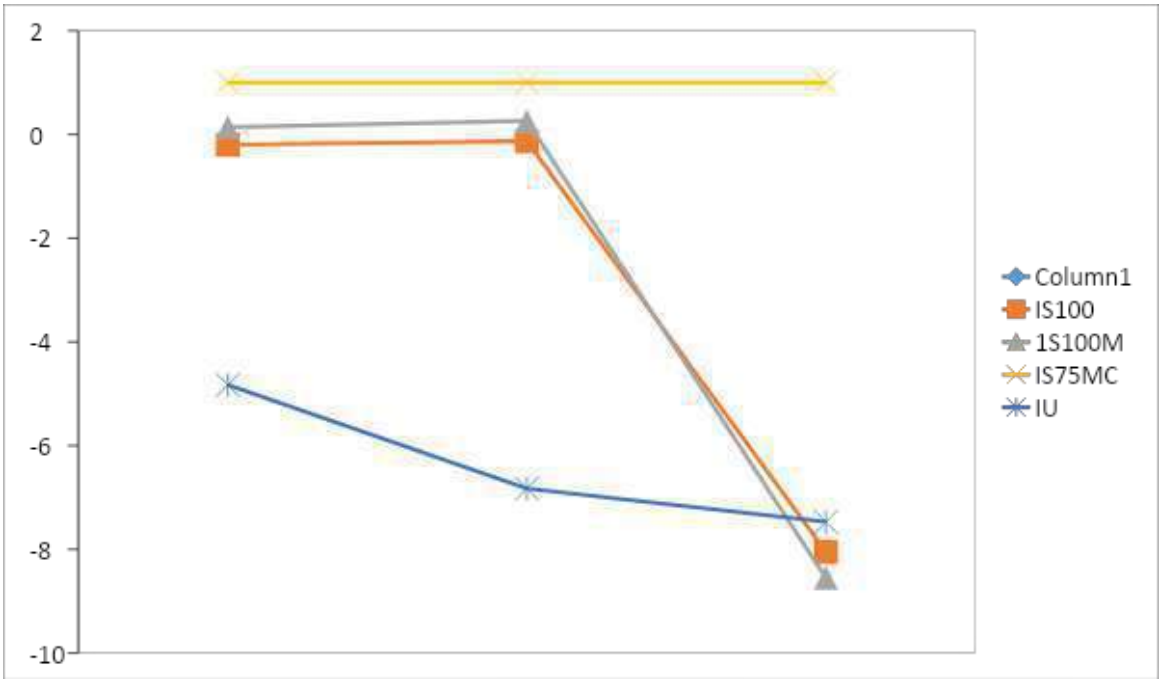


*Fig. 1:* Comparison of Reduction-Rates (%) of Streptomycin-Resistant *Salmonella tiphymurim* Infections, in Chicks Treated With Streptomycin-Medicinal Synthetic Aluminum Magnesium Silicate Formulation and Vitamin C

## IV. DISCUSSION

Discovery of drugs that inhibit pathogenic microorganisms (antimicrobials) was a major revolution in medicine. So, development of resistance against the drugs is also a major setback to Global health. Current increase in drug-resistant pathogenic microorganisms is a big challenge to medical researchers, world over. Efforts to keep developing new drugs to replace those that disease-agents overcome is faced with many difficulties, including cost and time it takes to design new drugs. One strategy being tried to overcome AMR is development of adjuvants that could enhance efficacy of antimicrobials (Erin *et al.*, 2015).

As a stabilizing agent, AMS protects drugs against rapid degradation by metabolic processes thus prolonging time of their high bioavailability. Prolonging time of high bioavailability enhances efficacy and so, dosages of the drugs needed to achieve desired effects are reduced. When lower dosages are used for treatments, immune responses of patients enhance. Synergy between enhanced efficacy and enhanced immunity could clear ≥ 95 % of treated infections so that AMR is prevented (Brent *et al,* 2001). Even already resistant infections could be cured. Also, since AMS-units are *Nanoparticles,* they enhance delivery of drugs to targets and across

physiological barriers, including blood-brain barrier.

Drugs have both desired effects and side effects. Most antimicrobial drugs cause immune-suppression when used at high dosages. Formulating antimicrobials with the MSAMS makes it possible for their lower dosages to achieve desired effects so that their side effects which occur with high dosages could be reduced. Reducing side effects of antimicrobials improves immune responses of patients. Improving immune responses of patients help to clear infections.

Trials of the MSAMS on efficacy of different antimicrobials, so far, have shown that it improves efficacy of the antimicrobials to help them clear enough infections so that AMR is prevented. Formulating other drugs and MSAMS has led to prevention of AMR against Ampicillin trihydrate by bacteria (Ezeibe, *et al* 2012 a). It also prevented AMR by *Heligosomodes bakeri,* (helminths) against Piperazine citrate (Ezeibe *et al*, 2012 b). Formulating MSAMS with Chloroquine sulphate also led to enough clearance of Plasmodium *berghei* such that development of AMR by the malaria parasite may no longer occur (Ezeibe 2020). That strategy of formulating MSAMS with antimicrobials and supporting their treatment with antioxidants has also restored efficacy to Ampicillin trihydrate against resistant *E. coli* (Ezeibe et al 2013) and to Cotrimaxazole against resistant *Salmonella pulorum*. (Ezeibe *et al* 2019)

In current trial of MSAMS-Streptomycin formulation supported with Vitamin C against resistant *Salmonella typhimurium* infections, all that Streptomycin alone at its recommended dosage (25 mg/kg) could achieve was to slow rate at which the infection was increasing on day-3 of the treatment and on day-1 post treatment but by day-4 post treatment, the infection increased even more than that of the untreated group. That reduced effect of Streptomycin at the recommended dosage is a confirmation that the *S. typhimurium* infection was Streptomycin-resistant. The antimicrobial had lost efficacy against the infection and so could no longer cure its disease. Sudden rise in infection-rate in that group, 4 days after treatment, suggests that while Streptomycin had only negligible effect on the resistant infection, its side effects depressed immunity of the chicks which was the only defense left for the patients. So, when the treatment was withdrawn, there was nothing to hinder the infection.

In the group of chicks treated at same recommended dosage of the antimicrobial, stabilized with MSAMS, the treatment reduced (not just slowing multiplication of the infection) the resistant infection on both day-3 on the treatment and on day-1 PT but again following withdrawal of treatment, the infection flared up above any other group. That the infection actually reduced in this group while it did not reduce with Streptomycin alone, suggests that formulating Streptomycin with MSAMS improved its efficacy such that even the already resistant infection became sensitive. The sudden increase of the infection, higher than both the untreated group and the group treated with Streptomycin without MSAMS, suggests that MSAMS potentiated both desired effect of Streptomycin (efficacy) and its side effect (immune suppression) so that with withdrawal of the treatment, the infection (which treatment could not terminate), had the least resistance.

Reducing dosage of Streptomycin by 25% to use its 75%- dosage (18.75 mg/kg) for treatment with the Streptomycin-MSAMS formulation, terminated the resistant infection, after only 3-days on the treatment. The 100 % infection load reduction achieved in that group of 75% Streptomycin-dosage in MSAMS plus Vitamin C remained both on day-1 PT and on day-4 PT, confirming that the treatment terminated the resistant infection.

Apart from terminating the resistant infection which means cure for AMR, that the treatment achieved such an effect with reduction both in dosage of the drug and in course of the treatment means reduction in cost of treatment and reduction in residues of the drug in human foods of animal origin. Such reduction in drug-residues in foods will reduce incidences of AMR in humans.

When same treatment-strategy (using 75% of recommended dosages of MSAMS-stabilized antimicrobials, supported with antioxidants) was applied to Ampicillin trihydrate (Ezeibe *et al* 2013) and Cotrimoxazole (Ezeibe *et al* 2019) against resistant infections, though they achieved enough infection-reduction that could lead to cure and prevention of AMR (≥ 95 %), they could not terminate the infections. Some infections (≤ 5 %) were left which immunity could clear with time (Brent *et al*, 2001). In this study with Streptomycin, the strategy terminated the resistant infection (100 %-infection reduction). Level of resistance by isolate used in each trial and side effect of each antimicrobial being tested may be responsible for differences in rates (%) of clearance that result with that strategy of using 75 % of recommended dosages of MSAMS-stabilized antimicrobials supported with antioxidants to treat resistant infections. However, that the treatment-strategy restores efficacy to antimicrobials has remained consistent.

Results of these trials of antimicrobials-MSAMS (Nano-stabilizing agent) formulations and antioxidants on both sensitive and resistant infections of different bacteria, protozoa and helminths suggest that formulating antimicrobials with Nano-stabilizing agents and supporting their treatments with antioxidants may be an effective treatment-strategy for prevention and treatment of AMR. Also, since a reduced dosage of Streptomycin, stabilized with MSAMS, achieved 100 % clearance of the resistant infection after only three days, the strategy may also lead to reduction in course of treatments for Streptomycin and possibly for other antimicrobials, too.

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