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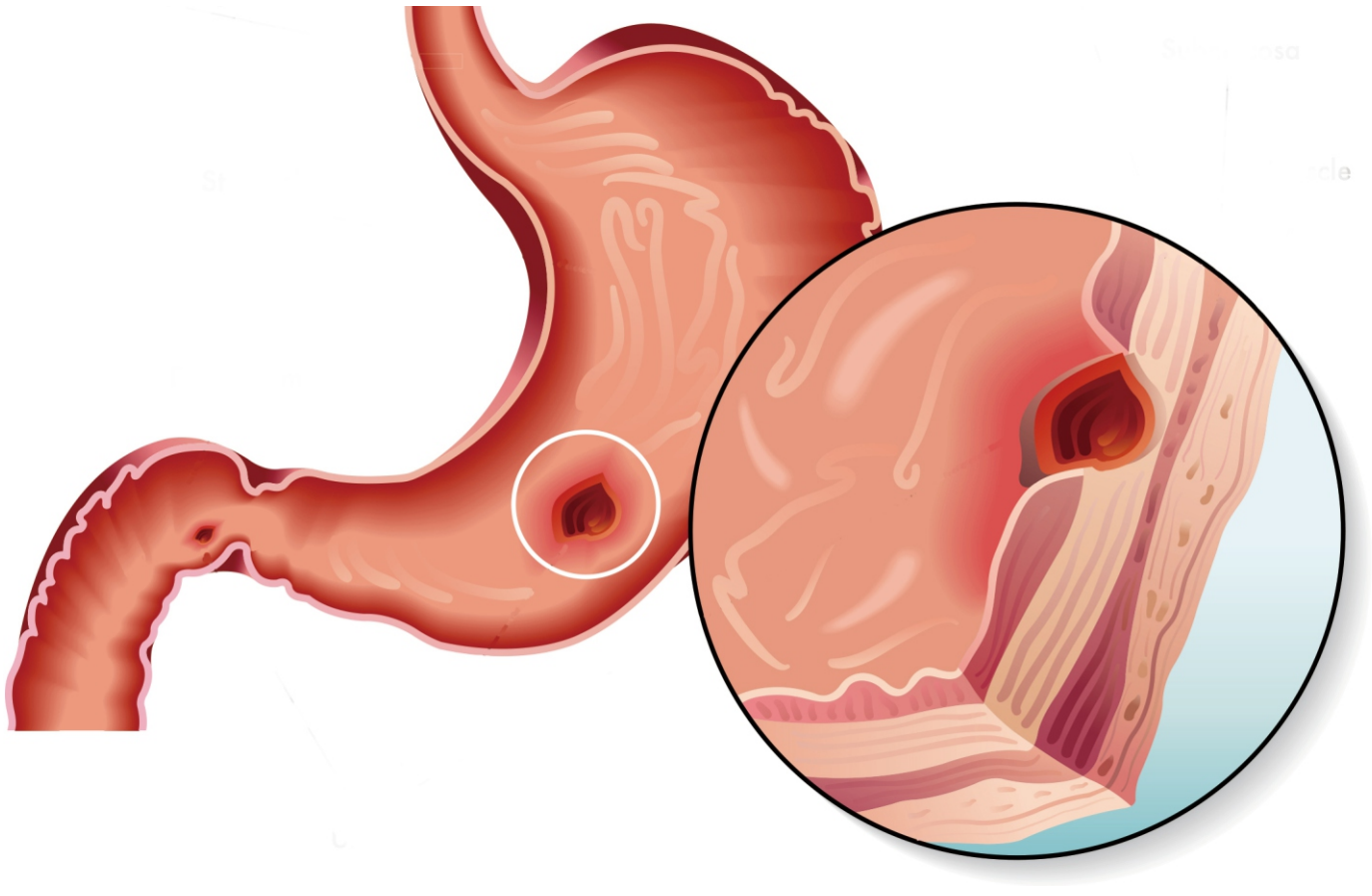

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# Literature Review of Inflammatory Bowel Disease in South Asian Populations

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## Abstract

**Background:** South Asians have been recently identified as having rapidly rising incidence of inflammatory bowel disease (IBD). There is a paucity of data regarding the phenotypic and genotypic associations of IBD among the patients of this region. Due to the rising disease prevalence, a study on South Asian population can disclose more information about the etiopathogenetic causes of the disease. **Methods:** Here we did a review article of IBD among South Asians. In order to get a correct sense of factors associated with the disease, we have reviewed approximately 150 articles through the PubMed search and google scholar. **Results:** We attempted to find temporal trends of IBD among south Asian population, compared phenotype and genotype of IBD among South Asians and western patients and looked at the patterns of IBD presentation in different countries of South Asia. We have also reviewed the differences in the incidence of IBD among South Asian immigrants and discussed the treatment challenges of IBD among this special population. **Conclusion:** We identified that both patients in South Asia as well as South Asian patients living in Western countries are at greater risk for all types of IBD. This geographical region provides an opportunity for revealing possible etiopathogenetic factors. Further population-based studies, comparison of studies in South Asians and immigrants from South Asian countries, and large-scale biologic treatment models need to be accelerated to control the disease burden in South Asians, as well as to achieve reduced burden globally.

## Keywords

Inflammatory Bowel Disease, South Asians, Phenotype and Genotype

## 1. Introduction and Background

Due to global industrialization in recent decades, multiple diseases have in-

creased dramatically in many populations. The exponential rise of inflammatory bowel disease (IBD) in industrialized countries and the emergence of IBD in countries with a traditionally low prevalence, highlight the importance of environmental triggers in the pathogenesis of this disease [1]. In addition, the high incidence of IBD observed in the South Asian immigrant population in Canada and the United Kingdom further reinforces the contribution of environmental triggers [2] [3] [4].

Crohn's disease (CD) and ulcerative colitis (UC) are two clinicopathological subtypes of IBD related to mucosal immune responses of the digestive tract in genetically susceptible individuals. IBD has multifactorial etiologies, including intestinal dysbiosis, altered immune responses, and environmental triggers. Recent additional findings related to the disease include epigenetic changes, inflammasome, and damage-associated molecular patterns [5] [6] [7].

As the two clinicopathological subtypes of IBD have multiple underlying factors and environmental triggers contributing to the disease pathogenesis, this literature review seeks to explain these factors in context of the South Asian population. We first discuss the temporal trends and patterns of IBD in various countries of South Asia and then compare phenotypic differences in IBD between the South Asian and the Western populations. We compared various genetic factors, differences in the treatment approaches, and the effectiveness of biological agents among South Asian and non-South Asian patients. Finally, we have reviewed the pattern of IBD in the South Asian immigrant population and how do they differ from the local population of that region. Through this review, we intend to identify the impact of environmental factors in the pathogenesis of IBD, the challenges present in the treatment of IBD, and to identify a specific area of research which could improve our understanding of IBD.

## 2. Epidemiology: Incidence and Prevalence Rates and Temporal Trends

South Asia is a term used to represent the southern region of the Asian continent, which includes the territories of the sub-Himalayan countries that are a part of the South Asian Association for Regional Cooperation. South Asia is surrounded by other subcategories of the Asian continent including West Asia, Central Asia, Southeast Asia, and East Asia. It is also confined by the Indian Ocean on the south. The countries of this region include Afghanistan, Bangladesh, Bhutan, Maldives, Nepal, India, Pakistan, and Sri Lanka, which cover a total of 5.2 million $km^2$ of land. South Asia is a home of 1.75 billion people, accounting for about one-fourth of the world's population, which makes it the most densely populated region globally. Since the turn of the 21$^{st}$ century, IBD has become a global disease with accelerating incidence in industrializing countries, especially of South Asia [8]. The prevalence of IBD in westernized countries appears to have stabilized [9]. Yet, many studies in South Asia show evidence of a rising incidence of IBD in the last two decades [10]. Increasing

awareness and improved diagnostic methods have resulted in a higher rate of IBD prevalence in South Asia. However, population studies demonstrate the emerging trend of the disease incidence every year [11]. The overall estimated prevalence of IBD in India was 1.4 million in 2010, making it the second country with the highest IBD prevalence after the USA with 1.64 million.

Although the prevalence of IBD in India is less compared to the Western countries, but the total population in India is more than 120 million which makes the total patients of IBD in India to be the highest in the world [12]. Two epidemiological studies on UC have been conducted in northern India. In the first study, a house-to-house survey conducted in the State of Haryana revealed a UC prevalence of $45.5/10^5$ in 1980 [13]. The second study, conducted in the neighboring State Punjab in 2010, revealed a crude incidence of $6.02/10^5$ and a prevalence of $44.8/10^5$. Although the incidence and prevalence found are the highest in Asia, they are lower than across North America and Europe [14]. As the population-based studies have not been conducted which could better determine the burden of CD, the data collected from the hospital is used to determine the prevalence of CD in the population. A multicenter study from northern and eastern India demonstrated a rise in the total number of patients with CD from being less than 5000 in 1987 to 21,061 in 2001. This indicates the increase in IBD cases as well as its prevalence over the years in a newly industrializing country of South Asia [15].

A hospital-based survey performed in two districts of Sri Lanka revealed a prevalence rate of Ulcerative colitis was $5.3/10^5$ and Crohn disease was $1.2/10^5$. The incidence rate was $0.69/10^5$ for Ulcerative colitis and $0.09/10^5$ for Crohn disease. The survey also showed the prevalence of Ulcerative colitis in females more predominantly [16]. In a recent retrospective tertiary care-based multicentric study in Sri Lanka, revealed a pattern of increase in CD prevalence overtime, compared to UC [17]. Another study published from a tertiary care center in eastern Nepal revealed IBD is not a rare disease, and there is evidence of increased detection of IBD cases which is attributed to their increased awareness and establishment of specialty services [18]. A study published on UC in Bangladesh revealed that more than 50% of patients who had diarrhea without an apparent cause actually fulfilled the diagnostic criteria of UC [19]. Studies have shown that varying clinical presentations of CD and UC [20] exist in Pakistan and should be considered in differential diagnosis; however, no data is available for the prevalence or the burden of the disease. The lack of a national IBD registry and few tertiary care referral centers for the specialist care of IBD patients may be the reason for the deficiency of data from the other regions.

## 3. Varying Patterns of Inflammatory Bowel Disease Subtypes by Geographic Region and Subpopulation

The IBD survey published in India in 2012 revealed the presence of patients with IBD in all geographic parts of North and South India [21]. However, a later

study published in 2020 identified South India as the most common region for patients with CD. Those suffering from UC were more likely to originate from West, Central, or North India than those with CD [22]. Likelihood of CD and UC was equal in the patients from the cities while patients from smaller towns were more likely to have CD, and those from villages were more likely to have UC [22]. Epidemiological studies in Western countries have shown that an increase of UC incidence preceded an increase in CD incidence by around 15 - 20 years [23]. This observation of an increased incidence and prevalence of IBD which occurred 50 years ago in the West, mirrors the current pattern of the disease in South Asian countries, as evidenced by various studies. However, as the disease load in the West has been stable for some time [24] [25], the gap between the rise of CD initially and UC later, has decreased; a shift that could be experienced in South Asian countries in future decades. A hospital-based study in Sri Lanka in 2018 revealed the burden of IBD is lower in the central province of Sri Lanka when compared to other Asian and Western countries. Lack of population-based studies and nature of hospital-based data from most of the South Asian countries (except India) are the hurdles to compare the prevalence and geographic differences in the pattern of IBD between the different regions.

## 4. Phenotypic Differences of Inflammatory Bowel Disease in South Asian versus Western Patients

The pattern of UC in South Asia was almost similar to the pattern of the disease found in Western countries. Data from an IBD survey of 714 patients with UC in India in 2020 indicated that the disease extent was pancolitis in 42%, left-sided colitis in 38.8%, and proctitis in 18.3% [21]. Another study also reported similar patterns in the extent of the disease in Asians as well as in Australians [26]. Hospital-based data in Sri Lanka revealed that among patients diagnosed with UC, the percentages of extensive disease, left-sided colitis, and proctitis were 15%, 24.3%, and 60.7%, respectively [16]. A recent study on different groups in Sri Lanka revealed no significant change in the disease phenotype of UC [17].

The phenotypic location of CD in South Asia also resembles to that found in Western countries. A multicenter study on 182 patients in India revealed L1 in 32%, L2 in 41%, L3 in 23%, and L4 in 4%. The perianal disease was seen in 19% of the patients [15]. An IBD survey of 394 CD patients in India also reported similar disease locations with 29% having L1, 31% having L2, 40% having L3, and 6% having L4 phenotype [21]. Two more studies done in India including one study on 178 patients from Mumbai [27] and another study done in Vellore [28], also reported a similar disease location. A study also reported similarity in disease location between Asians and Australians, with L1, L2, L3, and L4 phenotypes in 31%, 24%, 45%, and 5% of all patients, respectively [26]. This pattern was also observed in a recent study from Sri Lanka, where the L3 pattern predominated [17]. The behavior of CD in South Asia was also found to be similar to the behavior of the disease in western world. Inflammatory disease is the most

common pattern found in both Western and Indian studies [21]. A similar pattern was seen in Sri Lankan studies as well [17]. Temporal changes in phenotypic behavior are explained in patients with CD in 2016 by Kalarie and colleagues. Their retrospective analysis revealed similarity in the gender distribution and predominant ileocolonic location of the disease compared to earlier Asian reports. However, while one-fourth of Indian patients had an aggressive disease at diagnosis, the tendency to progress towards aggressive disease over time was less pronounced than in Western patients [27].

## 5. Genetic Determinants of Inflammatory Bowel Disease in South Asian versus Western Populations

IBD is a complex genetic disease instigated and amplified by the confluence of multiple genetic and environmental variables that perturb the immune-microbiome axis. Over the past decades, significant advances in understanding the genetic contributions to IBD have been made. Genetic testing and DNA sequencing allowed for genome-wide association studies that identified new single nucleotide polymorphisms (SNPs) [29]. Nucleotide-binding oligomerization domain containing 2 (NOD2) was the first susceptibility gene for CD discovered in 2001. From the various single nucleotide polymorphisms associated with IBD in White patients which are detected by metanalysis of genome-wide association studies, only 5 of 59 index ones studied in North India were found significant, showing limited replication in Indian patients [30]. Also, studies done more recently assessing the NOD2 polymorphisms in Indian patients were not able to find any similar association, and none of the three common CD-associated NOD2 polymorphism were found [31] [32] [33]. This raises the question of what impairs the common causative genes in the White population are non-causal in the Indian population, which could be due to differing environmental exposures, secondary factors, or immunological interactions.

However, two studies found a weak association of rs2066842 (Pro268Ser) with UC [31] [34]. Few studies have demonstrated a relation to the UC phenotype. UC response to steroids, early age (<29 years) of disease onset and left-sided disease are few of the characteristics found to be very well associated with some haplotypes of MDR1 (ABC B1) gene [35]. TNF alpha 863 AA genotype increased the risk of both UC and CD, especially for pancolitis related to UC. IL4 B2 carrier state was less in left-sided colitis than proctosigmoiditis and absent in colonic CD [36]. One study showed that the ancestral origin of North Indians from Indo-Aryans can explain the association with UC as well as the phenotypic and genotypic similarities [37].

Mahurkar and colleagues also reported that in Indian population, the protective allele of the Il23 gene (R381Q) called NOD2, was not associated with CD [21]. Another study conducted in India showed that TNFSF15 (tumor necrosis factor superfamily) gene polymorphisms were protective against IBD in the Indian population [38]. Studies done in Japan and UK have also demonstrated an

association between TNFSF15 and IBD risk [39]. The association of an autophagy-related gene as well as IRGM gene with CD in Indian population was also reported by the same group. This association had previously been reported in many European studies [40].

A Sri Lankan case-control study published in 2018 concluded heterogenicity of allelic mutations in South Asian patients when compared to White patients [41]. Surprisingly, most SNPs and disease associations reported in this study have not been reported previously in South Asian populations. The observed genetic heterogenicity across divergent populations at several risk loci can be explained by differences in risk allele frequency (NOD2), the effect size of TNFSF15, or a combination of these factors (IL23R or IRGM).

## 6. Clinical Presentations and Diagnosis of Inflammatory Bowel Disease

Despite a decrease in diagnostic delays in Western countries over the last decades, there is still a delay of one to two years and more larger delays in CD in western countries, despite widely available resources in health care [42]. This could result in a poorer medical outcome [43]. The major challenge related to the accurate and timely diagnosis of IBD is due to high prevalence of infectious enteritis and intestinal tuberculosis. Infections with chronic diarrhea can delay the diagnosis of IBD and sometimes cause complications for existing IBD. A scarcity of medical experts and advanced diagnostic facilities in South Asian communities' results in 37% of IBD patients receiving antituberculosis drugs [21]. CD and mycobacterium tuberculosis (MTB) are chronic granulomatous diseases with overlapping clinical, pathological, radiographic, and endoscopic findings. Additionally, the lack of sensitive and specific laboratory markers led to a 50% - 70% misdiagnosis rate [44]. Importantly, seven susceptibility loci including NOD2, IL23R, RIPK2, and TNFSF15 for Mycobacterium leprae infection, have also been associated with CD [45]. This raises the question of the coexistence of CD and MTB or a causal relationship of mycobacterium tuberculosis initiating CD by producing the altered gut mucosal immunity. Recent findings indicate that the disease can be exacerbated in patients on immunosuppressive therapy. Thus, large-scale studies exploring the association between CD and MTB are needed to identify the presence of association further. In addition to MTB infectious colitis, various other microbes can lead to gut involvement which can mimic the presentation of IBD such as ileitis due to Salmonella and Yersinia, colitis due to various other bacterial and parasitic organisms, and ileocolonic ulcers which due to amebiasis. As mentioned above, these infections can also complicate the course of IBD.

## 7. Differing Treatment Modalities of Inflammatory Bowel Disease in South Asia

According to an IBD survey from India, steroids were given to two-thirds of all

UC patients, Azathioprine (AZA) was given to 30% of the patients, and biologics were used as a treatment for less than even 1% of the patients [21]. This decreased use of biologics in Indians indicates the lack of insurance coverage and affordability, in the Indian healthcare system. In a recent retrospective analysis of 179 patients with a diagnosis of acute severe UC, followed from discharge to a median of 56 months, the rate of colectomy at admission was lower than that reported in Western countries but matched other similar Asian studies [46]. In the Leicestershire cohort, although all ethnic groups showed a similar disease extent, South Asian patients required less surgery and experienced fewer complications than European patients [47]. The overall colectomy rate was 12% in the diagnosed UC cohort from Oxford, UK [48]. These data indicate that overall colectomy rates are lower in Indian patients when compared to patients in Western countries, indicating a slightly milder disease severity in India. Other variables accounting for the lower rate of colectomy in India could include social factors or fewer Indian patients being receptive to a colectomy. One study from three different centers in India reported that surgery was required by 37% of all patients with CD [15].

The medication used in 78% of patients was 5-aminosalicylic acid (5-ASA) compounds, 42% of all patients were given steroids, 29% of all patients received Azathioprine, and 2% of all patients were given methotrexate. The IBD survey from India revealed 5-ASA was used only for 64% of patients, steroids for 69% of all patients, AZA for 63% of patients, and biologics were used in 2% of all patients [21]. In a study done on a cohort from Mumbai, 55% of patients required surgery within 15 years [27].

Medical treatment-induced remission in UC in a hospital-based study from Sri Lanka in 2018, showed positive results with 5-ASA in 99% of patients, while 68% of patients achieved remission with a combined treatment of oral steroids and 5-ASA. AZA was also used for 15% of the patients [49]. Biologic therapy (infliximab) was given as an induction treatment for almost 6% of nine UC patients, however, combination of other medications such as AZA, 5-ASA and steroids were used initially as a treatment for all these patients. For maintenance, oral 5-ASA was used for 71% patients of UC and combination therapy consisting of both oral 5-ASA and azathioprine was used for 24% of patients. In the said study, 40% of CD patients achieved remission with a combined treatment of 5-ASA drugs, systemic steroids, and azathioprine. Infliximab was used for induction in 23% patients of CD who did not achieve remission with the above-mentioned treatment. Maintenance of remission was achieved in 96% of CD patients with either a single or a combination of 5-ASA and AZA. Only two (3%) CD patients were on infliximab maintenance [49].

Importantly, there is a scarcity of data regarding treatment modalities for IBD in South Asian countries. This is due to diverse medical practices employed in these countries including alternative and complementary medicine such as Ayurveda and homeopathy. It can also be assumed that there must be a high number of unidentified patients with IBD who only present to these South Asian

traditional and modern alternative health practitioners, and therefore, data from these patients is not available.

## 8. Impact of Migration on Inflammatory Bowel Disease among South Asian Patients

Migration is associated with changes in the incidence, new environmental exposures, or movement away from such exposures. Studies to date done in different time and duration, as well as differences in second and third generations, complicate the outcome [50]. However, recent studies revealed different phenotypic characteristics among South Asians immigrants. One retrospective study conducted between 2000 and 2016 at two tertiary centers in the US randomly matched 171 South Asians with IBD to White controls. This revealed a more penetrating disease in those with CD, less proctitis among patients with UC, and altered medication use patterns [51]. A population-based cohort study in Canada showed that a younger age of migrating to Canada increased the risk of IBD. At the same time, Canadian-born children of immigrants from some regions especially from middle east/North Africa, South Asia and Sub-Saharan Africa assumed the high Canadian incidence of IBD, indicating that an underlying risk is activated with earlier life exposure to the Canadian environment [52]. Therefore, environmental exposure and a South Asian genetic profile could be contributing factors to this increasing incidence and variable phenotype among South Asian immigrants.

## 9. Discussion

Epidemiologic trends document an increasing incidence of IBD in South Asia, where the phenotypic expressions of their disease are like those in the Western societies. It is also worth noting that the emergence of various diagnostic modalities and lack of availability of specialists in South Asia cause difficulty in recognizing the trends and masking the disease burden. However, population studies, hospital-based reports, and other genetic studies indicate that the incidence of IBD is rising every year. Population-based data from all parts of South Asia remain scarce, which hinders any comparison of epidemiology, risk factors, phenotypic expression, and treatment modalities of IBD in South Asia to what is seen in the West. This highlights a need for future population-based prospective studies in a traditionally low-prevalence region like South Asia.

Current findings suggest that genetic susceptibility and environmental triggers differ between populations in South Asia and the West. Ongoing urbanization, industrialization, changing lifestyle and dietary patterns, increasing stress, pollution, unidentifiable environmental influences, and alteration of gut microbiota likely play a role in the rising incidence of IBD in South Asia. South Asian immigrants to the West showing a more severe initial presentation in their disease behavior and increased incidence compared to the western population of those regions, suggests that in addition to genetics alone, unique environmental exposures and a potentially unique genetic profile of South Asian patients may deli-

berate this variable phenotypic expression which consequently will influence the management of IBD in this population. The increase in incidence in this population also provides a unique opportunity to examine the multifactorial contributors of IBD.

Considering the current findings, future studies in South Asia should not only seek to replicate studies of environmental and genetic risk factors in the West but also attempt to detect novel associations which might specifically apply to the local populations. Epigenetic changes, modulation of the transcriptome and post-transcriptional events, as well as host-gut microbiota interactions also appear to contribute to the risk of IBD and should be considered alongside genetic and environmental risk factors. With a deeper understanding of the differences in the etiologic background and natural disease course of IBD in South Asia versus the West, we will be better equipped to stem the global rise of IBD.

IBD can no longer be considered a disease with a lower burden in South Asia. IBD affects individuals in their most productive years and is associated with significant morbidity and loss of functional capacity. It also increases the financial burden on the patients due to its prolonged treatment course. IBD in South Asia and IBD among South Asian migrants show an aggressive nature, like what can be observed in the West or in some cases even worse than what is seen in the Western population, therefore, it requires an equally aggressive treatment approach. Challenges in treating IBD include the expense of therapy, the lack of medical insurance coverage, and poor acceptance rates of patients for surgery. Moreover, most of the clinical trials, genetic studies, and biological treatment catered to the Western population in White or African Americans are unlikely to reproduce a comparable effect in South Asian populations. Further challenges may arise due to this during the escalation of therapy and in predicting the response in South Asians.

## 10. Conclusion

Concluding, this review identified that both patients in South Asia as well as South Asian patients living in Western countries are at greater risk for all types of IBD. Due to this increasing disease prevalence, this geographical region provides an opportunity for revealing possible etiopathogenetic factors. Further population-based studies, comparison of studies in South Asians and immigrants from South Asian countries, and large-scale biologic treatment models need to be accelerated to control the disease burden in South Asians, as well as to achieve reduced burden globally.

## Financial Disclosure

The authors have no financial relationships relevant to this article to disclose.

## Conflict of Interest

There are no financial conflicts of interest to disclose.

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# Gastric Variceal Bleeding: The Efficacy and Safety of N-Butyl-2-Cyanoacrylate Glue Injection

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## Abstract

Aims: To assess N-2-butyl cyanoacrylate injection's effectiveness and safety in the treatment of gastric varix hemorrhage. Methods: Endoscopic treatment with N-Butyl-2-cyanoacrylate injection was performed on 32 patients (21 males and 11 females) with gastric variceal bleeding. The socioeconomic status of the patients, initial hemostasis, rebleeding rate, complications, and mortality rate were all reviewed retrospectively. Patients with liver cirrhosis who presented with hematemesis or melena or whose endoscopy revealed gastric variceal bleeding were included. Therefore, patients with hemodynamic instability were excluded. Results: A total of 32 patients underwent Histoacryl® glue injection to treat bleeding gastric varices. The mean age was 56.09 ± 9.29 (mean ± SD) years old. Viral hepatitis is the leading cause of chronic liver disease, both hepatitis B and C accounted for 11 cases (34.4%). IGV1 was the most commonly seen, according to the Sarin classification, with 15 cases (46.8%), followed by GOV1 with 10 cases (31.3%) and GOV2 with 7 cases (21.9%). With 15 cases (46.9%), the majority of patients had a Child-Pugh (CTP) B score. 12 cases (37.5%) and 11 (34.4%), respectively, of hematemesis and melena, were reported. In all patients, initial hemostasis was achieved, and there was no documented complication rate. Conclusion: Given the higher rate of hemostasis and great results, our study's findings indicate that the injection of N-butyl-2-cyanoacrylate under endoscopic guidance is safe and effective in the management of GV hemorrhage. After the initial injection, hemostasis was achieved in all of our patients.

## Keywords

Upper Gastrointestinal Bleeding, Portal Hypertension, Gastric Varix, Initial

Hemostasis, Cyanoacrylate (Hystoacryl) Injection

## 1. Introduction

About 50% of patients with liver cirrhosis have gastroesophageal varices (GOV). Less frequently occurring than esophageal varices (EV), gastric varices account for 10% to 30% of GOV bleeding [1] [2]. Unless they bleed, GOVs typically have shown no symptoms. Hematemesis and/or melena, hematochezia, and possibly non-exterior bleeding are symptoms of variceal hemorrhage. Bleeding was suspected or considered to arise from FV (Fundal Varix) if one of the following criteria was present: 1) active bleeding from the GV was seen; 2) the presence of a clot or an ulcer over the FV; 3) occurrence of bleeding in the context of large FV in the absence of EV or other causes of upper GI bleeding. Meanwhile, rebleeding occurs in 35% to 90% of patients with gastric variceal bleeding (GVB), and GVBs typically have greater fatality rates and are more severe. Depending on the severity of the underlying condition, the size of varix, and the existence of signs that indicate bleeding, the mortality and morbidity rates range between 30 and 50%. Similar to the treatment for EV, endoscopic band ligation (EBL) is favored over sclerotherapy for GOV1 due to a lower risk of complications. However, due to high rates of rebleeding and the possibility of catastrophic bleeding from significant treatment-induced ulcers, EBL and sclerotherapy may not be viable treatments for fundal varices (GOV2 and IGV1). After the finding of Cyanoacrylate (glue), the management of GVB was updated. The tissue glue N-butyl-2-cyanoacrylate is a watery solution, which polymerizes and hardens within 20 seconds in a physiological milieu and instantaneously upon contact with blood. This makes it potential for obliterating vessels and controlling bleeding. Cyanoacrylate (glue) injection is recommended for first-line therapy for GVB with the initial control of bleeding in 90% to 100% of patients and rebleeding rates < 15% in the recent series [3] [4]. However, it is not widely used by all the countries in the world. Therefore, in this study, we have retrospectively reviewed the N-2-butyl cyanoacrylate injection's effectiveness and safety in the treatment of GVB at Khmer-Soviet Friendship Hospital, Cambodia.

## 2. Patients

This study involved 32 patients registered in the documents and meet the inclusion criteria of our study including age, the presence of hematemesis or melena or both with underlying history of chronic cirrhosis, the presence of esophagogastric varices bleeding identified by endoscopy at Khmer-Soviet Friendship Hospital, Cambodia, between January 2021 and June 2022. There were 21 male patients (65.6%) and 11 female patients (34.4%), 100% of Cambodian, aged 40 - 71 years old, and the mean age of 56.09 years old.

All the patients were found to be successful with a mean number of 1 session of Histoacryl® glue injection. Endoscopic obliteration was done in 31 cases re-

quiring 1 session while only one patient needed 3 sessions to get obliterated because the varices found in that patient were too large.

## 3. Methods

All patients were moved to the endoscopic room for the procedure after stabilization via IV hydration, blood transfusion, somatostatin, or occasionally with Linton tube compression. A large channel endoscope (Olympus C, Tokyo, Japan) and a disposable injectable 21-gauge needle catheter were used to administer Histoacryl® (diameter 0.8 mm, length 8 mm). In a ratio of 0.5 to 0.8 ml, Histoacryl® and Lipiodol (Guerbet, Aulnay-Sous-Bois, France) were combined. Senior gastroenterologists performed the majority of procedures while being supervised by knowledgeable staff. Before inserting the catheter, lubricant was pumped through the endoscopic suction channel. The endoscope was used to introduce the preload sclerotherapy catheter into the stomach, and the gastric varix was inserted directly with the needle. In order to reduce the possibility of needle embedment, Lipiodol was administered through the catheter to distribute the glue mixture into varix. The needle was then removed while the glue was still flowing. After that, sterile water was used to cleanse the catheter. Per injection, typically 1 ml of a lipiodol and Histoacryl® mixture was given. Repeated injections were given until the stomach varices seemed to occlude, as determined by blunt probe probing. General anesthesia was used for all of the patients. In three days, one month, and six months, the treatment was repeated. We consider it as Early re-bleeding if it occurred within 30 days after the index procedure and as Late re-bleeding if it occurred after 30 days. Based on Sarin *et al.*, gastric varix is classified by their anatomical location seen on the endoscopy [3]. It differentiates gastroesophageal varices (GOV) from isolated GV (IGV). GOV is classified into 2 types respectively, type 1 (GOV1 seen in 70% of GV) is found along the lesser curvature and the cardia, and GOV type 2-mostly along the gastric fundus and may extend to the cardia. IGVs are also classified into 2 types, type 1 is located in the fundus, and type 2 is distal GV or those located at other sporadic locations (see **Figure 1** and **Figure 2**). For all practical purposes, true GV or cardio-fundal varices are the GOV2. The size of these varices, the presence of surface red marks, and the severity of underlying liver disease (Child Turcotte Pugh Score) are predictive of bleeding. This raises the issue of prophylactic intervention for incidentally discovered gastric varices, although this question has not yet been fully answered: very little data exists to determine the risk and benefit ratio of preventive intervention.

## 4. Statistical Analysis

Program SPSS version 25.0 was used for assisting the quantitative analysis, and descriptive and comparative statistics.

## 5. Ethical Consideration

All collections of data were made only after an agreement between the Khmer-

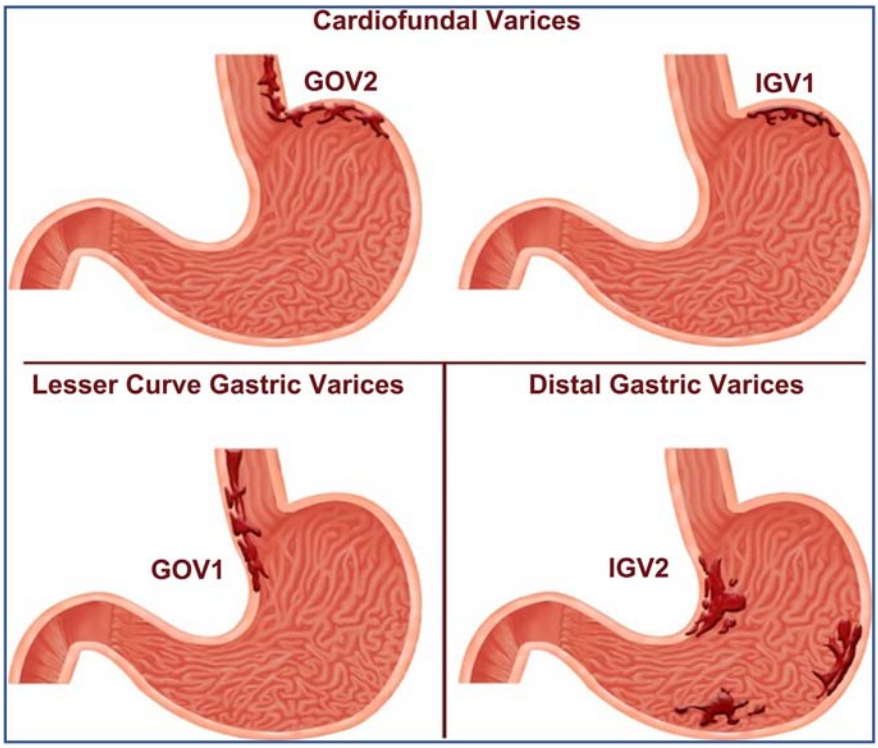


**Figure 1.** Classification of gastric varix according to their location within the stomach. GOV-1: Gastroesophageal varix type 1, GOV2: Gastroesophageal type 2, IGV1: Isolated gastric varix type 1, IGV2: Isolated gastric varix type 2 [5].

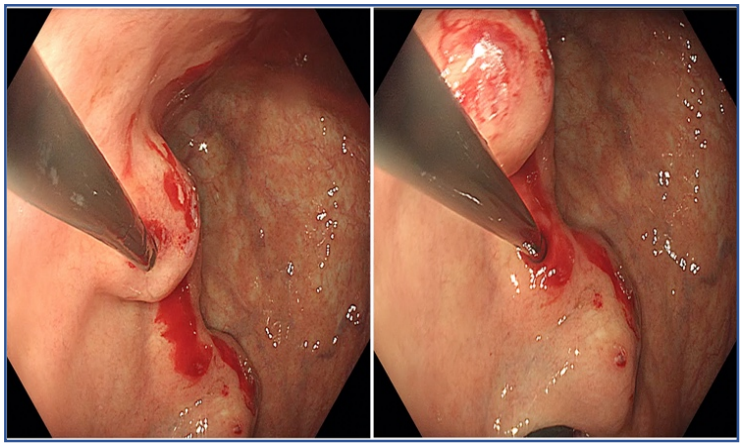

**Figure 2.** Technique of cyanoacrylate glue injection [5].

Soviet Friendship Hospital and the University of Health Sciences, Phnom Penh, Cambodia. The patient's identifications are not shown.

## 6. Results

All patients with bleeding gastric varices had endoscopic N-butyl-2-cyanoacrylate injections. The baseline Characteristics of our patients are shown in **Table 1**. The patients selected were aged from 40 to 71 years. The mean age was 56.09 years with a standard deviation of 9.29. We found that the majority of patient

**Table 1.** Baseline characteristics of patient with gastric variceal bleeding treated with Histoaryl glue injection.

| Effective | No. of patient | % |
|---|---|---|
| Total | 32 | 100 |
| Males/Females | 21/11 | 65.6/34.4 |
| Age, years (mean ± SD) | 56.09 ± 9.29 | |
| Etiology of liver cirrhosis | | |
| 1) Viral hepatitisB | 6 | 25 |
| 2) Viral hepatitis C | 2 | 8.3 |
| 3) Alcoholism | 9 | 37.5 |
| 4) Non-alcoholism nor viral hepatitis | 2 | 8.3 |
| Bleeding manifestation | | |
| - Hematemesis | 12 | 37.5 |
| - Melaena | 11 | 34.4 |
| - Both | 9 | 28.1 |
| Child-Pugh Classification (A/B/C) | 9/15/8 | 28.1/49.9/25 |
| Gastric varix form | | |
| - GOV1 | 10 | 31.3 |
| - GOV2 | 7 | 21.9 |
| - IGV1 | 15 | 46.9 |
| - IGV2 | 0 | 0 |
| Association with Hepatocellular carcinoma | 5 | 15.6 |

lives in a province with 24 patients (75%), while 8 patients (25%) live in Phnom Penh. Most of the patient who comes to the hospital with the bleeding presentation of hematemesis accounted for 12 cases (37.5%) followed by melena with 11 cases and both hematemesis and melena with 9 cases (34.4% and 28%), respectively.

The blood test result characteristic of all 32 patients was demonstrated in Table 2. The gastric variceal bleeding was found to be caused by portal hypertension in decompensated liver cirrhosis with various etiology. We noted that the two most common causes of chronic liver disease were related to viral hepatitis, HBV and HCV with 11 cases (34.4%) each, followed by alcohol with 8 cases (25%) and non-alcohol nor viral hepatitis with 2 cases (6.2%) (see Figure 3). All 32 patients enrolled were found to be successful with a mean number of 1 session of injection. The endoscopic obliteration was done in 31 cases requiring 1 session while only one patient needed 3 sessions to get obliterated because the varices found in that patient were too large. The average volume of Histoacryl® and Lipiodol combined calculated was in a ratio of 0.5 to 0.8 ml, initial hemostasis and completed variceal obliteration were achieved in all patients (see Table 3). Rebleeding in our study was defined by the presence of hemorrhage signs:

**Table 2.** The blood test results of 32 patients treated with N-butyl-2-Cyanoacrylate glue injection.

| Blood test result | Mean ± SD |
|---|---|
| Hemoglobin (g/dL) | 8.17 ± 2.16 |
| Platelets (K/μL) | 137.87 ± 89.94 |
| Prothrombin (%) | 54.69 ± 20.56 |
| Creatinine (mg/L) | 10.2 ± 2.92 |
| Total bilirubin (mg/dL) | 2.47 ± 3.23 |
| ALT/AST (IU/L) | 46.41 ± 44.70/85.53 ± 64.15 |
| Albumin (g/L) | 29.41 ± 2.97 |
| Transfusion (number of pack) | 1.81 (0 - 6 packs) |
| Glycemia (mg/dL) | 167.84 ± 96.60 |

**Table 3.** Number of sessions and volume of Histoacryl injection.

| Number of sessions | Number of patients |
|---|---|
| 1 | 31 |
| 3 | 1 |
| Mean number of sessions | 1 |
| Average volume of Histoacryl | 0.5 ml |

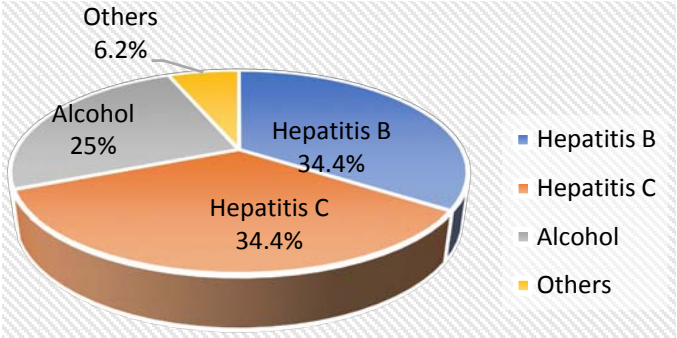


**Figure 3.** The etiologies of liver cirrhosis.

hematemesis or melena or hematochezia or decreased hemoglobin level > 2 g/dL within 5 days of hospitalization after glue injection. All 32 patients treated with N-bulyl-2-cyanoacrylate injection failed to face any rebleeding event. Embolism is the most concerning complication in the treatment of gastric varices with N-2-Butyl Cyanoacrylate. Fortunately, we didn't find any case of thromboembolism. Anyway, we noticed that there was one case of fever 48 h after injection but resolved spontaneously without any infectious source finding (see **Figure 4**). We also found that there was no case of death after glue injection therapy with Histoacryl®. All patients were discharged. We considered that among patients hospitalized, an average blood pack for transfusion was 1.81 packs ranging from 0 to 6 packs of red blood cells.

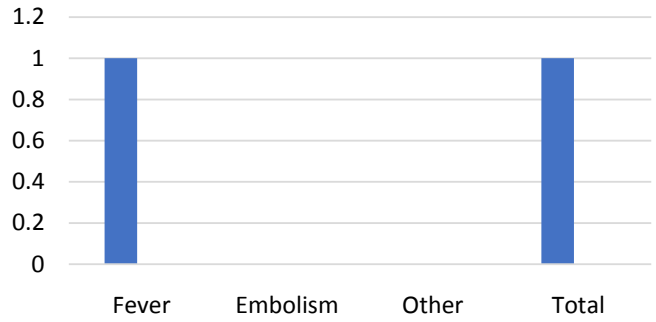


**Figure 4.** The complications of cyanoacrylate glue injection.

## 7. Discussion

GVs were less frequently found than esophageal varices in asymptomatic portal hypertensive individuals who underwent endoscopic monitoring for varices (EVs). Although there is a lower chance of GVs bleeding, it is nonetheless severe and sometimes fatal [3]. Mortality rates for the initial variceal hemorrhage range from 20% to 30% percent, and for the second occurrence, they can approach 50%. Recurrence of bleeding is observed in 30% of patients within the first 6 weeks of the first episode and in about 70% during the following year [3] [6]. The reported rebleeding rate after Histoacryl® injection for acute gastric variceal bleeding ranged from 22% - 59% [7]. Apart from band ligation and Cyanoacrylate injection (Histoacryl®), Balloon-Occluded Retrograde Transvenous Obliteration (BRTO) is a very effective technique in temporarily controlling bleeding with immediate action in 80% of patients [7]. Unfortunately, its use is associated with potentially lethal complications such as aspiration, migration, and necrosis/perforation of the esophagus with mortality rates higher than 20%. Therefore, it should be restricted to patients with uncontrollable bleeding for whom a more definitive therapy (e.g TIPS) is planned within 24 hours of placement. It is strongly recommended for airway protection when balloon tamponade is used [8] [9]. Transjugular Intrahepatic Portosystemic Shunt (TIPS) is widely used as a salvage therapy for GV bleeding and is increasingly used as first-line treatment, especially in the United States and Europe while BRTO remains more commonly used in Eastern countries. TIPS was first shown to be successful for GV bleeding in a 1998 study that showed outcomes for TIPS in acute GV versus OV bleeding were equal with hemostasis being achieved in all but one patient. Re-bleeding occurred in 4/28 patients due to shunt thrombosis or occlusion, which the authors report was easily diagnosed and managed. The study, therefore, established the role of TIPS as a rescued procedure in the management of uncontrolled GV bleeding [4]. However, Cyanoacrylate (glue) injection is still recommended for first-line therapy for GVB [3] [10] with the initial control of bleeding in 90% to 100% of patients and rebleeding rates < 15% in recent series [11] [12]. The mean age of the patients in our study was 56.09 years. This finding might be aligned with numerous studies in the literature, where viral hepatitis was primarily the cause of chronic liver disease because it took the disease more than two decades

to progress from a healthy liver to a decompensated liver and cause gastric varices [13] [14] [15] [16] [17]. A series by Seewald S, *et al.* conducted in Germany and Egypt in 2008 [11], a study by Muhammad M, *et al.*, a study conducted by Jun CH, *et al.* in 2014 in Korea [18], and the study conducted by Lean Sopheak in Cambodia in 2017 [19] found the mean age: 57.2 years old, 57.65 years old and 59.6 years old respectively. Our study's sex distribution was primarily in male patients with a sex ratio of 2:1, which was similar to research done by Seewald S. *et al.* in Egypt and Germany in 2008 [11] and by Noophun P. *et al.* in Thailand in 2005 [16]. According to the study conducted in Taiwan in 2000 by Huang YH, *et al.* [20], the sex ratio was 4:1 which was significantly different from our result with a sample size of 90 cases (78% were male and 22% were female). We noticed that study was carried out for 6 years from 1992 to 1998 with a total sample size of 893 patients and lately selected only 90 patients with bleeding from gastric varices. Viral hepatitis was the leading cause of chronic liver disease with 67 cases (74.5%). So, dominance in men and viral hepatitis in this series could be explained by the low quality of public health during that period and unprotected sex for male patients. Gastroesophageal varix type 1 is the most prevalent kind reported in the literature, making up 74% of all GV. However, IGV 1 and GOV 2 have the highest rates of bleeding, respectively [21]. The majority of fundal varices (FVs) enter the inferior phrenic vein, which subsequently connects to either the left renal vein to create the gastro-renal shunt (GRS) (80% - 85%) or the inferior vena cava [22]. This is because fundal varices (FVs) consist of GOV2 and IGV1. Many studies have found that the mean hepatic venous portosystemic pressure gradient (HVPG) is lower in fundal varices (FV) compared to esophageal varices (EVs), and this gradient is believed to be caused by the presence of these shunts. However, unlike EVs, a significant proportion of FVs (36.8%) still bleed with an HVPG < 12 mm Hg because of the large size of FV and the resultant higher wall tension [23]. This finding could be explained that GV type IGV1 and GOV2 are the most common type of GV bleeding in many studies. As for initial hemostasis current study's population resulted in a 100% rate which was almost identical to some different studies shown in **Table 4**. However, the procedure-related complication of Histoacryl® in our study was observed in 3.12% of the overall results which is slightly lower than the local study conducted by San Polen in Cambodia in 2016 with 9.61%

**Table 4.** The comparison of initial hemostasis in different studies.

| Author | Country | Year | Initial hemostasis (%) |
|---|---|---|---|
| Current study | Cambdia | 2022 | 100 |
| Seewald S, *et al.* [11] | Germany and Egypt | 2008 | 100 |
| Chang YJ, *et al.* [27] | Korea | 2009 | 100 |
| Prachayakul V, *et al.* [25] | Thailand | 2013 | 97.8 |
| Jun CH, *et al.* [18] | Korea | 2014 | 96.9 |

[24] and is lower than one study in Thailand done by Prachayakul V, *et al.* in 2013 with 13.9% [25]. Systemic embolization is a serious side effect of N-butyl-2-cyanoacrylate injection (NBCA). According to a study, NBCA glue can have embolic side effects such as stroke as a result of thromboembolism in the anterior or posterior circulation, pulmonary embolism (PE), splenic embolism, or portal vein thrombosis. It may also cause multi-organ infarction in the presence of patent foramen ovale or the presence of any arteriovenous (AV) pulmonary shunt [23]. Fortunately, there is no case of complication related to thromboembolism event found in our study. This is similar to the study of Prachayakul V, *et al.* in Thailand which showed there is no complication of embolism in all 90 cases receiving therapy with Histoacryl® [25]. The absence of death cases could be explained by the standardized technique adopted in our study. Fever is the only complication related to Histoacryl® sclerotherapy in the current study accounting for 3.12% but it was resolved spontaneously without any source of infection noticed within 48 h. This may not be of clinical impact if it is only a matter of transient bacteremia. In addition, the current standard of care for cirrhotic patients with GI bleeding already includes prophylactic antibiotics to prevent bacterial infections [26].

## 8. Conclusion

Gastric variceal bleeding represents numerous complications of chronic liver disease, known as cirrhosis. Men are mostly affected than women. The most affected age group ranges between 40 and 71 years old. The most frequent clinical symptom of gastric variceal bleeding is hematemesis. The endoscopic aspects findings are gastric varix type IGV1. Viral hepatitis is the leading cause of liver cirrhosis. No complication related to glue injection was noted in our series. Our study result demonstrated that the injection of N-butyl-2-cyanoacrylate with endoscopic guidance is safe and effective in the management of GV bleeding due to a higher rate of hemostasis and excellent outcome. 100% of our patients got hemostasis after the initial injection.

## Authors' Contributions to the Manuscript

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: SOU, MEAS, NOV, UONG, EK, CHEY.
- Drafting the article or revising it critically for important intellectual content: SOU, UNN, CHEY, NY, CHHIT, KHUON.
- Final approval of the version to be published: SOU, MEAS, EK, UNN, NOV, KANG, UN, KAING, KHUON, NY, MON, KANN, CHHIT, UM, CHEY.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: SOU, MEAS, EK, UONG, CHEY, UNN, NOV, KANG, UN, KAING, KHUON, NY, MON, KANN, CHHIT, UM, CHEY.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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# Factors Associated with Antibody Levels among Children Aged 15 to 59 Months Vaccinated against Hepatitis B during the Expanded Program on Immunization in Cameroon

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## Abstract

Background: the hepatitis B virus infection remains a major public health problem worldwide. It can lead to a liver cirrhosis and/or hepatocellular carcinoma. The World Health Organisation (WHO) has recommended the implementation of generalised vaccination programs against hepatitis B. In Cameroon, this vaccine was introduced in the expanded program on immunization (EPI) in 2005, but few studies have assessed the immune response. Objective: the general objective of this study was to identify factors associated with antibody levels among children aged from 15 to 59 months vaccinated against hepatitis B during the EPI in Cameroon. Method: this was a cross-sectional study carried out from December 2021 to June 2022 in a paediatric centre of Yaoundé (Cameroon). We analysed the antibody level in children vaccinated against hepatitis B within the framework of the EPI. We enrolled children who had received a series of 3 intramuscular doses of hepatitis B vaccine at 6, 10 and 14 weeks after birth. Some children could receive a 4$^{th}$ booster dose between 12 months. The antibody level was assessed by measuring the anti-HBs in such children, aged 15 - 59 months. A good immunization was defined as a serum level of anti-HBs antibody level above 100 IU/mL; a poor immunization, for an anti-HBs antibody level between 10 and 100 IU/mL; and a non-immunization, for an anti-HBs antibody level < 10 IU/mL. Asso-

ciation between explored factors and poor or non-immunization was evaluated through the Chi square test. The significance threshold was defined at $p < 0.05$. Results: sixty subjects were included in the study with a slight female majority: 31 cases (52%). The average age was 38.5 ± 15.7 months (range 15 - 59 months). We found 32 (53%) cases of good immunization; 21 (35%) of poor immunization; and 7 children (12%) with a non-immunization. The only factor associated with poor or non-immunization was the age between 37 - 59 months ($p = 0.016$). Conclusion: Anti HBs Antibody levels in children vaccinated against hepatitis B virus were globally satisfactory in our series. Results show an association between low antibody levels with older age (over 36 months), suggesting a circulating antibodies levels decrease over time, yet deemed protecting until 59 months.

## Keywords

Hepatitis B, Vaccination, Children, Antibody Levels, Immunization, Cameroon

## 1. Introduction

The hepatitis B virus (HBV) remains wildly expanded in the world. The prevalence in sub-Saharan Africa (SSA) is high, varying from 7% - 21% [1]. A chronic infection could lead to liver cirrhosis and/or liver cancer. The prevalence of HBV exposure is estimated at 60% among children between 0 and 5 years old [2]. Therefore, the World Health Organization (WHO) has recommended the implementation of generalized vaccination programs against the HBV into routine national infant immunization programs [3]. In Cameroon, this vaccine was introduced in the Expanded Program on Immunization (EPI) in 2005 [3]. This one is included in a pentavalent vaccine associated diphtheria-tetanus-pertussis (DTwP) and Haemophilus influenzae type b (Hib) [4] [5]. The three doses of the pentavalent vaccine are administrated according to the recommended schedule: first dose 6 weeks after birth and intervals between 2 injections of at least 30 days. For children born from a mother infected by the HBV, a first dose should be done at birth. For all children, another 4$^{th}$ booster dose at 12 months is recommended but not included on the EPI. And children born from a mother infected by HVB have also received a prior dose at the birth. The objective is to obtain an antibody titled anti-HBs ≥ 10 mUI/ml. Studies have shown that this serologic response is observed in almost 90% of cases. After a vaccination campaign, we observed a significant reduction in liver cirrhosis and hepatocellular carcinoma some years later in Taiwan [6]. Some factors may negatively affect the immunization and the child will risk an infection despite the vaccine administration. Among these factors, in literature we have: a hepatitis B infection in the mother [7], the poor nutritional status [8], an HIV infection of the child [9], the low number of doses [10], the poor type of vaccine [11], and the male sex of the

child [3]. In SSA, problems associated with conservation and cold chain of these vaccines could also affect their efficiency [3]. For this reason, the serologic response to the hepatitis B vaccine, and factors associated, have to be assessed in children in our area.

## 2. Objective

The general objective of this study was to identify factors associated with the antibody level among children aged from 15 to 59 months vaccinated against hepatitis B during the EPI in Cameroon.

## 3. Materials and Methods

We carried out a cross-sectional study from December 2021 to June 2022 at the Mother and Child Centre of the Chantal Biya Foundation (Yaoundé-Cameroon). It is a public health care centre specialized in children disease. We included all children aged from 15 to 59 months coming for any reason vaccinated before against the HVB during the EPI. The protocol recommends a series of 3 intramuscular doses of hepatitis B vaccine at 6, 10 and 14 weeks after birth. The programme has been adjusted to coincide with the oral poliomyelitis virus and diphteria-pertussis-tetanus vaccination schedule. Some children could receive a 4$^{th}$ booster dose at 12 months. Children without a complete HBV vaccination attested by an immunization card were excluded.

Through a questionnaire, we collected sociodemographic data (age, sex, birth weight, HIV status and HBV status of the mother through the HBs Antigen), and we measured the weight of children. The weight-for-age Z-score (WAZ) was used to assess the nutritional status. The WAZ evaluation was using the Centres for Disease Control and Prevention 2000 child growth charts (CDC-2000). A poor nutritional status was defined when the WAZ $\leq -2$. With the immunization card, we noted the time and the number of HVB vaccine dose.

Then we collected a 5 ml of venous blood sample at the elbow for analysis. All samples were tested for anti-HBs by VIDAS Anti-HBs Total II® with a specificity of 99% (95% confidence interval: [98.1% - 99.5%]) and a sensitivity of 99% (95% confidence interval: [98.2% - 99.5%]).

Anti-HBs antibodies were expressed in international units per milliliter (IU/mL). A good immunization was defined as a subject with an anti-HBs antibody level $\geq$ 100 IU/mL; a poor immunization was defined as an anti-HBs antibody level between 10 and 99 IU/mL; and a non-immunization was defined as an anti-HBs antibody level < 10 IU/mL.

Statistical analysis was carried out using Microsoft Excel and SPSS version 21 software. The association between factors and a poor or a non-immunization has been assessed through the Chi square test. The significance threshold was defined at $p < 0.05$. Parents of children gave their consent and the National Ethics Committee of the Faculty of Medicine and Biomedical sciences (University of Yaoundé 1/Cameroon) approved the study.

## 4. Results

A total of 77 children have been included. We excluded 17 due to the absence of an immunization card. Thus, we enrolled 60 children for the study with 29 males (48%). The mean age was 38.5 ± 15.7 months with a majority, 30 children (50%), aged between 37 - 59 months.

Most of children (56/60) had a birth weight ≥ 2500 grams. Looking at the WAZ, the nutritional status was good in 51/60 children (85%). One child over sixty have a mother infected by HIV and three others a mother infected by HBV. These children born from a mother infected by HBV received the first dose of HVB vaccine at the birth as recommended. All the 60 children received the three doses of vaccine at 6, 10 and 14 weeks after birth included in the EPI, and 12 children (20%) received a 4$^{th}$ booster dose at 12 months.

Regarding Anti-HBs levels, there were 32 (53%) cases of good immunization, 21 (35%) of poor immunization and 07 (12%) of non-immunization to hepatitis B virus (Figure 1).

The only factor associated wi poor or non-immunization was the age of 37-59 months ($p = 0.016$). The sex ($p = 0.809$), the weight birth < 2500 grams ($p = 0.106$), the poor nutritional status ($p = 0.384$), the 4$^{th}$ booster dose ($p = 0.301$), an HIV or HBV infection of the mother ($p = 0.970$) were not associated with the antibody level (Table 1).

## 5. Discussion

We approached 77 children but enrolled 60. We excluded 17 of them due to the absence of an immunization card to attest that the child received the injection. Some children came to the hospital for a care different from vaccination. For this reason, parents did not come with the immunization card. This document is useful to ensure the observation of the EPI schedule.

All the children have received the 3 doses of vaccine at 6, 10 and 14 weeks after birth. Children born from a mother infected by HVB have also received a prior dose at the birth [9]. This dose is a monovalent HVB vaccine, which is not

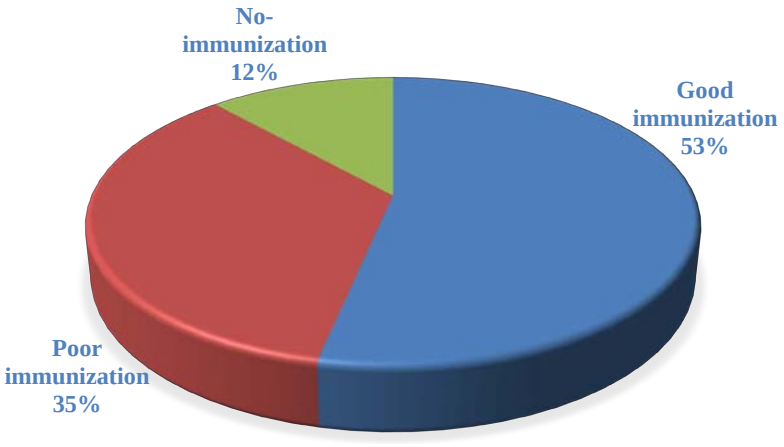


Figure 1. Classification of children according to the vaccine response.

**Table 1.** Factors associated with the immune response.

| Factors | Number | Poor or non-immunization n = 28 | p |
|---|---|---|---|
| **Age (months)** | | | |
| 15 - 24 | 16 | 04 | |
| 25 - 36 | 13 | 04 | **0.016** |
| 37 - 59 | 31 | **20** | |
| **Sex** | | | |
| Female | 31 | 14 | 0.809 |
| Male | 29 | 14 | |
| **Vaccination protocol's** | | | |
| 03 doses of vaccine | 48 | 24 | 0.301 |
| 03 dose of vaccine and a 4th booster dose at 12 months | 12 | 04 | |
| **Nutritionnal status** | | | |
| Good | 51 | 25 | 0.384 |
| Poor | 09 | 3 | |
| **Mother infected by HIV or HBV** | | | |
| Oui | 04 | 02 | 0.970 |
| Non | 56 | 26 | |

yet included in the EPI schedule in Cameroon. Thus, parents have to pay by themselves to protect the baby. The cost could reduce the access to this prior dose of vaccine.

The nutritional status of children was quite good, despite the fact that we carried out the study in a developing country where malnutrition is common/prevalent. The explanation is the fact that our sample is coming from Yaoundé, the capital of the country. In urban area, parents have a better educational level and prevent malnutrition from their infants. Thus, the effect of the nutritional status on antibody levels was mild in our sample.

The antibody level in children vaccinated against the hepatitis B virus was globally satisfactory in our series with 88% of children with anti-HBs ≥ 10 UI/mL (53% of good immunization and 35% of poor immunization). On the other hand, 12% of children vaccinated are non-immunized. They remain exposed to an HVB infection. Identifying the cause of this poor response in some children is a challenge in improving immunization rate. In developed countries, the quality of vaccine should be discussed looking the storage conditions [3].

As concerned with associated factors, we did not find any association between the sex and the nutritional status with the serologic response to the vaccine as described in some other studies. We did not observe a difference between children born from a mother infected by HIV and other children. This result is probably due to methods of preventing mother-to-child transmission of HIV implemented in the country. It has been described in Botswana where they observed a high response to the HBV vaccine among children exposed to HIV but uninfected [8].

Concerning children from women infected by HVB, we did not observe a difference in anti-HBs levels with those with non-infected women. The vaccination at birth significantly reduces the transmission risk of the HBV to the baby [12] [13].

The factor associated with non or poor immunization was the age between 37 - 60 months. This result suggests the importance of serological monitoring of vaccination efficiency as age increases [3].

The limit of the study is the small size of the sample. We recommend carrying out an observational study about the vaccine against HBV efficacy in the general Cameroonian population, 17 years after its introduction in the EPI [14]. A study carried out in US shows that the antibody level remains satisfactory until the adolescence [15].

## 6. Conclusion

Antibody levels in children vaccinated against hepatitis B virus were globally satisfactory in our series. Results show an association between low antibody levels and increased age, over 36 months, suggesting circulating antibodies levels decrease over time but remain acceptable until 59 months.

## Acknowledgements

We wish to assess the antibody level in children vaccinated against HVB during the EPI. In children with a poor immunization status, we want to identify factors leading to a poor antibody level. Thus, we can define a strategy to improve the protection against the HVB.

## Ethical Approvals

Parents of children gave their consent and the National Ethics Committee of the Faculty of Medicine and Biomedical sciences (University of Yaoundé 1/Cameroon) approved the study. All children anti-HBs-negative were invited to return to receive an HBV vaccination.

## Authors' Contributions

NDJITOYAP NDAM Antonin Wilson, principal investigator, conceptor, drafted the manuscript.

NDAM MEFIRE Alpha Hamed Béchir, investigator, data collection and analysis

BEKOLO Winnie, investigator.

NSENGA DJAPA Guy Roger, investigator.

NGO UM SAP Suzanne, interpretation of results.

KOKI NDOMBO Paul, materials tools, reviewer.

NDJITOYAP NDAM Elie Claude, the guarantor.

## Conflicts of Interest

The authors declare no competing interests.

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