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## Closed Suction Drain to Prevent Postoperative Seroma after Lichtenstein Hernioplasty in Complete Inguinal Hernia: A Comparative Study

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### Abstract:

**Background:** There is 5-12% chance of postoperative scrotal hematoma and seroma formation after Lichtenstein hernioplasty, which is attributed to complete hernia sacs, extensive dissection, and the foreign body reaction due to polypropylene mesh.

**Objective:** The aim of the study is to evaluate the efficacy of closed suction drain to prevent postoperative seroma after Lichtenstein Hernioplasty.

**Methods:** This prospective study was conducted in 80 patients of complete inguino-scrotal hernia. We compared incidence of post-operative seroma/hematoma and surgical site infection in drain vs. drainless group.

**Results:** Incidence of hematoma, seroma and surgical site infection in drain and drainless group was 2.5% vs 17.5%, 2.5% vs 22.5% and 2.5% vs 17.5% respectively.

**Conclusion:** Closed suction drain placement in the distal sac prevents formation of seroma/hematoma after Lichtenstein hernioplasty of complete inguino-scrotal hernia.

**Keywords:** Complete inguinal hernia, Lichtenstein's hernioplasty, Closed suction drain

### Introduction

Inguinal hernia repair is one of the most commonly performed surgeries by general surgeons. The Lichtenstein hernioplasty (LH) is considered as the gold standard repair and the most commonly used mesh is the polypropylene mesh to achieve a tension-free repair.<sup>1</sup> However, there is 5-12% chance of postoperative scrotal hematoma and

seroma formation after LH, which is attributed to complete hernia sacs, extensive dissection, and the foreign body reaction due to polypropylene mesh.<sup>2</sup> In most instances, small seromas resolve spontaneously but large seromas require percutaneous aspirations or the insertion of drains however, the acceptance for suction drainage differs among investigators.<sup>3-5</sup> We studied

the efficacy of the closed suction drain to prevent seroma and hematoma in complete inguino-scrotal hernia.

### Patients and methods

This prospective study was conducted between Jan 2017 and December 2019 in the Department of Surgery in a tertiary referral teaching hospital in Central India. Institutional ethics committee's approval and written informed consent by the patients were duly obtained. The complete inguinal hernia was defined as an inguinal hernia that extends up to the base of the scrotum. Obstructed, strangulated, incomplete inguinal hernias and other hernias (femoral, female, and sliding) were excluded.

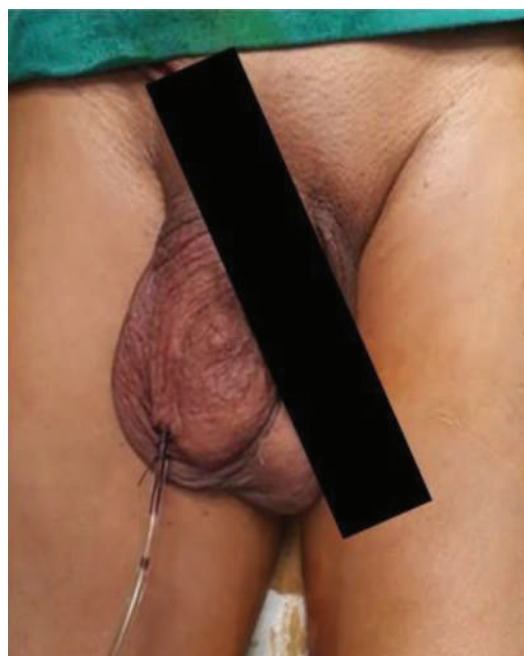
All patients underwent LH using polypropylene mesh fixed by 2-0 Prolene sutures (both by Johnson & Johnson Private Limited, 501 Arena Space, Behind Majas Bus Depot, Off Jogeshwari Vikhroli Link Road, Jogeshwari (E), Mumbai 400060 India) under spinal/ general anaesthesia. As per pre-decided protocol for this study, all the patients were operated by Consultants and received the same antibiotic – 3<sup>rd</sup> generation Cephalosporin (intravenously at the time of induction of anaesthesia and then orally for 5 days).

The allotment of the patients was done alternately in two groups (Drain group and Drainless group) and in the drain group, a negative pressure closed suction drain (Romovac, Romsons® Romsons Scientific & Surgical Pvt. Ltd, 63 Taj Expressway Link Rd, Nunhai Rd, Industrial Estate, Agra, Uttar Pradesh India 282006) was inserted over the mesh and extending through the residual distal hernial sac, was brought out through the scrotum (Figure 1). The drain was kept for a minimum of 48 hours and removed after the drainage was <10 mL. The patients were sent home after 48 hours with the drain if the drain was kept for a longer period due to ongoing drainage. Results

were assessed by a consultant surgeon by clinical examination for the presence of hematoma and seroma in both groups using Morales-Conde classification for seroma by laparoscopic ventral hernia repair.<sup>6</sup> The severity (Morales-Conde type), consequences (surgical site infection, extrusion of mesh and hernia recurrence), and outcome (spontaneous resolution, need of aspiration, and open drainage) were documented. Statistical analysis was performed using Medcalc® online software. Chi-square test using 2x2 contingency tables was used to compare frequencies between two groups and the 't' test was used to compare means while a value of  $p < 0.05$  was considered as statistically significant.

### Results

During the study period 142 inguinal hernia patients were operated in the department and 80 fulfilled inclusion criteria for this study, all men with age ranged from 18-60 years (mean: 44.98 years). They were divided into two groups and patients in each group were assigned alternately. The two groups were comparable, their demographic details and outcome are shown in Table 1.



**Figure 1** Closed suction drain

**Table 1** Demographic and outcome parameters in Drain and Drainless groups

Parameter	Drain (n=40)	Drainless (n=40)	P-Value
Age (years)	45 ± 15	47 ± 14	0.5394
BMI (kg/m <sup>2</sup> )	22.36 ± 11	22.72 ± 12	0.9060
Right: Left	26:14	25:15	0.7440
Pre-op albumin (g/dL)	3.69 ± 0.3	3.76 ± 0.3	0.2999
Pre-op Hb (g/dL)	11.2 ± 1.1	11.1 ± 1.3	0.7114
Incarcerated hernia	6	7	0.6773
Operating time (minutes)	60 ± 10	60 ± 11	0.0366
Hematoma formation	1 (2.5%)	7 (17.5%)	0.0125
Seroma formation	1 (2.5%)	9 (22.5%)	0.0025
Severity of Seroma	Type I-1	Type II- 6 Type III- 3	-
Surgical site infection	1 (2.5%) (All superficial)	7 (17.5%) (All superficial)	0.0125

Mean operative duration was comparable ( $p > 0.05$ ) in both the groups. The incidence of hematoma, seroma and surgical site infection was significantly higher ( $p = 0.0125$ ,  $0.0025$  and  $0.0125$  respectively) in the Drainless group (Table 1). The severity of seroma was higher in all the nine patients in the Drainless group, and three of them required open drainage while the other six required repeated aspiration. One patient each developed type I seroma and small hematoma in the Drain group which subsided with conservative treatment. The mean drain output was 70 mL (range: 50-100 mL); and drain was kept for a mean 3 days (range: 2-5 days). None of the patients in either group developed deep or organ space SSI or extrusion of mesh. Long term complications like chronic pain and recurrence were not seen in any of the patient during 6 months follow up.

## Discussion

LH is currently the gold standard for inguinal hernia and polypropylene mesh is most commonly used due to its low cost and easy availability.<sup>1</sup> Furthermore, the use of polypropylene mesh for contaminated and dirty strangulated hernias as well as for repair of abdominal wall following perforation peritonitis is effective and safe, with acceptable morbidity and good short-term results.<sup>7,8</sup> However, inguinal mesh hernioplasty is associated with a different set of complications including postoperative scrotal hematoma and seroma formation in 5-12% cases after LH, which is attributed to complete hernia sacs, extensive dissection, disruption of lymphatic, foreign body reaction due to polypropylene mesh and when the mesh is placed in contaminated hernia.<sup>2, 9-11</sup> The seroma or the hematoma in dead space surrounding the mesh and, in the scrotum becomes an excellent media for surgical site infection which may lead to mesh extrusion, visceral complications, and recurrence.<sup>6</sup> The scrotal hematoma or

seroma can be a distressful situation for the patients which may result in longstanding swelling, discomfort, pain, cellulitis, and multiple visits to the hospital.<sup>12</sup> The seroma requires either repeated aspirations or surgical drainage if it is deep-seated.<sup>13</sup> Therefore, the main focus of researchers has been to identify the existing issues with the time-tested surgery like LH and further minimize its complications.

The inherent foreign-body nature of polypropylene mesh has been debated but changing the type of mesh has not reduced the mesh or dissection related complications.<sup>14</sup> However, few reports show that the use of the Prolene Hernia System reduces such complications.<sup>11</sup> The resource-poor settings are faced by their own challenges where many patients present late when the hernia is complete i.e., has reached the bottom of scrotum.<sup>15</sup> Moreover, in the teaching centers, most of these surgeries are done by general surgery residents and the prevention of complications in a difficult hernia is another challenge.<sup>16</sup>

The opinion on keeping a closed suction drain after Lichtenstein hernioplasty in inguinal hernia differs among investigators.<sup>3-5</sup> The suction drain has been used for various extra-peritoneal and laparoscopic repairs, but their efficacy has always fallen short of a high level of evidence.<sup>17-19</sup> There has been limited research on the therapeutic utility of a closed suction drain in a complete inguinal hernia which is known to be associated with a large redundant sac, extensive dissection, and higher incidence of seroma and hematoma.<sup>20,21</sup> The concerns associated with drain include fear of introducing infection in the presence of prosthetic material, questionable efficacy and a principle against the philosophy of day-care procedure; however, suction drains are useful in a similar type of settings in many other fields of surgery.<sup>17, 22-24</sup>

In the present study, the overall incidence of postoperative seroma and hematoma formation was significantly higher if a closed suction drain was not used. This can be explained by our focussed observation which otherwise may have gone unnoticed. Moreover, if the closed suction drain is not deployed in a complete hernia, the complications like deeper infection, need for repeated aspiration/open drainage, are likely to be significantly increased for a gold standard procedure like LH. Contrary to popular belief, there was no iatrogenic mesh infection in the drain group. Suction drain is a closed system drain which would drain the collecting fluid and its negative pressure would facilitate the collapse of the potential space and prevent entry of infection from atmosphere.<sup>24</sup>

There are certain alternatives proposed for prevention of seroma such as leaving the distal sac undissected, medical talc powder (hydrated magnesium silicate), Triamcinolone acetonide, fibrin sealant or use of quilting sutures.<sup>13,25-28</sup> However, their efficacy is questionable and there is fear of introducing infection and foreign body granuloma. In the present study, no dissection of distal sac was done in either of the groups; however seromas could not be avoided completely, because of other factors like foreign body reaction of mesh and dead space in the left out sac may be responsible for post-operative seromas.

The frequency and severity of the problem and the efficacy of our intervention make us believe that the philosophy of postoperative drainage using closed suction drain is advantageous to minimize complications, patient discomfort, and hospital visits. However, the limitations of the present study include a smaller number of patients for comparison and performance of surgery by the trainees in a significant number of cases.

## Conclusion

The closed suction drain is an effective intervention in Lichtenstein hernioplasty for complete inguinal hernia for the prevention of postoperative seroma, hematoma and surgical site infections. Drain placement does not increase the chances of surgical site infections and there is no added economic burden or added skill required for performing this maneuver.

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## Conflicts of interest/Competing interests None

## Availability of additional data and material NA

## Code availability NA

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## The Study of Association between COVID-19 Pandemic and Blood Pressure Control among Hypertensive Patients in Tha Luang Hospital, Lopburi Province, Thailand

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### Abstract:

**Background:** COVID-19 infection, a coronavirus (SARS-CoV-2) infection causing severe acute respiratory distress syndrome is pandemic starting in December 2019 in Wuhan, China and then spreading rapidly throughout the world. This has an impact on every aspect of people life. In Thailand, the first case report was in January 2020 and spreading to the whole country rapidly. Due to the policy of Thai government to control this infection such as staying home, wearing masks, social distancing and limited going to any crowded places including hospitals. This would impact on people's health because many underlying diseases needed medical attention and regular medication, one of which was hypertension. However, during this situation, there was hospital service called 'home delivery pharmacy' of which the patients can register their preference with the hospital to deliver their routine medications to their home in order to reduce their risk of exposure to crowded places. However, there was still lack of the studies on the effects of COVID-19 pandemic on blood pressure control as well as efficacy of 'home delivery pharmacy' service.

**Objective:** The study aimed to study the impact of the COVID-19 pandemic on blood pressure control in hypertensive patients at Tha Luang Hospital, Lopburi Province.

**Methods:** This was a cross-sectional study conducted in Tha Luang Hospital, Lopburi Province between 2019 and 2020. Demographic data and blood pressure level of hypertensive patients were retrieved from the electronic medical records under the hospital permission. The data was collected into 2 durations 2019 (normal situation) and 2020 (COVID-19 pandemic). Uncontrolled blood pressure (BP) was defined by systolic BP > 140 mmHg, or diastolic BP > 90 mmHg in the latest visit. The demographic and prevalence of

uncontrolled blood pressure was analyzed by descriptive statistics. The average of SBP and DBP of hypertensive patients between in normal situation and COVID-19 pandemic were compared and analyzed by independent t-test.

**Results:** There were 4,045 and 4,063 hypertensive patients attended Tha Luang Hospital in 2019 and 2020 respectively. The prevalence of uncontrolled BP among these patients during 2 durations was 28.00% and 25.00% respectively ( $P = 0.003$ ). The mean SBP was 132.87 mmHg in 2019 and 132.94 mmHg in 2020 ( $P < 0.05$ ) and DBP was 74.96 mmHg in 2019 and 75.63 mmHg in 2020 ( $P < 0.05$ ). The patients with a higher BMI tended to have better control of their blood pressure ( $P < 0.05$ ).

**Conclusion:** During COVID-19 pandemic, the prevalence of uncontrolled BP in hypertensive patients attended at Tha Luang Hospital was lower than in 2019. This could be explained by the policy of Tha Luang Hospital that had a home delivery pharmacy to NCD patients, which made it more convenient for patients to access public health services. But during the pandemic, patients tended to have unhealthy lifestyle compared to the normal situation due to the government policy interfering healthy lifestyle such as confinement in home and closed public health care service which could affect blood pressure level. However, the patients with hypertension should have weight reduction for good blood pressure control and decreased further complication.

**Keywords:** COVID-19, Blood pressure control, Home delivery pharmacy, Lopburi, Thailand

## Introduction

In December 2019, pneumonia of the unknown cause was firstly reported in Wuhan, China. This pneumonia was caused by novel coronavirus or severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which resulted in coronavirus disease 2019 (COVID-19). The first case in Thailand was reported in 13 January 2020 and by 1 March 2020, total cases rising to 42 with first death by COVID-19 infection. These events caused the government to issue measures to control the disease, which started on 26 March, such as prohibiting entering designated areas. By 3 April, the government announced nation-wide lockdown which ban people from leaving their homes during the night across the country and limitation to go outside, especially to crowded areas such as market, malls, public parks and also hospitals with penalties on disobedience. The issued measure had significant impacts on patients

with chronic diseases such as hypertension, diabetes and cancer, etc. by limited healthy eating habits, reduced physical activities, increased stress from confinement, poor socioeconomic from unemployment, limited access public health services and uses of tobacco and alcohol<sup>1</sup>. Most hospitals had policy to limit services in both outpatients and inpatients to prevent crowding in hospitals and extending services for COVID-19 patients. As a result, people with non-communicable diseases such as hypertension, diabetes and heart diseases which required regular health check-up had fewer accessibility for medical care and this might have impact on health conditions of these patients. As mentioned, the lack of medical services and supplies or delayed treatment would increase complications, disability and mortality among these patients during the COVID-19 pandemic<sup>2</sup>.

On the other hand, instead of neglecting these patients entirely, most hospitals had

other measurements for them in order to deliver managements to them as best as hospitals could. One of these measurements was 'home delivery pharmacy' of which the patients can register their preference with the hospital to deliver their routine medications to their home in order to reduce their risk of exposure to crowded places i.e., hospitals. Other previous studies demonstrated that 'home delivery pharmacy' service as well as telemedicine met some levels of effectiveness in maintaining contacts and health care to these patients<sup>3</sup>. However, there was still lack of studies about efficacy of this method in Thailand.

### **Objectives:**

The study aimed to study the relationship between the COVID-19 pandemic period and the inability to control blood pressure (uncontrolled blood pressure) in hypertensive patients at Tha Luang Hospital, Lopburi Province during COVID-19 pandemic.

The secondary objective was to study the prevalence of inability to control blood pressure (uncontrolled blood pressure) in hypertensive patients and the factors related to uncontrolled blood pressure among hypertensive patients.

### **Methods**

#### *Study design*

This was the quantitative, serial cross-sectional study of prevalence, associated factors of ineffective control of blood pressure in hypertensive patients in Tha Luang Hospital, Lopburi Province during COVID-19 pandemic.

#### *Study date and setting*

This study was conducted during 1 January 2019 to 1 June 2019 and 1 January 2020 to 1 June 2020 at Tha Luang Hospital. Tha Luang Hospital was a government medium-sized community hospital in Tha Luang District, Lopburi Province in central

Thailand. Major tasks of medium-sized community hospitals included primary and secondary care of patients in the rural areas.

#### *Target population*

This study targeted at patients with primary hypertension who were treated and monitored at Tha Luang Hospital, Lopburi Province.

#### *Sample selection and data collection*

The inclusion criteria included being a patient diagnosed as hypertension by physician with follow up and treated at Tha Luang Hospital and granted consent to provide information to the researcher. Exclusion criteria included patients who did not receive treatment and monitored symptoms during the assessment and did not agree to provide information to the study. The study was retrieved from electronic records which contain of demographic data of the population, comorbidity, body mass index and blood pressure level.

#### *Statistical analyses*

The data divided in to 2019 and 2020. The demographic data and prevalence of uncontrolled blood pressure was analyzed by descriptive analysis. The mean systolic and diastolic blood pressure in 2019 and 2020 was analyzed and compared by independent t-test.

#### *Ethical consideration*

This study was approved by institutional board of Thai Army Medical Department. The approval code was R103h/63\_Exp

### **Result**

#### *General characteristics*

During 1 January 2019 to 30 June 2019, there were 4045 hypertensive patients who got check-up and treated at Tha Luang Hospital which 2913 (72.01%) patients could control blood pressure and 1132 (27.99%) could not control blood pressure. During 1 January 2020 to 30 June 2020, there were 4063 patients which 3046 (74.97%) could control blood pressure and 1017 (25.03%)

could not control blood pressure. The data was shown in table 1.

In 2019, the majority of the population was in 60-69 age group (29.74%) with an average age of 61.2 years old. BMI was mostly in the range of 25.00-29.99 (33.98%). In this population we found a comorbidity disease such as diabetes 1373 patients (33.94%) and other comorbidity such as gout, hyperlipidemia, cardiovascular disease and asthma (89.93%). The data was shown in table 2.

According to the data in 2020 the mean age of the patient was 62.5 years, mostly during 60-69 years (30.56%). BMI was mostly in the range of 25.00-29.99 (33.01%). In our population we found comorbidity diseases such as diabetes 1339 patients (32.95%) and other comorbidity such as gout, hyperlipidemia, cardiovascular disease and asthma (89.40%). The data was shown in table 3.

#### ***Risk factors of uncontrolled hypertension in 2019***

The factor that related to uncontrolled hypertension among population during 2019 which analyzed by multivariate analysis shown as in the age group 40-49, 50-59, 60-69, 70-79 and  $\geq 80$  having a chance of uncontrolled hypertension compared to age  $< 40$  shown as 0.93, 0.92, 1.05, 0.91 and 1.19 times respectively. The unemployed had a higher chance of uncontrolled hypertension compared to farmer 1.71 times. Patients who had other comorbidity (such as dyslipidemia, cardiovascular disease, asthmas, emphysema, allergies) had a higher chance to have uncontrolled hypertension compared to not having other comorbidity 2.91 times. Sub-district where the patient lived, including Hua Lam and areas outside Tha Luang District had a higher chance of uncontrolled hypertension compared to Tha Luang sub-district by 1.52 and 1.61 times respectively. BMI level in range of 18.50-22.99, 23.00-24.99, 25.00-29.99

had a lower chance of uncontrolled hypertension compared to  $<18.49$  by 0.55, 0.58, 0.67 times respectively. Risk factors were shown in Table 2.

#### ***Risk factors of uncontrolled hypertension in 2020***

The factor associated with uncontrolled hypertension among population during 2020 which analyzed by multivariate analysis shown in the age group 40-49, 50-59, 60-69 and 70-79 having a chance of uncontrolled hypertension compared to age  $< 40$  shown as 0.41 0.44 0.46 and 0.46 times respectively. People with diabetes had a higher chance of uncontrolled hypertension compared to those who had no diabetes 1.38 times. The patients with other comorbidity (such as dyslipidemia, cardiovascular disease, asthmas, emphysema, allergies) had a higher chance of uncontrolled hypertension compared to having no other comorbidity 2.89 times. As compared to Tha Luang district patients who lived in Kaeng Phak Kut, Sap Champa, Nong Phak Wan, Thalaewang wat, Hua Lam and areas outside Tha Luang district had a higher chance of uncontrolled hypertension by 1.50, 1.38, 2.13, 1.39, 1.68 and 1.53 times respectively. BMI in the range of 18.50-22.99 and 23.00-24.99 had a lower chance of uncontrolled hypertension compared to  $<18.49$  by 0.68 and 0.64 times respectively. Risk factors were shown in Table 3.

#### **Discussion**

This hospital-based, cross-sectional study, designed to find out the factors associated in hypertension control during the COVID-19 pandemic. The study found that in year 2020, which had COVID-19 outbreak, patients had better control of blood pressure levels which contradicted to study of the World Health Organization. This could be explained by the policy of Tha Luang Hospital that had home delivery pharmacy to NCD patients, which enabled

convenience for patient accessibility to health care services<sup>5</sup>. This delivery program sent the medication to NCD patient house which ensured continuity of care and adherence to epidemiological safety during the COVID-19 crisis. From the analysis of the data obtained in 2019, significant variables of uncontrolled hypertension included occupation, comorbidity, sub-district and BMI. In 2020, significant variables were diabetes, other diseases (gout, hyperlipidemia, cardiovascular disease and asthma), sub-district and BMI. In 2019, it was found that unemployed and merchant were less likely to control blood pressure compared to the farmer. This could be explained by the study that people who were in the lower class and repetitive tasks under time pressure, recognition of completed tasks and jobs with productivity-related income tended to have higher blood pressure level<sup>4</sup>. People with other diseases were less likely to control their blood pressure compared to those who did not. Sub-districts other than Tha Luang sub-district which was nearest to the hospital tended to have less well blood pressure level and ability to control blood pressure was decreased in relation to distance from Tha Luang hospital. The farthest district from the hospital is Hua Lam Sub-district with a distance of 23 kilometers had a chance of uncontrolled blood pressure 1.52 times compared to Tha Luang sub-district, which could explain by the difficulties in obtaining public health services and home delivery system. The patients with a higher BMI tended to have better control of their blood pressure, which could be explained by these groups having regular monitoring of body weight, pressure and nutritional status from public health volunteers and community hospitals.

In 2020, diabetic patients had a higher chance of uncontrolled hypertension 1.38 times compared to non-diabetic. The two variables mentioned were consistent with

the study of Sakboonyarat, et al.<sup>6</sup> Besides that, during the COVID-19 period people tended to have unhealthy behavior during lockdown.<sup>7</sup> The confinement to residents and the interruption of the work-related routine could lead to irregular eating patterns and frequent snacking, both of which were associated with increased food intake and consequently more positive caloric balance. During the quarantine, continuously hearing of or listening to the pandemic spread and its associated mortality could be so stressful. The other diseases (e.g., high blood lipids, heart disease, asthma, etc.) were have a higher chance of uncontrolled blood pressure were 2.89 times higher than those who were not suffering from the disease. Sub-districts other than Tha Luang sub-district which was the closest to the hospital tended to have worsen blood pressure level and controlling of blood pressure was decreased in relation to distance from Tha Luang hospital. As mentioned above, in 2020 Tha Luang hospital was using home delivery pharmacy policy but in the area outside the Tha Luang sub-districted had a higher chance of missed and delayed delivery due to the size of area and the area topography of farm and forest. As mentioned above the authors suggested patients and physicians to promote regular blood pressure measurement and appropriate practice to control blood pressure to reduce inability of blood pressure control. In addition to home delivery of medicine by mail, hospitals should provide clinical examination services for hypertension people by nurses and doctors in order to facilitate access to public health services during the COVID-19 outbreak which limited travel and public transport to help solve problems in some patients who had uncontrolled blood pressure. This study was based on the database of Tha Luang Hospital only not from other part of Thailand. Comparison of blood pressure control by collecting data from the last

follow-up visit in 2019 and comparing with COVID-19 pandemic period (1 January - 30 June 2020). There were some limitations from the obtained information only in the patients who visited the hospital. According to the hospital policy some patients who received treatment at the nearby sub-district health promotion centers or received drug refill promptly after emergency visit for other reasons would not be included in the home delivery pharmacy. These patient data was not used to analyzed in this research which might affect the research results.

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**Table 1** Comparison of number of controlled and uncontrolled hypertension patients at Tha Luang Hospital in 2019 and 2020

Year	Total	Uncontrolled (%)	Controlled (%)	Odds ratio (95% CI)	P-value
2019	4045	1132 (28)	2913 (72)	1 (Reference)	0.003
2020	4063	1017 (25)	3046 (75)	0.859	

**Table 2** Demographics of population with hypertension in year 2019

Variables	Total	Uncontrolled (%)	Controlled (%)	Crude ratio (95% CI)	P-value	Adjusted odds ratio (95% CI)	P-value
<b>Gender</b>							
Male	1514	439 (29)	1075 (71)	1 (Reference)			
Female	2531	693 (27.4)	1838 (72.6)	0.923 (0.802-1.063)	0.268		
<b>Age groups</b>							
<40	114	42 (36.8)	72 (63.2)	1 (Reference)		1 (Reference)	
40-49	489	135 (27.6)	354 (72.4)	0.654 (0.426-1.004)	0.052	0.930 (0.497-1.742)	0.821
50-59	1126	281 (25)	845 (75)	0.570 (0.381-0.854)	0.006	0.915 (0.502-1.671)	0.774
60-69	1195	331 (27.7)	864 (72.3)	0.657 (0.440-0.981)	0.04	1.047 (0.572-1.917)	0.882
70-79	733	215 (29.3)	518 (70.7)	0.712 (0.471-1.075)	0.106	0.911 (0.485-1.711)	0.772
≥ 80	361	121 (33.5)	240 (66.5)	0.864 (0.557-1.340)	0.515	1.186 (0.608-2.313)	0.616
<b>Occupations</b>							
Agriculture	1269	346 (27.3)	923 (72.7)	1 (Reference)		1 (Reference)	
Employee	2163	584 (27)	1579 (73)	0.987 (0.844-1.153)	0.866	0.974 (0.775-1.224)	0.819
Merchant	160	51 (31.9)	109 (68.1)	1.248 (0.875-1.780)	0.221	1.438 (0.875-2.361)	0.152
Unemployed	331	113 (34.1)	218 (65.9)	1.383 (1.068-1.791)	0.014	1.712 (1.196-2.451)	0.003
Others	112	38 (31.1)	84 (68.9)	1.207 (0.807-1.805)	0.36	1.365 (0.785-2.313)	0.616
<b>Education</b>							
Illiterate	314	94 (29.9)	220 (70.1)	1 (Reference)		1 (Reference)	
Primary	1649	418 (25.3)	1231 (74.7)	0.795 (0.609-1.037)	0.09	0.800 (0.607-1.056)	0.115
Secondary	132	43 (32.6)	89 (67.4)	1.131 (0.731-1.750)	0.581	1.159 (0.713-1.885)	0.551
University	20	4 (20)	16 (80)	0.585 (0.191-1.797)	0.349	0.517 (0.158-1.691)	0.275
Diploma	11	3 (27.3)	8 (72.7)	0.878 (0.228-3.381)	0.85	0.841 (0.211-3.360)	0.807
Unknown	115	32 (27.8)	83 (72.2)	0.902 (0.562-1.449)	0.671	0.861 (0.529-1.401)	0.548
<b>Health coverage</b>							
Universal (UC)	3249	907 (27.9)	2342 (72.1)	1 (Reference)			
Other	796	225 (28.3)	571 (71.7)	1.017 (0.856-1.208)	0.844		
<b>Smoking</b>							
Non	3481	962 (27.6)	2519 (72.4)	1 (Reference)			
Current smoke	552	166 (30.1)	386 (69.9)	1.324 (1.013-1.732)	0.04		
Ex-smoke	12	4 (33.3)	8 (66.7)	0.971 (0.742-1.271)	0.831		



**Table 2** Demographics of population with hypertension in year 2019

Variables	Total	Uncontrolled (%)	Controlled (%)	Crude ratio (95% CI)	P-value	Adjusted odds ratio (95% CI)	P-value
<b>Alcohol drinking</b>							
No	3432	934 (27.2)	2498 (72.8)	1 (Reference)		1 (Reference)	
Yes	613	198 (32.3)	415 (67.7)	1.279 (1.063-1.539)	0.009	1.207 (0.922-1.579)	0.171
<b>Diabetes Mellitus</b>							
No	2672	836 (31.3)	1836 (68.7)	1 (Reference)		1 (Reference)	
Yes	1373	296 (21.6)	1077 (78.4)	0.604 (0.518-0.703)	<0.001	1.197 (0.975-1.469)	0.085
<b>Chronic kidney disease</b>							
No	3989	1119 (28.1)	2870 (71.9)	1 (Reference)			
Yes	56	13 (23.2)	43 (76.8)	0.775 (0.415-1.447)	0.424		
<b>Other diseases</b>							
No	407	172 (42.3)	235 (57.7)	1 (Reference)		1 (Reference)	
Yes	3638	960 (26.4)	2678 (73.6)	0.49 (0.397-0.604)	<0.001	2.917 (1.947-4.370)	<0.001
<b>Region</b>							
Tha Luang	1201	290 (24.1)	911 (75.9)	1 (Reference)		1 (Reference)	
Kaeng Pak Kut	568	145 (25.5)	423 (74.5)	1.077 (0.855-1.356)	0.529	1.298 (0.947-1.778)	0.105
Sap Champa	621	178 (28.7)	443 (71.3)	1.262 (1.015-1.570)	0.037	1.347 (0.989-1.834)	0.059
Nong Pak Wan	480	155 (32.3)	325 (67.7)	1.498 (1.187-1.890)	0.001	1.323 (0.948-1.846)	0.099
Thale Wang Wat	342	72 (21.1)	270 (78.9)	0.838 (0.626-1.121)	0.234	0.905 (0.606-1.350)	0.624
Hua Lum	664	235 (35.4)	429 (64.6)	1.721 (1.399-2.116)	<0.001	1.521 (1.121-2.063)	0.007
Other	169	57 (33.7)	112 (66.3)	1.599 (1.132-2.258)	0.008	1.616 (1.021-2.560)	0.04
<b>BMI</b>							
<18.5	307	116 (37.8)	191 (62.2)	1 (Reference)		1 (Reference)	
18.5-22.99	991	243 (24.5)	748 (75.5)	0.535 (0.407-0.702)	<0.001	0.550 (0.379-0.797)	0.002
23.00-24.99	673	180 (26.7)	493 (73.3)	0.601 (0.451-0.801)	0.001	0.585 (0.394-0.869)	0.008
25.00-29.99	1373	380 (27.7)	993 (72.3)	0.630 (0.486-0.817)	<0.001	0.667 (0.462-0.962)	0.03
≥30	696	212 (30.5)	484 (69.5)	0.721 (0.544-0.956)	0.023	0.9 (0.602-1.345)	0.606

**Table 3** Demographics of population with hypertension in year 2020

Variables	Total	Uncontrol (%)	Control (%)	Crude ratio (95% CI)	P-value	Adjusted odds ratio (95% CI)	P-value
<b>Gender</b>							
Male	1505	385 (25.6)	1120 (74.4)	1 (Reference)			
Female	2558	632 (24.7)	1926 (75.3)	0.955 (0.824-1.105)	0.534		
<b>Age groups</b>							
<40	88	31 (35.2)	57 (64.8)	1 (Reference)		1 (Reference)	
40-49	461	116 (25.2)	345 (74.8)	0.618 (0.381-1.004)	0.052	0.413 (0.212-0.803)	0.009
50-59	1098	247 (22.5)	851 (77.5)	0.534 (0.337-0.845)	0.007	0.442 (0.234-0.838)	0.012
60-69	1235	280 (22.7)	955 (77.3)	0.539 (0.341-0.852)	0.008	0.456 (0.239-0.868)	0.017
70-79	762	204 (26.8)	558 (73.2)	0.672 (0.422-1.071)	0.095	0.456 (0.234-0.890)	0.021
≥ 80	396	130 (32.8)	266 (67.2)	0.898 (0.553-1.460)	0.666	0.693 (0.345-1.390)	0.302
<b>Occupations</b>							
Agriculture	1268	292 (23)	976 (77)	1 (Reference)		1 (Reference)	
Employee	2187	549 (25.1)	1638 (74.9)	1.120 ((0.952-1.318)	0.171	1.160 (0.916-1.469)	0.219
Merchant	160	38 (23.8)	122 (76.2)	1.041 (0.707-1.533)	0.838	1.145 (0.666-1.968)	0.623
Unemployed	331	106 (32)	225 (68)	1.575 (1.208-2.053)	0.001	1.386 (0.951-2.019)	0.089
Others	117	32 (27.4)	85 (22.6)	1.258 (0.821-1.929)	0.292	1.638 (0.925-2.900)	0.113
<b>Education</b>							
Illiterate	318	98 (30.8)	220 (69.2)	1 (Reference)		1 (Reference)	
Primary	1638	383 (23.4)	1255 (76.6)	0.685 (0.526-0.892)	0.005	0.766 ((0.580-1.012)	0.061
Secondary	124	40 (32.3)	84 (67.7)	1.069 (0.685-1.669)	0.769	1.015 (0.609-1.692)	0.955
University	22	10 (45.5)	12 (54.5)	1.871 (0.782-4.476)	0.159	1.787 (0.676-4.726)	0.242
Diploma	15	5 (33.3)	10 (66.7)	1.122 (0.347-3.371)	0.837	1.487 (0.471-4.692)	0.499
Unknown	111	26 (23.4)	85 (76.6)	0.687 (0.417-1.132)	0.14	0.796 (0.475-1.335)	0.387
<b>Health coverage</b>							
Universal (UC)	3360	843 (25.1)	2517 (74.9)	1 (Reference)			
Other	703	174 (24.8)	529 (75.2)	0.982 (0.814-1.185)	0.851		
<b>Smoking</b>							
Non	3536	870 (24.6)	2660 (75.4)	1 (Reference)		1 (Reference)	
Current smoke	270	92 (34.1)	178 (65.9)	1.584 (1.218-2.060)	0.004	1.266 (0.857-1.868)	0.236
Ex-smoke	235	50 (21.3)	185 (78.7)	0.819 (0.594-1.130)	0.224	0.843 (0.541-1.312)	0.449

**Table 3** Demographics of population with hypertension in year 2020

Variables	Total	Uncontrol (%)	Control (%)	Crude ratio (95% CI)	P-value	Adjusted odds ratio (95% CI)	P-value
<b>Alcohol drinking</b>	3517	871 (24.8)	2646 (75.2)	1 (Reference)		1 (Reference)	
	546	146 (26.7)	400 (73.3)	1.109 (0.904-1.360)	0.322	1.029 (0.632-1.676)	0.907
<b>Diabetes Mellitus</b>	2724	769 (28.2)	1955 (71.8)	1 (Reference)		1 (Reference)	
	1339	248 (18.5)	1091 (81.5)	0.578 (0.492-0.679)	<0.001	1.379 (1.186-1.603)	<0.001
<b>Chronic kidney disease</b>	4018	1008 (25.1)	3010 (74.9)	1 (Reference)			
	45	9 (20)	36 (80)	0.747 (0.358-1.555)	0.435		
<b>Other diseases</b>	430	156 (36.3)	274 (63.7)	1 (Reference)		1 (Reference)	<0.001
	3626	854 (23.6)	2772 (76.4)	0.541 (0.438-0.658)	<0.001	2.887 (2.092-3.984)	<0.001
<b>Region</b>	1235	241 (29.5)	994 (80.5)	1 (Reference)		1 (Reference)	
	584	154 (26.4)	430 (73.6)	1.477 (1.172-1.862)	0.001	1.504 (1.086-2.082)	0.014
	628	153 (24.4)	475 (75.6)	1.329 (1.055-1.672)	0.016	1.376 (0.994-1.904)	0.054
	491	164 (33.4)	327 (66.6)	2.069 (1.636-2.615)	<0.001	2.128 (1.533-2.952)	<0.001
	310	72 (23.2)	238 (76.8)	1.248 (0.925-1.682)	0.147	1.392 (0.927-2.089)	0.11
	677	188 (27.8)	489(72.2)	1.586 (1.273-1.975)	<0.001	1.676 (1.222-2.299)	0.001
	138	45 (32.6)	93 (67.4)	1.996 (1.361-2.926)	0.008	1.528 (0.900-2.592)	<0.001
<b>BMI</b>	332	216 (65.1)	116 (34.9)	1 (Reference)		1 (Reference)	
	1033	799 (77.43)	234 (22.6)	0.545 (0.417-0.713)	<0.001	0.677 (0.464-0.987)	0.042
	684	526 (76.9)	158 (23.1)	0.559 (0.420-0.745)	<0.001	0.641 (0.422-0.972)	0.036
	1338	1000 (74.7)	338 (25.3)	0.629 (0.487-0.814)	<0.001	0.757 (0.517-1.108)	0.152
	666	498 (74.8)	168 (25.2)	0.628 (0.472-0.836)	0.001	0.820 (0.535-1.256)	0.362

## Vaccinating against COVID-19 in Allergic Patients

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### Abstract:

It is over a year since the outbreak of coronavirus (COVID-19) and we are still facing an ongoing pandemic. Whilst the number of infected patients and death rates are increasing everyday, newly developed vaccines are the main hope for humanity to end this misery. From December 2020, emergency authorized vaccines had been distributed to many parts of the world. Studies of the vaccine have confirmed effectiveness with only very rare severe adverse reactions. There are no absolute contraindications for use of the vaccines in people with a history of allergy and preexisting allergic diseases. However, risk assessment and stratification are crucial to ensure ongoing safety for vaccine injection services. The precautions in place for use of the COVID-19 vaccines within high-risk populations include patients with a history of anaphylaxis to previous vaccinations, severe/uncontrolled asthma, and underlying mast cell disorders. These patients should have their vaccine injections under healthcare provider supervision. A consultation with an expert will provide deeper evaluation and shared decision-making for use of the appropriate vaccine. The observation period for the patients with risks of allergic reactions should be at least 15-30 minutes. If anaphylaxis occurs, prompt treatment improves the survival outcomes. Anaphylaxis is a treatable condition without long-term effects. Taking all of this into account, we encourage everybody to join the immunization campaign. Do not let the fear of the reactions outweigh the advantages of being vaccinated.

**Keywords:** COVID-19, Vaccine, Anaphylaxis, Allergy

### Introduction

Since the outbreak of coronavirus (COVID-19) and emerging of SARS-CoV-2 variants, over 170 million confirmed cases and 3.5 million deaths have been reported globally, according to the World Health Organization (WHO) as of June 2021<sup>1</sup>. The disease has affected people differently,

from asymptomatic or mild illness cases, to critical respiratory failure and shock<sup>2, 3</sup>. For over a year, people around the world are now living in a “New Normal” lifestyle, under strict social restrictions, to prevent viral transmission. Despite this a rising number of cases and death rates are still occurring everyday. To end this ongoing

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pandemic, vaccination is an effective intervention to provide protective immunity against the virus and significantly reduce morbidity and mortality among large populations<sup>4,6</sup>. From December 2020, more than 1.5 billion doses of vaccines have been administered, with good efficacy and low rates of serious adverse events<sup>7</sup>. In Thailand, 3.7 million doses of vaccines have already been given and currently a plan on mass distribution of vaccines is due to start on June 7, 2021. Although the vast majority of people are willing to get vaccinated, some people may refuse to join the immunization program due to multiple factors. Concerns about unknown future effects and misinformation are known to lead to vaccine hesitancy. This situation might delay success in the control of the pandemic<sup>8,9</sup>. This article aims to review adverse events following COVID-19 immunization, in which the author will focus on allergic reactions to vaccines and immunization in allergic patients. The aim is to encourage and build confidence in vaccination among the general population and healthcare providers.

### **Adverse event following immunizations (AEFIs)**

An adverse event following immunization (AEFI) is "...Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine..."<sup>10</sup>. The adverse events can be any unintentionally noxious signs and symptoms or abnormal laboratory results. The reactions may range from minor or local reactions to severe reactions. Minor reactions are mild unfavorable symptoms

such as pain and swelling at the site of injection or a systemic reaction, such as fever. Minor reactions resolved spontaneously after a short period. The severe reaction may cause patients disability for a definite of time but not results in long-term morbidities, such as seizure or allergic reactions to vaccines. Rarely, a severe reaction results in death. Subjects with underlying conditions are likely to have severe adverse events after vaccination<sup>11</sup>. To monitor medication safety, authorities in each country have set up surveillance systems of suspected adverse events on vaccines, such as the Vaccine Adverse Event System (VAERS) in the United States [VAERS - Report an Adverse Event (hhs.gov)], the European medicines agency (EMA) in Europe [European Medicines Agency (europa.eu)], (MHRA) in the UK and the Active surveillance system for COVID-19 Vaccine (App-Based Monitoring or Hospital-Based Safety Monitoring) at <https://co-vaccine.moph.go.th> in Thailand.

The causality assessment or determination of a relationship between the two events is a tool for healthcare providers to find potential causes of AEFI, based on evidence studies to avoid bias and confounders. Several factors may precipitate unwanted events. However, if the link to the vaccines is suspected, the events must occur only after the injections. Other considerations that could alternate the causes of the events including, preexisting diseases, and newly acquired illness, exposure to drugs or toxins, and infections preceding the vaccinations.<sup>12</sup> Classification of AEFIs, definitions and examples are shown in table 1.

**Table 1** Classifications, definitions, examples and cluster characteristics of AEFIs (Adapted from World Health Organization. (2014). Global manual on surveillance of adverse events following immunization, 2016 update. Available from <https://apps.who.int/iris/handle/10665/206144>)<sup>13</sup>

Classification of AEFI	Definition	Example	Cluster characteristics
<ul style="list-style-type: none"> <li>Vaccine product-related reaction</li> </ul>	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product	<ul style="list-style-type: none"> <li>Biological plausibility of the vaccine products</li> <li>Individual's reactions to the properties of vaccines such as allergic reactions to vaccines, aseptic meningitis following mumps vaccine</li> </ul>	<ul style="list-style-type: none"> <li>Cases received the same vaccine or lot</li> <li>No similar cases in the community</li> <li>Increased frequency reported from multiple settings to known vaccine reactions</li> </ul>
<ul style="list-style-type: none"> <li>Vaccine quality defect-related reaction</li> </ul>	An AEFI that is caused or precipitated by a vaccine due to one or more quality defects of the vaccine product, including the administration device, as provided by the manufacturer.	<ul style="list-style-type: none"> <li>Insufficient inactivation of wild-type vaccine agent</li> <li>Contamination during manufacturing process</li> </ul>	
<ul style="list-style-type: none"> <li>Immunization error-related reaction</li> </ul>	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and that thus, by its nature	<ul style="list-style-type: none"> <li>Error in vaccine preparation by health care workers</li> <li>Contamination during preparation, transportation, or storage</li> <li>Defect in vaccine storage and transportation</li> <li>Error in administration techniques</li> <li>Identification error</li> </ul>	<ul style="list-style-type: none"> <li>Cases received vaccines from the same healthcare worker or facility and there are no other cases</li> </ul>

Classification of AEFI	Definition	Example	Cluster characteristics
<ul style="list-style-type: none"> <li>Immunization anxiety-related reaction</li> </ul>	An AEFI arising from anxiety about the immunization	<ul style="list-style-type: none"> <li>Not related to properties of the vaccines</li> <li>Individual's psychological reactions</li> <li>Top four frequent reactions (faint, hyperventilation, vomiting, convulsions)</li> </ul>	<ul style="list-style-type: none"> <li>Cases of symptoms after immunization are well-recognized as anxiety-related reactions during immunization programs targeting adolescent girls</li> </ul>
<ul style="list-style-type: none"> <li>Coincidental event</li> </ul>	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety	<ul style="list-style-type: none"> <li>Not related to properties of the vaccines</li> <li>Inevitable events could occur especially during the mass campaign</li> <li>Example: death of the infant following days after DTP vaccination (could be from the vaccine or a coincidental death at a normal death rate of the infancy period)</li> </ul>	<ul style="list-style-type: none"> <li>Cases in the unvaccinated population are occurring at about the same rate/proportion as among the vaccinated from the same area in the same age group</li> <li>Calculating the expected rate of an adverse event may be helpful for investigators.</li> </ul>

Cases selection for causality assessment is crucial. Serious AEFIs that result in death, hospitalization, significant disability or congenital anomaly, the events that happened at an unusual rate or severity and clusters that largely impacted public health policy are the main focus for causality assessment.<sup>12</sup>

### Assessing reactions to vaccines

Currently (June 2021), there are seven vaccines in use worldwide, of these five are verified for use by WHO and available for use in Thailand. These emergency authorized COVID-19 vaccines, the recommended schedules of administration, and frequent reported adverse reactions, are shown in table 2. The majority of the cases report only mild symptoms, usually self-limited and not requiring additional treatment.

**Table 2** Authorized COVID-19 vaccines, recommended schedules of administration, and frequent adverse reactions.<sup>14-20</sup>

Platform	Developer/ Vaccine name	Dose schedule and administration	Common side effects
<b>RNA-based vaccine</b>	BioNTech–Pfizer (BNT162b2)	Two doses (day 0, day 21) Intramuscular	<u>Injection site</u> : pain, swelling, redness <u>Systemic</u> : fatigue, headache, muscle pain, chills, fever, joint pain
	Moderna (mRNA-1273)	Two doses (day 0, day 28) Intramuscular	<u>Injection site</u> : pain, swelling, redness <u>Systemic</u> : fatigue, headache, muscle pain, chills, fever, nausea, joint pain
<b>Adenovirus vector (Nonreplicating)</b>	AstraZeneca and University of Oxford (AZD1222)	One (day 0) or two (day 0, day 28 or 8-12 weeks) doses Intramuscular	<u>Injection site</u> : pain <u>Systemic</u> : fatigue, headache, muscle pain, nausea, fever, joint pain
	Janssen (Johnson & Johnson)	One (day 0) or two (day 0, day 56) doses Intramuscular	<u>Injection site</u> : pain, redness, swelling <u>Systemic</u> : fatigue, headache, muscle pain, nausea, fever
<b>Inactivated</b>	BBIBP-CorV (Sinopharm)	Two doses (day 0, day 21-28) Intramuscular	<u>Injection site</u> : pain, swelling <u>Systemic</u> : fatigue, headache, muscle pain, nausea, fever, diarrhea
	CoronaVac (Sinovac)	Two doses (day 0, day 14-28) intramuscular	<u>Injection site</u> : pain, redness, swelling <u>Systemic</u> : fatigue, headache, muscle pain, nausea, fever, diarrhea

### Hypersensitivity reactions to COVID-19 vaccines

Despite safety profiles of vaccine phase 3 trials, hypersensitivity reaction is the issue that raises the public fear of vaccination. Nevertheless, at the date of the VAERS report, confirmed anaphylaxis occurred at

a rate of 11.1 per million doses of BioNTech–Pfizer vaccines, 71% of the onsets were within 15 minutes after injection, over 95% have been discharged home without any deaths.<sup>21</sup> Clinical recognition of anaphylaxis is very important to ensure provision of early essential initial treatments, before taking



of a thorough history, physical exam, and other investigations. Mechanisms of immediate reactions are divided into three main categories, Immunoglobulin E (IgE) mediated reaction, Non-IgE mediated reaction, and non-immune reaction (vasovagal reaction). For IgE-mediated reaction, the symptoms can be mild, such as urticaria and pruritus, to presenting with a severe multi-systemic reaction, known as anaphylaxis. The

previously used term “Anaphylactoid” represents reactions that resemble anaphylaxis without evidence of IgE. These clinical features may result from direct mast cell and basophil activation, activation of complement pathways, and many other pathways. In this case, serum for tryptase will be of benefit to distinguish between the two conditions.<sup>22</sup> Comparison of anaphylaxis and vasovagal features are shown in table 3.

**Table 3** Comparison of anaphylaxis and vasovagal features (Adapted from Banerji et al)<sup>23</sup>

Characteristics	Anaphylaxis	Vasovagal reactions
<b>Onset after vaccination</b>	15-30 minutes	Within 15 minutes
<b>Signs and symptoms</b>		
<b>Consciousness</b>	Anxiety, may progress to unconsciousness	Fainting sensation, dizziness, loss of consciousness in some cases
<b>Pulse</b>	Rapid, weak, and irregular	Slow, weak but regular
<b>Blood pressure</b>	Hypotension (SBP<90) In children: SBP <70 mmHg +2 x age (year) in 1-10 years old	Variable; may have hypotension, or bradycardia during syncope event
<b>Respiratory</b>	Difficulty breathing; coughing, sneezing, wheezing, stridor	Variable; if accompanied by anxiety, may have an elevated respiratory rate
<b>Cutaneous</b>	- Warm skin, progressing to clammy and pallor - pruritus urticaria in >90% of cases - angioedema	- pallor, diaphoresis, clammy skin sensation, facial warmth
<b>Gastrointestinal</b>	Nausea, vomiting, abdominal pain, diarrhea	Nausea, vomiting

### Patients at risk for COVID-19 vaccines anaphylaxis

For newly developed vaccines, it is always a challenging question of who is at risk of anaphylaxis. Ongoing research is needed to identify specific risk factors. A detailed history, including allergy to vaccine

components, previous drug allergy, atopic history (especially asthma), and drugs or substance use/ activities before vaccination must be obtained. Currently, proposed risk factors for COVID-19 vaccines anaphylaxis are as followed<sup>24</sup>

- Patients with previous anaphylactic episode to vaccines
- Patients with mastocytosis and other mast cell disorders
- Patients with severe/uncontrolled asthma.

Investigation of the culprit agents responsible for the patient's reaction, allergic testing (skin prick test, intradermal skin test, and blood testing), and allergist consultation are crucial to lowering the risks of future vaccination.

**Table 4** Current emergency approved COVID-19 vaccines and excipients<sup>27</sup>

Vaccines	Excipients
<b>BioNTech–Pfizer (BNT162b2)</b>	(4-hydroxybutyl) azanediyl) bis (hexane-6,1-diyl) bis (2-hexyldecanoate)] (ALC-0315), <b>2-[(polyethylene glycol)-2000]</b> -N,N ditetradecylacetamide (ALC-0159), 1,2-distearoyl-sn-glycero-3-phosphocholine cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, sucrose, water for injection
<b>Moderna (mRNA-1273)</b>	Lipids (SM-102, 1,2-dimyristoyl-rac-glycero3- <b>methoxy-polyethylene glycol-2000 [PEG2000-DMG]</b> , cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose
<b>AstraZeneca and University of Oxford (AZD1222)</b>	L-Histidine, L-Histidine hydrochloride monohydrate, Magnesium chloride hexahydrate, <b>polysorbate 80</b> , Ethanol, Sucrose, Sodium chloride, Disodium edetate dihydrate, Water for injection
<b>Janssen (Johnson &amp; Johnson)</b>	Sodium chloride, citric acid monohydrate, <b>polysorbate 80</b> , 2 hydroxypropyl-B-cyclodextrin (HBCD), ethanol (absolute), sodium hydroxide
<b>BBIBP-CorV (Sinopharm)</b>	<b>Aluminum hydroxide</b> , disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, sodium hydroxide, sodium bicarbonate, M199
<b>CoronaVac (Sinovac)</b>	<b>Aluminum hydroxide</b> , disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride

Frequently, the immediate allergic reaction is due to excipients components (Inactive ingredients in the vaccine that helps formulate the product, to increase stability, efficacy, and sterility, such as egg protein, gelatin, formaldehyde, thiomersal, etc.)<sup>25,26</sup>

A list of excipients in the vaccine is shown in table 4

For the mRNA vaccines, Polyethylene glycol (PEG, also known as macrogol) and polysorbate, the additives used to improve water solubility in the vaccines, are the

key components that contribute to IgE-mediated reactions.<sup>28</sup> PEG is contained in many household and cosmetic products, such as toothpaste and skin creams. A variety of medications e.g., laxative agent for bowel preparation in colonoscopy, Methylprednisolone acetate (Depo-Medrol), Medroxyprogesterone acetate (Depo-Provera) contain PEG 3350. Hence, this specific formulation of PEG in the mRNA vaccine is designed to stabilize the liposome portion, and is in use for the first time for vaccination purposes. Polysorbates, on the other hand, are extensively used in common injectable medications and vaccines, including influenza vaccine (Fluarix quad, Flulaval Quad), DTaP (Infanrix), and Rotavirus (RotaTeq). Polysorbate 80 is used in AstraZeneca and Johnson & Johnson. These two chemicals have potential cross-reactivity due to their structural similarity. Though allergies to the substances are rare, sensitization in the prior exposure to polysorbate 80 had been reported before the first dose of vaccination<sup>23,28,29</sup>

Aluminum is a strong adjuvant that enhances immunogenicity in classical inactivated vaccines. Several vaccines, for instance, Diphtheria and Tetanus vaccines, within controlled injectable limits, have used this adsorbed compound, with a good safety profile, for decades. The aluminum itself can cause local reactions, such as granuloma formation and skin rash, and anaphylaxis can occur.<sup>30,31</sup> In phase 3 and phase 1/2 study of inactivated COVID-19 vaccines, no anaphylaxis had been observed.<sup>19,32</sup> Though all of these reactions are rare, to date (June 2021), in the real world, 17 per million anaphylaxis episodes were reported in Chile and Thailand.<sup>33,34</sup> Further research and monitoring of the reactions are ongoing.

### **COVID-19 Vaccination in patients with preceding allergic diseases<sup>35</sup>**

The allergy, asthma and immunology Association of Thailand (AAIAT) recommend that there is no absolute contraindication for COVID-19 vaccine in patients with preceding allergic diseases. The details for each allergic disorders are as followed,

#### **Patients with asthma**

Patients with asthma can be vaccinated with COVID-19 vaccines. Patients with controlled asthma should continue their controller medications even on the day of vaccination. For uncontrolled asthma and severe asthma patients, however, there are precautions for these groups, especially those who are using the systemic steroid for controlling symptoms at the time of vaccination. Patients who are not well-controlled asthma should consult with their physician before getting vaccinated. For the patients who currently receiving biologic therapy, such as omalizumab, benralizumab, or dupilumab, at least 7 days intervals after the last dose of biologic medication is recommended before vaccination.

#### **Patients with food allergy**

Patients with any food allergy can go on vaccinating with covid-19 vaccine without special precautions.

#### **Patients with drug allergy**

Patients with a history of drug allergy including antibiotics (i.e. penicillin, sulfa), Non-steroidal anti-inflammatory drugs (i.e. ibuprofen, naproxen, aspirin), anti-convulsants, gout treatment, and radiocontrast media allergy can be vaccinated with COVID-19 vaccine. However, a 30-minute observation period under health care provider supervision is recommended.

### Patient with history of vaccine allergy

Patients who previously had severe allergic reactions to other vaccines and who previously had severe reactions or urticarial rash after the first dose of COVID-19 vaccine should consult their physician before getting COVID-19 vaccines.

### Vaccination safety measures and precautions

According to the CDC, "...people should get vaccinated even if they have a history of severe allergic reactions not related to vaccines or injectable medications..." Since the benefits of COVID-19 vaccinations greatly exceed the risks of allergy, everyone should be encouraged to join the campaign.

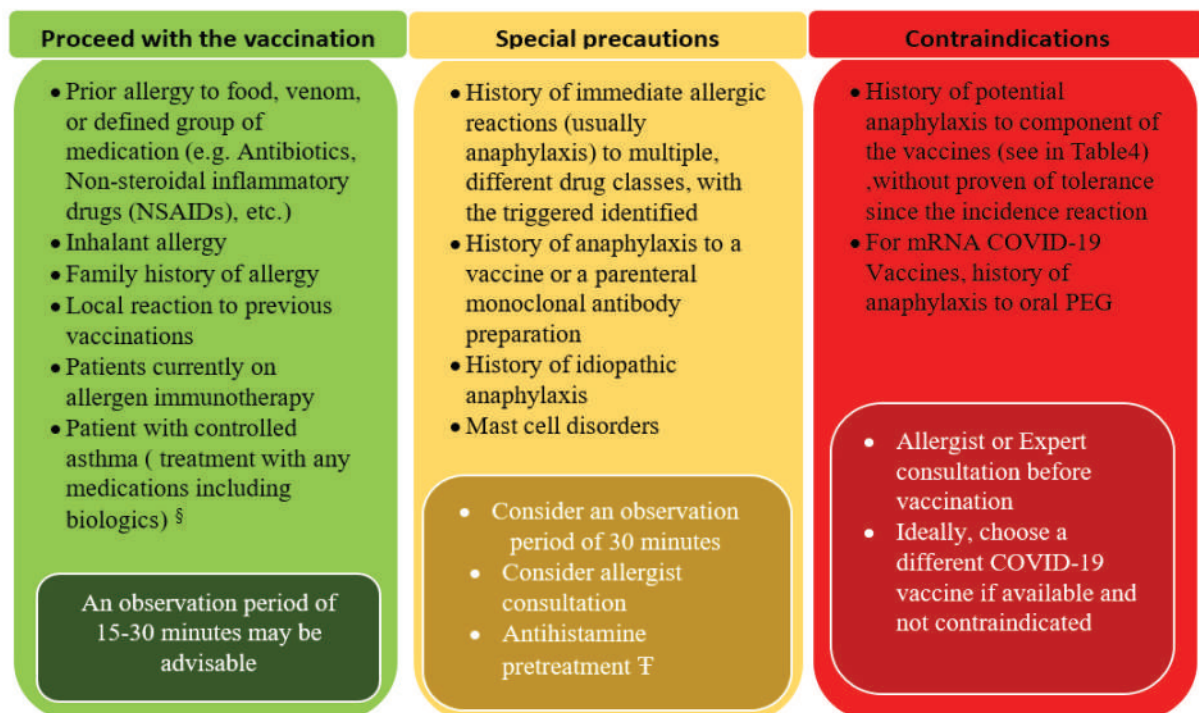
### The first dose of COVID-19 vaccination

Before the first dose of COVID-19 vaccination, The European Academy of Allergy and Clinical Immunology (EAACI) and The American College of Allergy,

Asthma, and Immunology (ACAAI) recommend a list of questions for physicians and other providers to ask patients, to screen for the risks of allergic reactions. The example of the questions are as following,

- Do you have a history of severe allergic reaction to an injectable medication?
- Do you have a history of severe allergic reaction to a previous vaccine?
- Do you have a history of a severe allergic reaction to polyethylene glycol (PEG), a polysorbate, or polyoxyl 35 castor oil (e.g., paclitaxel)?
- Do you suffer from allergies or allergy-like diseases? (e.g., mast cell disorder)

These questions triage the patient whether to proceed with the vaccination, referral for further evaluations, or using other alternative vaccines. In addition, people with higher risks should be monitored for a longer period. Schematic for screening question and risk stratification is shown in figure 1.<sup>27,36,37</sup>



**Figure 1** Schematic for screening question and risk stratification. (Adapted from Turner *P et al.*)<sup>27</sup>

*(Detailed in red box is newly arranged)*

§ British Thoracic Society (BTS) and Global initiative for asthma (GINA) recommend that Patients with asthma who currently on biological therapy should not receive COVID-19 vaccine on the same day, a 7- day interval is advisable (recommendation as of Mar 2021)<sup>38,39</sup>

¶ No clear evidence on pretreatment of antihistamine with COVID-19 vaccine, the medication may mask initial symptoms or reactions

In figure 1, the green box, yellow box and red box represent the low, medium and high risk for severe allergic reactions following the first dose of COVID-19 vaccination, respectively. Patient with previous allergies, mild or local reaction to previous other vaccines, patients currently on immunotherapy and patients with controlled asthma can proceed to COVID-19 vaccination safely. A routine 15- to 30- minute observation is generally recommended. Patients with a history of anaphylaxis to multiple drugs or previous vaccination are at medium risk. These patients may need detailed evaluation before getting vaccinated. A premedication with antihistamine (e.g. cetirizine, fexofenadine) may reduce mild discomforting symptoms such as mild rash or itching. However, this may delay early signs of anaphylaxis and may delay treatments, which could lead to morbidity and mortality. Since the anaphylaxis episodes usually occur at 15 to 30 minutes after injection, therefore at least 30 minutes of observation after vaccination is needed. Health care providers should consult expert or allergist before giving the vaccines to the high risk patients who had history of anaphylaxis to any component of COVID-19 vaccines. For mRNA vaccine, skin test with polysorbate 20 and 80 is important to confirm diagnosis of PEG allergy. If possible, patients with positive skin test should be injected with other alternative types of COVID-19

vaccines. This risk stratification ensure safety for all patients for current and future vaccination.

During the observation period, healthcare providers should obtain the patient's vital signs and look for any abnormal clinical symptoms. Emergency Supplies and medications should be readily prepared. In the case of anaphylaxis, early recognition and appropriate initial management improve the outcomes. In some situations, patients might not fulfill all the diagnostic criteria. However, from the expert panel discussion, whenever severe allergic features are in doubt, epinephrine is the treatment of choice<sup>40</sup>. For all patients with suspected allergic reactions, a detailed history, physical examination, and initial blood sampling (e.g., tryptase) is recommended. Consider referral for allergist for further evaluation.

For local reactions, a self-treatment by cold compression at the side of injection, exercising the arms, over-the-counter pain-reliever medications, and drinking plenty of water can reduce the symptomatic discomfort. Some people might experience delayed localized hypersensitivity reactions. Magaret et al. reported a case series of 16 patients who received mRNA vaccine (Moderna) with erythematous rash, pruritus, induration, and tenderness at the site of injection, in which the median onset was 7 days after the first dose and 5 days after the second dose. The lesions may persist for up to 21 days. All the skin lesions resolved spontaneously and so are not considered as contraindications for the second dose of the vaccine<sup>41</sup>.

### **Second dose of COVID-19 vaccination**

It is crucial to follow up on patients' clinical symptoms after the first dose of vaccinations. According to the CDC recommendation as of Mar 2021<sup>42</sup>, "...if a person

has received the first dose uneventfully, then they can proceed to the second dose in the same manner...”

If the patients experience mild allergic reactions, likewise, only pruritus or urticaria, a second dose can be given with precautions. Pretreatment with fexofenadine or cetirizine 1-2 hours before the injection might reduce the discomforting symptoms. A 30-minute observation period is required to ensure patient safety. However, once a person has severe allergic reactions, healthcare providers should consider further evaluation and shared decision-making, related to the risks and benefits of receiving the vaccine, with the patient and an allergist. Even though the non-irritating concentration of the vaccine’s component had not been standardized, skin testing may be utilized to identify the potential component-related symptoms. For re-challenging of the COVID-19 vaccines, there is a lack of evidence of efficacy of this<sup>23</sup>. Also the American Academy of Allergy Asthma & Immunology COVID-19 response task force states that in the present situation, with often limited vaccine resource, it would be more beneficial for the vaccine to be used for vaccination rather than for evaluation of the reactions.<sup>43</sup>

### Conclusion

In the battle against COVID-19, vaccination is the prime key to success. There are no absolute contraindications for COVID-19 vaccine use in any patients with pre-existing allergic conditions and diseases. While the benefits of vaccination are clear and the risks of severe adverse events are rare, fear of adverse reactions must be addressed. Healthcare providers have a role in promoting the COVID-19 immunizing campaign. Well-prepared and prompt treatment of any emergency conditions, at the time of vaccination, helps improve the

outcomes and will ensure patient’s safety, and vaccine confidence, as part of the vaccination service.

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## Rapid Antibiotics Guideline for Treatment and Management of COVID-19 Pneumonia with Bacterial Co-infection

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### Abstract:

**Background:** There are many patients having serious or critical illness will require hospital admission due to SARS-CoV-2 pneumonia. While antibiotics are ineffective for treatment of viral infections, they are prescribed in patients with suspected or documented SARS-CoV-2 for a variety of reasons. This raises concerns of antibiotic overuse or receiving unnecessary antibiotics and increase antimicrobial resistance (AMR).

**Objective:** The authors would like to develop a rapid antibiotic guideline for the treatment of patients with SARS-CoV-2 who have coinfections. These recommendations are intended to ensure the better antibiotic management of suspected or confirmed bacterial pneumonia in adults during the SARS-CoV-2 pandemic.

**Methods:** We used MEDLINE, OVID Epub and EMBASE searches complemented with extensive use of Web engine to identify guidelines on empirical treatment of community and hospital-acquired pneumonia in the last 10 years.

**Results:** We could develop antibiotic prescribing recommendation for patients with suspected community-acquired pneumonia, that has developed before or within 48 hours and patients with suspected hospital acquired pneumonia at more than 48 hours of admission.

**Conclusion:** Patients who develop SARS-CoV-2 pneumonia can have guideline for antibiotic prescription in case of suspected secondary superimposed bacterial infection.

**Keywords:** COVID-19 infection, Pneumonia, Antibiotics

## Introduction

The SARS-CoV-2 cases were first reported from Wuhan, China in early December 2019, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)<sup>1,2</sup>. Within a span of months, SARS-CoV-2 has become pandemic spreading across countries with the number of cases and deaths rising daily<sup>2-9</sup>. Although most infected individuals exhibit a mild illness, and some have serious or critical illness will require hospital admission due to SARS-CoV-2 pneumonia<sup>2-8</sup>. Approximately 10% will require ICU care, including invasive ventilation due to acute respiratory distress syndrome (ARDS)<sup>2-8</sup>. While higher mortality among elderly individuals and those with comorbidities, such as chronic lung disease, cardiovascular disease, hypertension, and diabetes<sup>2-8</sup>.

While antibiotics are ineffective for treatment of viral infections, they are prescribed in patients with suspected or documented SARS-CoV-2 for a variety of reasons<sup>6,10</sup>. This raises concerns of antibiotic overuse or receiving unnecessary antibiotics and increase antimicrobial resistance (AMR). First, agents are being explored in clinical trials as potential direct therapies for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), such as azithromycin<sup>6,10</sup>. Second, antimicrobials are commonly prescribed for the management of presumptive or confirmed bacterial co-infection directly related to SARS-CoV-2 pneumonia<sup>6,10</sup>. During influenza pandemics bacterial co-infection in patients has been reported to be as high as 20–30% and is associated with a severity of illness, prolong hospital or ICU admission, and increased risk of

mortality<sup>6,10,11</sup>. Current evidence suggests that prevalence, incidence and characteristics of bacterial infection in patients with SARS-CoV-2 is low, but prescribing rates and use of broad-spectrum antimicrobial agents is increased<sup>6,10,11</sup>.

Given the rapid global spread of SARS-CoV-2, limited guidelines advocate the use of empirical antibiotics for patients with severe SARS-CoV-2 based on data and literature from past influenza pandemics<sup>6,10,11</sup>. This raises concerns of antibiotic overuse or receiving unnecessary antibiotics and increase antimicrobial resistance (AMR). In a retrospective cohort analysis of 191 patients from two hospitals in Wuhan, 95% of patients were treated with antibiotics and 21% were treated with antivirals<sup>7</sup>. However, a retrospective case series of 393 SARS-CoV-2 patients in New York revealed that only 5.6% of patients had bacteremia and none of them received antibiotics during treatment<sup>6,8,10,11</sup>.

As it can be difficult to differentiate SARS-CoV-2 from bacterial pneumonia and increase the risk of patients without bacterial infections are receiving unnecessary antibiotics. Therefore, we have recognized the necessity of developing a rapid antibiotic guideline for the treatment of patients with SARS-CoV-2 who have coinfections. These recommendations are intended to ensure the better antibiotic management of suspected or confirmed bacterial pneumonia in adults during the SARS-CoV-2 pandemic. This includes people presenting to hospital with moderate to severe community-acquired pneumonia and people who develop pneumonia while in hospital.

## Development process of treatment guidelines

We used methodologically rigorous process for evaluating the best available evidence, clinical syndrome specific guidance and providing treatment recommendations. In addition, we used MEDLINE, OVID Epub and EMBASE searches complemented with extensive use of Web engine to identify guidelines on empirical treatment of community and hospital-acquired pneumonia in the last 10 years. This is to be ensured that our guidelines are rational and best available evidence for antimicrobials. The search was structured to include SARS-CoV-2 terms,

viral pneumonia and bacterial infection was defined as an acute infection including either (a) co-infection on presentation, or (b) secondary infection emerging during the course of illness or hospital stay. We assessed the extent to which recommendations considered resistance, in addition to efficacy and safety, when recommending antibiotics. This guideline was developed using the GRADE approach for evidence assessment. In addition, the methodological approach was modified according to the Guidelines International Network/McMaster checklist for the development of rapid recommendations.

**Table 1** Antibiotics Recommendations for SARS-CoV-2 infected adult (Age >18) with suspected community-acquired pneumonia

<b>Empirical treatment</b>	<b>Antibiotics and dosage</b> (oral doses are for immediate-release medicines)
Oral antibiotics for moderate or severe pneumonia	Options include: Doxycycline: 200 mg on first day, then 100 mg once a day  Co-amoxiclav: 500 mg/125 mg three times a day with Clarithromycin: 500 mg twice a day  In severe pneumonia, and if the other options are unsuitable:  Levofloxacin: 500 mg once or twice a day  *consider the safety issues with fluoroquinolones
Intravenous antibiotics for moderate or severe pneumonia	Options include: Co-amoxiclav: 1.2 g three times a day with Clarithromycin: 500 mg twice a day  Cefuroxime: 750 mg three or four times a day (increased to 1.5 g three times a day if infection is severe) with Clarithromycin: 500 mg twice a day  In severe pneumonia, and if the other options are unsuitable:  Levofloxacin: 500 mg once or twice a day  *consider the safety issues with fluoroquinolones

**Table 2** Antibiotics Recommendations for suspected hospital-acquired pneumonia in adults with SARS-CoV-2 (Age >18)

<b>Empirical treatment</b>	<b>Antibiotics and dosage</b> (oral doses are for immediate-release medicines)
Oral antibiotics for non-severe pneumonia when there is not a higher risk of resistance	Options include: Doxycycline: 200 mg on first day, then 100 mg once a day Co-amoxiclav: 500 mg/125 mg three times a day Co-trimoxazole: 960 mg twice a day (see the BNF for information on monitoring of patient parameters) If the other options are unsuitable: Levofloxacin: 500 mg once or twice a day (consider the safety issues with fluoroquinolones)
Intravenous antibiotics for severe pneumonia; for example, symptoms or signs of sepsis or ventilator-associated pneumonia or when there is a higher risk of resistance	Options include: Piperacillin with tazobactam: 4.5 g three times a day, increased to 4.5 g four times a day if infection is severe Ceftazidime: 2 g three times a day If the other options are unsuitable: Levofloxacin: 500 mg once or twice a day (use a higher dosage if infection is severe; consider the safety issues with fluoroquinolones)
Antibiotic to be added if meticillin-resistant <i>Staphylococcus aureus</i> infection is suspected or confirmed; dual therapy with an intravenous antibiotic listed above	Vancomycin: 15 mg/kg to 20 mg/kg two or three times a day intravenously, adjusted according to serum vancomycin concentration. Maximum 2 g per dose. Teicoplanin: Initially 6 mg/kg every 12 hours for 3 doses intravenously, then 6 mg/kg once a day (see the BNF for information on patient parameter and therapeutic drug monitoring) Linezolid: 600 mg twice a day orally or intravenously (with specialist advice only; see the BNF for information on monitoring of patient parameters)

## Discussion

As antibiotics save lives, most antibiotic treatments for pneumonia depend on the empirical method<sup>6</sup>. Adequate antibiotic treatment is crucial during SARS-CoV-2 pandemic to prevent secondary bacterial infections<sup>6,10,11</sup>. However, the appropriate use of antibiotics for the treatment of pneumonia is the key to addressing the issues of antimicrobial resistance while ensuring access to lifesaving antibiotics<sup>6,10,11</sup>. But defining what appropriate means remains problematic

given the ongoing substantial challenges in diagnosing SARS-CoV-2 pneumonias. In the case of SARS-CoV-2, better understanding and predicting disease severity, which can help guide treatment and management decisions, are essential to effectively combatting pandemic<sup>6,10,11</sup>. Since the distribution of causative bacteria and antibiotic resistance vary between countries, it is necessary to develop an appropriate antibiotic treatment guideline based on epidemiological data and literature.

To guide decision making about antibiotics, use antibiotic prescribing recommendation Table 1 for patients with suspected community-acquired pneumonia, that has developed before or within 48 hours of admission. However, antibiotic prescribing recommendation Table 2 for patients with suspected hospital acquired pneumonia that develops 48 hours or more after admission and that was not incubating at admission. For both recommendations, when choosing antibiotics, also take account of local antimicrobial resistance data and other factors such as their availability, toxicity, and previous history of allergies. If the patient can take oral medicines and their condition is not severe enough to need intravenous antibiotics, oral antibiotics were recommended. However, importantly review all antibiotics at 24 to 48 hours or as soon as bacteria culture sensitivity results are available and switch to a narrower spectrum antibiotic when appropriate. Also, if the pneumonia is due to SARS-CoV-2 only and there is no evidence of bacterial infection, discontinued the antibiotic treatments<sup>6,10,11</sup>. Moreover, if antibiotics are continued, administered them for a total of 5 days, then discontinued them unless there is a clear bacteria culture test is positive.

For intravenous antibiotic recommended to reviewed within 48 hours and consider about switching to oral antibiotics if the patient progress prominent. In specific populations, such as hepatic impairment, renal impairment, pregnancy, and breastfeeding, and when administering intravenous antibiotics followed the guidelines for appropriate use and dosing<sup>6,10,11</sup>. It is necessary to consult a local microbiologist for alternative options in case of complications. If patients have history of penicillin allergy, avoid using co-amoxiclav and use cefuroxime with caution. For fluoroquinolones, it is necessary to followed the

appropriate guidelines because of very rare reports of disabling and potentially long-lasting or irreversible side effects affecting musculoskeletal and nervous systems<sup>6,10,11</sup>. Discontinued the treatments if signs of a serious adverse reaction, such as tendonitis, prescribing with special caution for people over age 60 years and avoiding coadministration with corticosteroid.

The recommendations in this guideline are based on evidence from the best available clinical studies with patient important endpoints. Our recommendations highlight the important need to focus on antibiotic prescribing in patient with SARS-CoV-2, and to ensure that antibiotic stewardship programs are well positioned to improve prescribing and minimizing the antibiotic resistance.

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### **Conflicts of interest and competing financial interests**

No author declares any potential conflict of interest or competing financial or non-financial interest in relation to the manuscript.

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## Developing on Implant Biorubber Materials without Using Acid for Coagulation

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### Abstract:

**Background:** Natural rubber latex (NRL) from *Hevea brasiliensis* is a colloidal anionic system formed by rubber particles (1,4-cis-polyisoprene) stabilized by phospholipids and protein molecules. Rubber biomaterials using as a novel technology could develop to apply as biomaterial based on a new manufacturing process, several new biomedical applications have been proposed since NRL is very biocompatible, stimulating cellular adhesion, the formation of the extracellular matrix, and promoting the replacement and regeneration of tissue.

**Objective:** This study aimed to deproteinization from fresh natural rubber latex (NRL) and to coagulate the deproteinized natural rubber latex (DNRL) for using as implant biomaterials with novel technology without using acid for coagulation.

**Methods:** Coagulated DNRL films is often used to prepare the blended films by solution-casting technique. Its films presents interesting physical properties in elasticity.

**Results:** The deproteinized NRL containing various CaO gave lower modulus values comparing with the control films.

**Conclusion:** In this experiment, the blended films of DNRL and various CaO could form appropriate films. The physical and mechanical properties of the blended films depended on type and content of CaO addition. From the good elasticity of blended films, they could develop to apply as the production of a biomaterial of NRL that has been used to replace vessels, esophagus, pericardium, and abdominal wall.

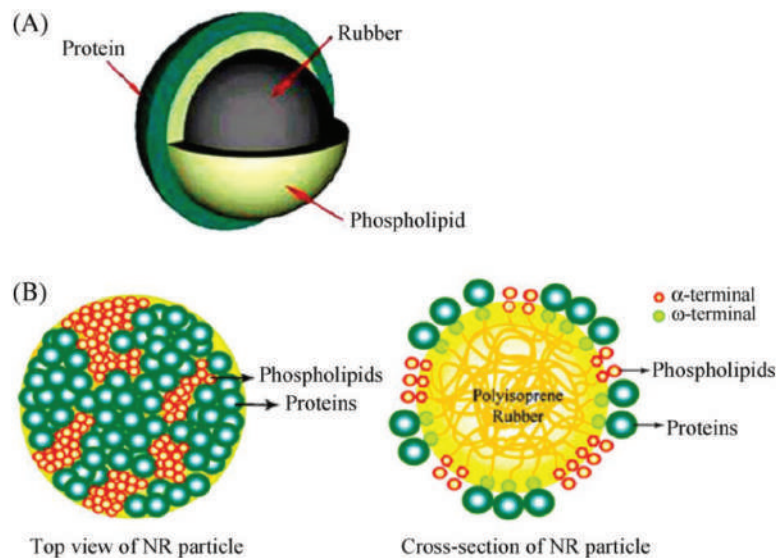
**Keywords:** Deproteinization, Fresh natural rubber latex, Rubber, Biomaterials, CaO



## Introduction

*Hevea brasiliensis* (*H. brasiliensis*), popularly known as the Para rubber tree, is a plant species that belongs to the Euphorbiaceae family. It is the most economically important member of the genus *Hevea* because the milky latex extracted from the tree is the primary source of natural rubber<sup>1</sup>. Most of the harvested latex is coagulated for the manufacture of dry rubber products, including automotive tires. The latex of *H. brasiliensis* can be stabilized in an uncoagulated form with the use of ammonia, which allows the latex to be used for the manufacture of other products, such as surgical gloves<sup>2</sup>. Natural

rubber latex (NRL) from *H. brasiliensis* is a colloidal anionic system formed by rubber particles (1,4-cis-polyisoprene) stabilized by phospholipids and protein molecules (Figure 1)<sup>3,4</sup>. One-third of the weight of *H. brasiliensis* latex is made of natural rubber, but 1–2% of its weight consists of hundreds of proteins<sup>5</sup>. Other constituents such as lipids, Quebrachitol, ribonucleic acids, and organic salts are also present<sup>6,7</sup>. Based on a new manufacturing process, several new biomedical applications have been proposed since NRL is very biocompatible, stimulating cellular adhesion, the formation of the extracellular matrix, and promoting the replacement and regeneration of tissue<sup>8</sup>.



**Figure 1** The structure model of the natural rubber latex particle surface.

(A) A current model of an NRL particle, and (B) the new model (adapted from Ref. 3).

Cockle shells (aragonite) is one of the more abundant crystalline polymorphs of calcium carbonate ( $\text{CaCO}_3$ ) with more than 95% purity. The trace elements were measured as mercury (Hg) < 0.25 ppm, arsenic (As) 0.75 ppm, lead (Pb) 0.31 ppm and cadmium (Cd) 0.31 ppm<sup>9</sup>. Moreover, it contains fractions of heavy metals from natural sources, but all elements are within the range permitted by ASTM's implant materials standard.

This work aims to deproteinization from fresh NRL and then to coagulate natural rubber biomaterials using active CaO extract from mollusk shells with novel technology without using acid for coagulation.

## Objective

In the present work, the purpose focused on the deproteinization from fresh NRL and to coagulate the deproteinized natural rubber latex for using as implant

biomaterials with novel technology without using acid for coagulation.

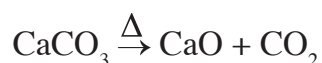
## Method

### Deproteinization Processes

The solutions were chosen for protein extraction: 2% sodium lauryl sulfate (SLS) and 0.1%w/w, 2.0 %w/w KOH. Natural rubber latex 250 g stirred in a 500 mL extract solution. After shaking at room temperature for 3 hours, the mixture was mixed with 2%w/w alum ( $\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$ ) and heat up to 60°C and then immediately subjected to protein precipitation. In the protein precipitation step, the low proteins rubber was collected by centrifugation at 10,000 rpm and 4°C for 10 minutes, and the collected cream fraction was diluted with distilled water. Finally, the deproteinized natural rubber latex (DNRL) was redissolved in deionized water and stored at 4°C.

### Active CaO preparation

Five hundred gram of fresh cockle shells were immersed with 15%v/v  $\text{H}_2\text{O}_2$  for 24 hours and then calcined at 900°C for 1 hour under an oxidation atmosphere. Thermal treatment in this condition has changed CaO into high purity and active to reaction<sup>9</sup>. Then milled calcium oxide into powders by using a high-speed ball mill and stored in a desiccator. The transform into calcium oxide by freeing carbon dioxide ( $\text{CO}_2$ ) according to the following equation:

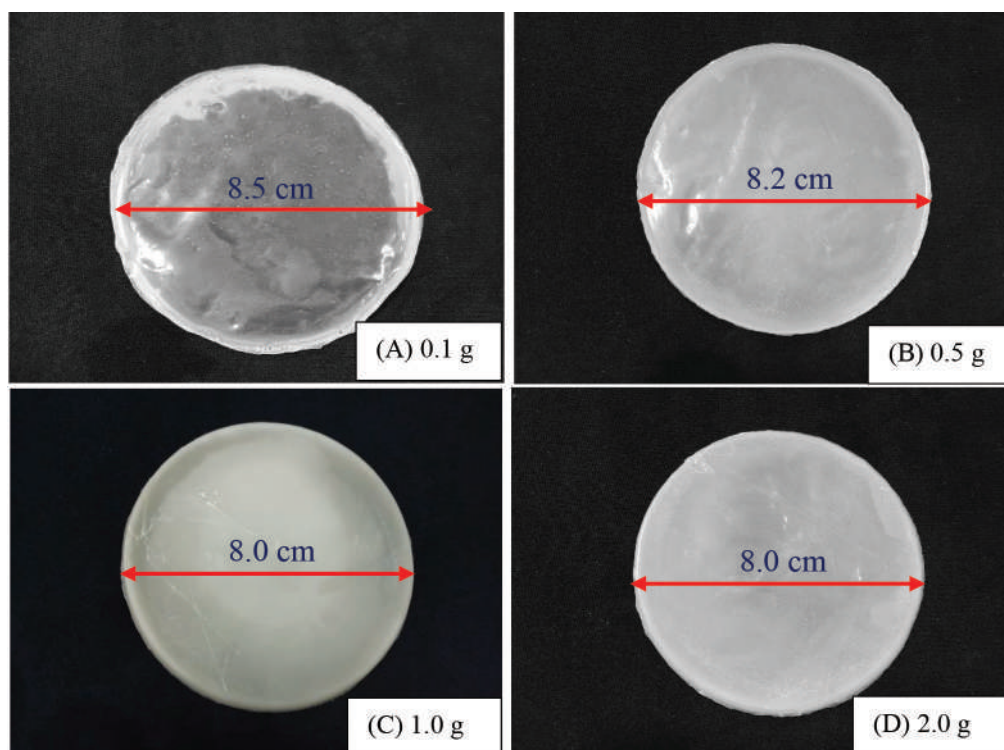


### Coagulating of Natural Rubber Biomaterials

Coagulation of DNRL studies was carried out in 1,000 mL beakers by 100 g of DNRL and various CaO addition for 0.1, 0.5, 1.0, and 2.0 g. The mixtures were stirred for 30 min at room temperature (27-30°C). Then each mixture was cast in the glass plates. After that, let dried at 60°C for 24 h using an air-circulating oven. The physical testing of dried rubber film was analyzed by a universal testing machine based on ASTM D 412. Five dumbbell test pieces were cut from each film and the average thickness was calculated and then attached between the grips of a tensile testing machine and pulled at a rate of 500 mm/min.

### Results

From the deproteinization process, the total protein content in NRL, determined by the methods as described in ASTM D3533<sup>10</sup>, it was reduced for more than 72.35% comparing with that in the fresh NRL<sup>5</sup>. Coagulated DNRL films is often used to prepare the blended films by solution-casting technique. Its films presents interesting physical properties in elasticity. The thickness of films was measured at five different areas using a micrometer. Figure 2 show the coagulated DNRL films could form the yellowish transparent films. The physical and mechanical properties of the DNRL blended films are shown in Table 1.



**Figure 2** Coagulated DNRL films by different amount of CaO addition; 0.1, 0.5, 1.0 and 2.0 g of CaO are present in (A), (B), (C) and (D), respectively.

**Table 1** Physical and Mechanical Properties of Coagulated DNRL films

Sample	Component		Properties	
	Deproteinized NRL (g)	CaO (g)	Thickness (mm)	Young Modulus (MPa)
A00	100	-	0.92±0.01	4.55±0.08
A01	100	0.1	1.70±0.02	3.86±0.06
A02	100	0.5	2.52±0.01	3.24±0.02
A03	100	1.0	3.47±0.01	2.39±0.05
A04	100	2.0	3.95±0.02	1.41±0.02

### Discussion

The deproteinized NRL films containing various CaO gave lower modulus values comparing with the control films (A00 as films without CaO). This result indicated that additive CaO provided thickness and softness films. The UTM of the samples with various CaO were lower than that of the control films. UTS of A01

and A02 which contained 0.1 and 0.2 g of CaO, respectively, which suggesting the immiscibility of the components. The physical and mechanical properties of the blended films depended on type and concentration of CaO. From the good elasticity of blended films, they could develop to apply as biomaterial films.

## Conclusion

In this experiment, the blended films of DNRL and various CaO could form appropriate films. The physical and mechanical properties of the blended films depended on type and concentration of CaO. From the good elasticity of blended films, they could develop to apply as the production of a biomaterial of NRL that has been used to replace vessels, esophagus, pericardium, and abdominal wall. Moreover, NRL was also coated with calcium phosphate (Ca/P) and tested for biomedical application. Biomaterials added with Ca/P present biological, chemical, and mechanical properties very similar to the mineral phase of the bone besides the ability to bond to the host tissue. A hemolytic test was performed, and this material did not affect the blood cells, being so ready for animal tests.

## Acknowledgement

This work was carried out with support from Mae Fah Luang University.

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## Diabetic Striatopathy: A Rare Microvascular Neurological Diabetic Complication

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### Abstract:

Diabetic striatopathy is a rare neurological diabetic complication which has an incidence of 1:100,000 population. This report presents a female with poorly controlled type 2 diabetes and hypertension, who presented with right sided choreoathetosis. No other neurological abnormalities were found on physical examination. Brain imaging showed hyperdensity of the left caudate and left lentiform nuclei on non-contrast CT scan. The patient made a complete recovery from the abnormal movements following tight glucose control and introduction of trihexyphenidyl and haloperidol. A follow up CT scan 6 months following presentation revealed resolution of the previous striatal abnormalities.

**Keywords:** Diabetic striatopathy, Choreoathetosis, Hemichorea/hemiballism, Corpus striatum

### Introduction

Type 2 diabetic patients can present with abnormal movement called choreoathetosis or hemichorea/hemiballism. This movement disorder is known to develop in association with stroke, Wilson's disease, neoplasm, infection and thyrotoxicosis<sup>1</sup>. However, this choreoathetosis was possibly directly related to complications of diabetes. As already known, one of the microvascular neurological complications of diabetes is diabetic neuropathy, in which patients present with glove and stocking numbness or painful sensations affecting their limbs. There is also another microvascular neurological diabetic complication called "Diabetic Striatopathy". This case report presents one case of poorly controlled type 2 diabetes, that presented with abnormal movements and abnormal brain imaging.

### Case presentation

A 76-year-old Thai woman with history of type 2 diabetes and hypertension presented with fatigue, dizziness and vomiting. Her regular medications had consisted of glipizide and metformin for her diabetes and amlodipine and enalapril for high blood pressure. She had never received insulin therapy for glucose control. For unknown reasons she had stopped her oral hypoglycemic agents and all of her other medications for 3 months, prior to development of the presenting symptoms. On physical examination, she had normal mental status without any focal neurological deficit. Biochemical investigations revealed random blood glucose 408 mg/dL, creatinine 1.75 mg/dL (estimated GFR 28 mL/min), Hb 12.2 g/dL, Hct 34.3%, WBC  $11.7 \times 10^9/L$ . Non-contrast CT scan of the brain showed

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relative hyperdensity at the left caudate nucleus and left lentiform nucleus without surrounding brain edema. Diffuse brain atrophy was also seen (Figure 1A-C). Because of the very high glucose level, the patient received insulin treatment. Her blood glucose at 4 weeks follow up had declined to 120 mg/dL. However, 2 weeks later, 6 weeks following her first appointment, she came to the hospital with pain and numbness of her left arm with uncontrolled movements of her right shoulder and right arm. These abnormal movements had persisted all day and night for 3 days. She did not have muscle weakness or facial weakness. Furthermore, her speech was normal, and she did not have headache, dizziness or vomiting. On physical examination her blood pressure was 175/82 mmHg, she had normal mental status and normal cranial nerves examination. Obvious continuous low amplitude choreoathetoid movements of the right shoulder, arm and wrist were noted. There was normal muscle power with no sensory deficit. No evidence of muscle rigidity nor bradykinesia was observed. Non-contrast CT brain revealed obviously increased hyperdensity of both the left caudate nucleus and left lentiform nucleus. without peripheral brain swelling, compared with the previous imaging. The CT findings were compatible with non-ketotic hyperglycemic hemichorea (diabetic striatopathy), (Figure 2A-C). She was commenced on trihexyphenidyl for the abnormal movements with no therapeutic effect so haloperidol was added in 2 weeks later. Her blood glucose at follow-up visit was 124 mg/dL, HbA1c 7.3%. Medical treatment for diabetes included Insulin (NPH) and glipizide. Fourteen weeks after treatment, the choreoathetosis disappeared and her glycemic profile remained within the normal range. (fasting plasma glucose 101 mg/dL and HbA1c 6.8%). Follow up CT scan done 6 months later showed resolution of

the previous hyperdensities of the left caudate and lentiform nuclei (Figure 3A-C).

## Discussion

“Diabetic striatopathy” was also known as hyperglycemic non-ketotic hemichorea/hemiballism or diabetic hemichorea/hemiballism or chorea hyperglycemia basal ganglia syndrome. Hemichorea and hemiballism are defined as random involuntary continuous jerking movements, involving one side of the body in which chorea, characteristically being described as more distal and of less amplitude than ballism<sup>1</sup>. Therefore, diabetic striatopathy is described as a hyperglycemic state accompanied by one of these conditions 1) chorea/ballism 2) striatal hyperdensity, as seen on non-contrast CT scan and as hyperintensity on a T1 weight MRI brain scan<sup>2</sup>.

The incidence of diabetic striatopathy is recorded as 1:100,000 population incidence and is composed of Asian (71.6%), European (8.5%), American (4%). Mean age was 67.6 years old, with a female to male ratio of 1.7:1<sup>2</sup>. Mean age of onset was 70 and 96 percent of cases were found in DM type 2 but only 3.4 percent was found in DM type 1. Fifty-four percent were associated with poorly controlled diabetes and 55 percent had high blood pressure<sup>3</sup>.

Hemichorea/hemiballism can involve symptoms in the face and trunk, in addition to the arm and leg, and showed bilateral involvement in less than 10 percent of cases.<sup>2</sup> Patients usually had hyperglycemia at presentation (random blood glucose 306-414 mg/dL, HbA1c 13.1-14.5%)<sup>2-5</sup>. As found in our case, the patient also had high blood glucose, 408 mg/dL, when striatal abnormality was detected on the CT scan. However, choreoathetosis was diagnosed 6 weeks later when the CT scan showed more obvious hyperdensity of both the left caudate nucleus and left lentiform nucleus.

On imaging of diabetic striatopathy, non-enhanced CT scan shows striatal (caudate nucleus and lentiform nucleus) hyperdensity and MRI scan reveals striatal (caudate nucleus, putamen and globus pallidus) hyperintensity on T1 weight with hypointensity on T2 weight<sup>4</sup>. Nevertheless, there is discrepancy between clinical hemichorea/hemiballism and striatal involvement as seen on CT and MRI. Furthermore, discrepancies, between CT and MRI findings, are related to differences in the location of the striatal abnormalities. Sensitivity of CT scan to detect striatal abnormality in diabetic striatopathy was 78.5 percent compared with 95.5 percent when using MRI, but CT scan can be useful to detect abnormalities on negative scans using MRI<sup>4</sup>. Using CT scan, the locations of striatal abnormality, 78.6% were found in putamen, 47.6% in the caudate nucleus and 27.8% in the globus pallidus. After treatment of hyperglycemia, complete or partial resolution of striatal abnormalities were seen on MRI and CT scan<sup>2</sup>.

The median time of resolution of striatal hyperintensity seen on MRI was 180 days and was 60 days on CT scan<sup>2</sup>. However, abnormalities on imaging can persist, as in a case of untreated diabetic striatopathy, reported by Lucassen<sup>4</sup>, in which symptoms persisted for 4 years, where MRI showed severe atrophy of the caudate nucleus. Homaida<sup>6</sup> has suggested that differential diagnosis of striatal hyperintensity, seen on CT scan or MRI, could be 1) petechial hemorrhage 2) mineral deposition 3) myelin destruction 4) infarction with astrocytosis.

The mechanism of pathogenesis of diabetic striatopathy could be formulated as shown in figure 4.

Abe<sup>7</sup> performed a needle biopsy of the corpus striatum in one case of diabetic striatopathy, a 50-year-old Japanese man found to have low intensity areas in the right

putamen and caudate nuclei on CT scan. Histopathology of his striatal specimen is shown in table 1.

In summary histopathology of diabetic striatopathy, can be characterized as striatal abnormalities due to 1) occlusive vasculopathy 2) patchy necrosis 3) prominent neovascularization. Treatment of diabetic striatopathy consists mainly of correction of hyperglycemia which results in partial or complete resolution of clinical symptoms of hemichorea/hemiballism and reduction of striatal abnormalities on neuroimaging. Anti-chorea medication includes haloperidol, tetrabenazine, risperidone, clonazepam, used as single medications or in combination. With high efficacy, haloperidol has become the most frequently used medication<sup>1,4,5,6,8,9</sup>. The median recovery time after commencement of anti-chorea medication was 14 days<sup>3</sup>.

## Conclusion

Diabetic striatopathy is a rare microvascular neurological diabetic complication which can be seen in poorly controlled diabetic patients, especially in the elderly Asian females. Such patients commonly present with hemichorea/hemiballism. Diagnosis is composed of the triad of 1) unilateral involuntary movements and 2) contralateral striatal abnormality on imaging and 3) hyperglycemia. Pathology of diabetic striatopathy is microangiopathy that is confined to the corpus striatum. Patients have a good prognosis with complete clinical remission after successful treatment of hyperglycemia.

## Acknowledgement

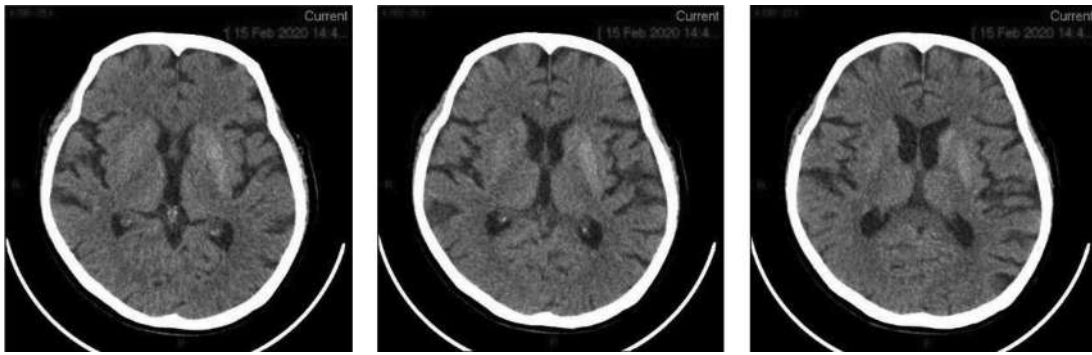
The author would like to thank to Roger Timothy Callaghan MB, ChB. a family physician and lecturer, for his suggestion on English writing following careful reading of the manuscript and Kwinnart Wongsirodkul, M.D. a radiologist



and lecturer for her suggestion of appropriate CT scan cuts. The author also has special thanks to the patient for permission to publish her clinical details presented in this report.

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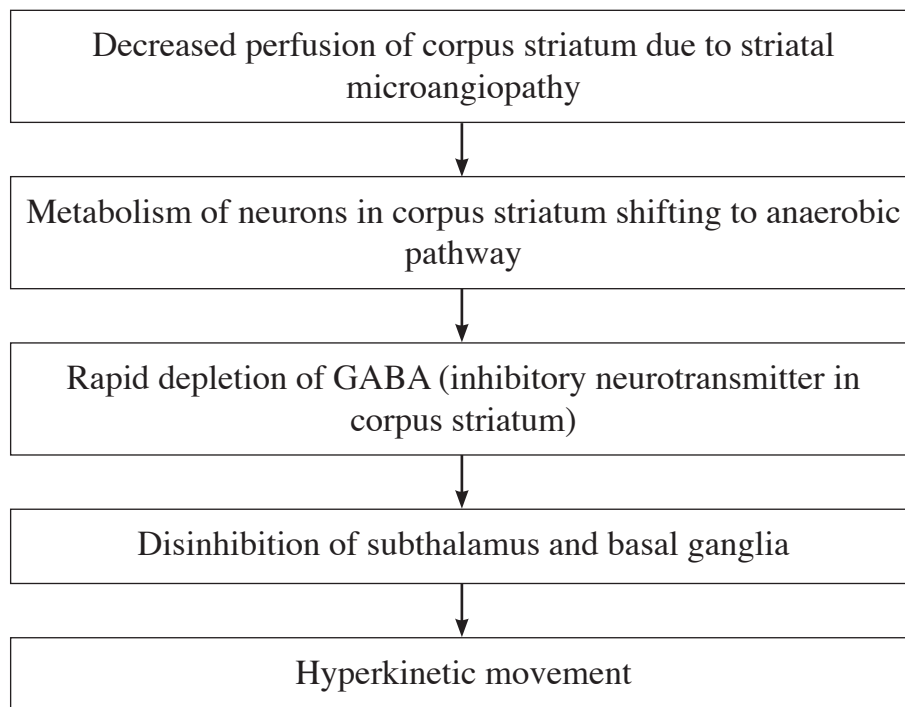
**Figure 1 A-C** Non-contrast CT scan at first presentation



**Figure 2 A-C** Non-contrast CT scan at presentation with choreoathetosis, 6 weeks from the first presentation



**Figure 3 A-C** Non-contrast CT scan at follow up period, 6 months after treatment



**Figure 4** Hypothesized mechanisms in pathogenesis of diabetic striatopathy<sup>1,2</sup>

**Table 1** Histopathology of corpus striatum in diabetic patient with striatal abnormalities on CT scan<sup>7</sup>

- Marked thickening media with hyaline changes of vessel wall
- Obliteration of arteriolar lumen
- Focal cell infiltration, red blood cell extravasation
- Lymphocyte infiltration and macrophage invasion
- Capillary proliferation and neovascular formation

## An Uncommon Presentation of Hypercalcemia in Chronic Lymphocytic Leukemia

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### Abstract:

Hypercalcemia is a common paraneoplastic syndrome in both solid and hematologic malignancies. There are three mechanisms involving in hypercalcemia. Firstly, the cancer increases the resorption of bone minerals resulting in releasing calcium and phosphate into plasma. Secondly, parathyroid hormone-related peptide (PTHrP) increases a reabsorption of calcium and excretion of phosphate at kidneys. Finally, calcitriol (1,25 dihydroxy vitamin D) induces vitamin D absorption in small bowel. Multiple myeloma or T-cell leukemia-lymphoma are usually presented with a symptomatic hypercalcemia. However, chronic lymphocytic leukemia (CLL) is uncommonly associated with hypercalcemia. Hypercalcemia occurring in CLL patients mostly indicates a relapsed or a refractory disease. In addition, it may imply an advanced stage as well as the transformation of disease to Richter's syndrome. This report presents an 81-year-old woman diagnosed with CLL, Rai stage III. She developed symptomatic hypercalcemia with an osteolytic lesion at left iliac wing together with an increased absolute lymphocyte count.

**Keywords:** Chronic lymphocytic leukemia, Hypercalcemia, Paraneoplastic syndrome, Osteolytic lesion

### Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in the western world and it frequently affects the elderly at a median age of 72 years.<sup>1</sup> The incidence of CLL is not known in the USA but accounting for 1.2% of all new cancer cases.<sup>2</sup> In Thailand, the incidence of CLL is around 1.5% of new cancer cases between 2007 and 2014. The median age of CLL patients in Thailand was around 60 years old.<sup>3</sup> CLL is a chronic disease and not all cases need chemotherapy. A combination of chemotherapy was administered in patients with an advanced stage, symptomatic, organomegaly, lymphadenopathy and progressive lymphocytosis in order to improve quality of life and

prolong survival.<sup>4,5</sup> Previously, a complete remission rate has been reported around 41% of managed cases and the 5-year overall survival was 52%.<sup>3</sup>

Prevalence of hypercalcemia in all malignancies is 0.67% and the most common cancers associating with this condition are lung cancers, multiple myeloma, and renal cell carcinoma.<sup>6</sup> Hypercalcemia in CLL is uncommon and was rarely reported. Usually, organomegaly, lymphadenopathy, anemia and constitutional symptoms are common clinical findings at presentation in Thai CLL patients.<sup>7</sup> CLL patients presenting with hypercalcemia has been reported in few literatures and was only 7 patients in 1,200 (0.58%).<sup>8</sup>

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The purpose of this report is to present a condition of symptomatic hypercalcemia in an 81-year-old woman who was diagnosed with advanced stage CLL.

### Case Presentation

An 81-year-old woman with medical history of hypertension, dyslipidemia and chronic kidney disease stage 3B. Her metabolic diseases were controlled with amlodipine, losartan and simvastatin. She was transferred to Saraburi hospital for an evaluation of slipping and falling. The x-ray of lumbosacral spine revealed no fracture but her complete blood count showed lymphocytosis. She noticed constipation and malaise for one week. She did not have any fever, night sweating, weight loss or backache.

The physical examination revealed anemia together with enlargement of multiple lymph nodes along both anterior cervical regions. Other body parts were unremarkable. The initial blood tests were WBC  $204.7 \times 10^9/L$ , PMN 15%, L 83%, M 1%, atypical L 1%, platelets  $226.0 \times 10^9/L$ , hemoglobin 8.6 g/dL, hematocrit 27.5%, MCV 94.5 fL, MCH 29.6 pg, MCHC 31.3 g/dL, and RDW 14.6%. The blood chemistry profiles showed BUN 38.7 mg/dL, creatinine 1.82 mg/dL, eGFR 25.67 mL/min/1.73 m<sup>2</sup>, corrected calcium 14.8 mg/dL, phosphate 4.2 mg/dL, and iPTH 5.12 pg/mL (15-88). Otherwise, normal liver function tests and serum electrolytes. Electrocardiogram showed normal QTc interval. Her blood smear showed numerous small-matured lymphocytes with non-cleaved nuclei and smudge cells (Figure 1).

Markers of peripheral blood flow cytometry were positive for CD19, CD5, CD23, but negative for FMC-7 and dim CD20. These markers were typically presented in CLL. Her bone marrow smear supported the diagnosis of CLL which showed hypercellularity, 85% infiltrated by small matured lymphocytes with non-cleaved nuclei, markedly decreased myeloid and erythroid series, and no abnormal large-sized mononuclear cell

(Figure 2). The majority of cells in the bone marrow biopsy were small mature lymphocytes with partially positive for CD20 and Bcl-2, strongly positive for CD5, focal positive for CD23, and negative for cyclin D1 and MPO (Figure 3). These results suggested that she had CLL infiltrating in the bone marrow, and therefore stage III (Binet C) CLL was diagnosed in this patient.

Because hypercalcemia presented in this patient and we were aware of a severe form called Richter's syndrome. Therefore, lymph node biopsy was done to identify this syndrome. Pathological profiles of cervical lymph nodes revealed diffuse infiltration by small lymphoid cell with proliferation center. No morphologic evidence of large cell transformation or plasmacytic differentiation were noted. The neoplastic cells marked focally positive for CD5, CD43, faintly positive for CD23, CD20, CD3, CD10, and negative for cyclin D1. There were occasional CD20 staining at medium to large-sized B-cells which also showed low Ki-67 (<10%) (Figure 4). CT chest and whole abdomen showed multiple para-aortic and mesenteric lymph nodes at size up to 1.8x1.5 cm. An ill-defined osteolytic lesion was detected at left iliac wing. Otherwise, liver and spleen are unremarkable (Figure 5). We concluded that she did not develop Richter's syndrome.

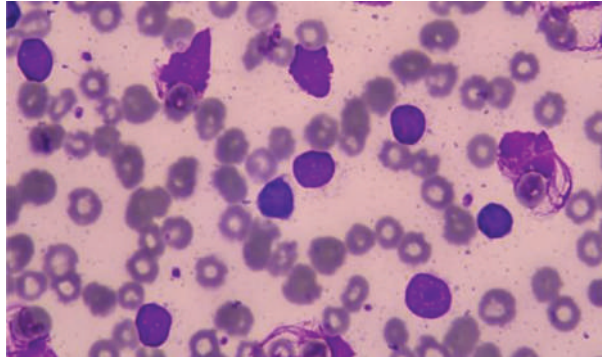
The final diagnosis was CLL Rai staging system III (Binet C) presenting with symptomatic hypercalcemia with osteolytic bone lesion.

### Management

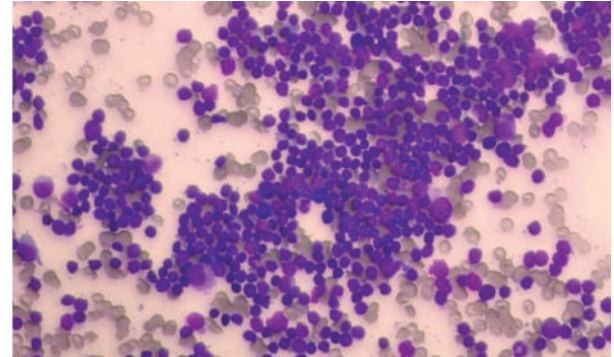
An aggressive normal saline resuscitation was given for treating hypercalcemia in this case. Intravenous zoledronic acid was contraindicated in this patient due to acute kidney injury with decreased creatinine clearance to 19 mL/min. The serum calcium level turned to normal range within 6 days. While she was waiting for flow cytometry reports, her renal function returned to baseline.

Consequently, chlorambucil and prednisolone were prescribed regarding to poor performance status (ECOG 3), aging, and limited financial condition. She was

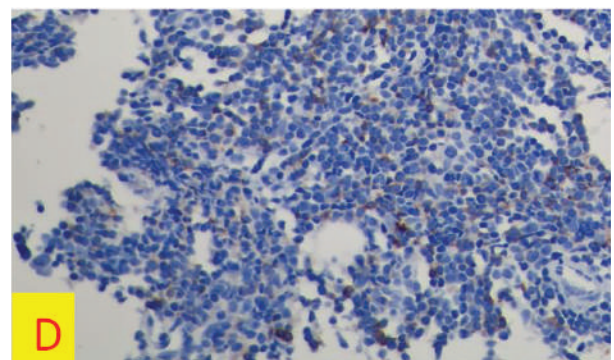
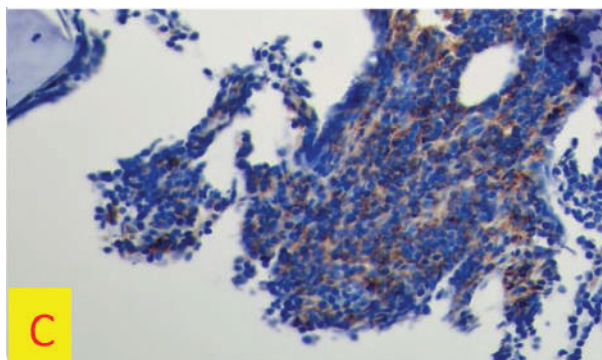
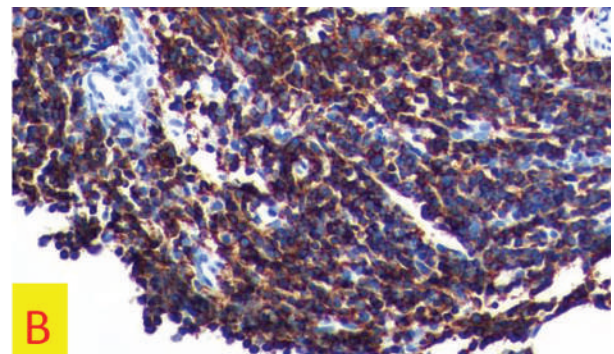
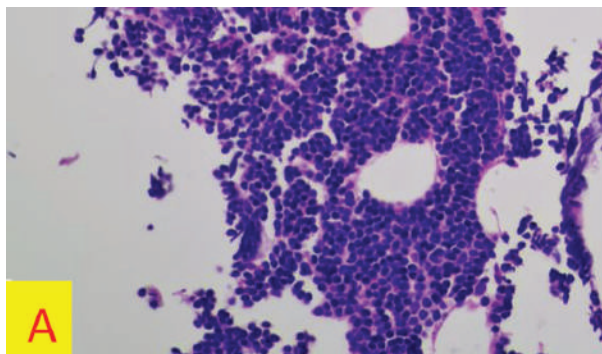
currently receiving second cycle of a monthly 5-day course of chlorambucil/prednisolone without serious adverse side effect.



**Figure 1** Blood smear showed numerous non-cleaved nucleus of small-matured lymphocyte. (x100)



**Figure 2** Bone marrow smear showed small matured lymphocytes with non-cleaved nuclei, markedly decreased myeloid and erythroid series, and no abnormal large-sized mononuclear cells. (x100)



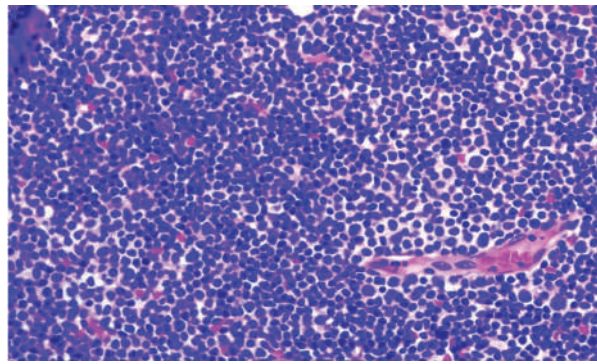
**Figure 3** Bone marrow core biopsy

A: H&E staining showed diffuse infiltration by small lymphoid cells. (x40)

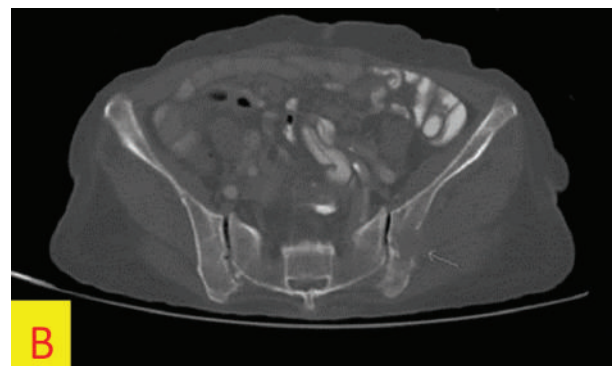
B: The malignant cells were partially stained CD20. (x40)

C: The malignant cells were positive CD5. (x40)

D: The malignant cells were focally positive CD23. (x40)



**Figure 4** Cervical lymph node biopsy showed diffuse infiltration by small lymphoid cells with proliferation center, no morphologic evidence of large cell transformation or plasmacytic differentiation. (x10)



**Figure 5** CT scan of whole abdomen

A: Multiple para-aortic and mesenteric nodes at mid abdomen

B: Ill-defined osteolytic lesion at left iliac wing

## Discussion

Hypercalcemia is a common paraneoplastic symptom in solid cancers and in some lymphoproliferative disorder such as myeloma or T-cell leukemia-lymphoma. However, it is rarely reported in B cell CLL.<sup>9</sup> Several mechanisms leading to malignancy-related hypercalcemia include:<sup>10-13</sup>

1. Osteolytic hypercalcemia activates osteoclasts by either a primary bony tumor or metastases. Cytokine relates to hypercalcemia such as tumor necrosis factor- $\beta$  (TNF- $\beta$ ), interleukin (IL)-1 $\beta$ , and IL-6.

2. Humoral hypercalcemia mediated by parathyroid hormone related peptide (PTHrP)

3. 1,25 dihydroxy vitamin D (calcitriol)

Osteolytic lesion is considered as a cause of hypercalcemia in this case as we found local osteolytic lesion at left iliac wing.

Furthermore, other causes of hypercalcemia were not detected including an excess of 25-OH vitamin D level and a suppression of iPTH from malignancy mimicking PTHrP. We could not directly measure circulating PTHrP, TNF- $\alpha$  and IL-6 levels because these tests are unavailable in Thailand. Hypercalcemia in CLL is a rare condition and only nine cases were previously reported in literatures.<sup>14</sup>

CLL and multiple myeloma (MM) are both monoclonal hematologic malignancies of differentiated B-cells which are associated with hypercalcemia. Simultaneous occurrence of both diseases are uncommon. Only 11 patients diagnosed with both CLL and MM had been reported in a study from J.C. Broutet and colleagues.<sup>15</sup> It is difficult to distinguish between these conditions as their clinical features are similar. In this case,

the differential diagnosis of concomitant MM was proposed. This patient had features identical to MM including elderly, symptomatic hypercalcemia and developed acute kidney injury on top of chronic kidney disease. Bone marrow study was done and showed negative results for MM (normal plasma cells).

Solid tumors associated with hypercalcemia were also excluded in this case. Although the data of CLL concomitant with other solid tumors is lacking. CLL increases risk of developing some solid cancers including skin, lung and breast cancer with the median interval time of 53 months.<sup>16</sup> Our physical examinations and radiologic investigations is currently unremarkable. However, long-term follow-up is needed.

Hypercalcemia has been known to be associated with relapsed/refractory CLL or a severe condition, called Richter's syndrome.<sup>12, 17-19</sup> One of these report from J. Beaudreuil et.al. found 11% (34/304) of low-grade lymphoma that later developed Richter's transformation and four of them had symptomatic hypercalcemia. Half of these cases were diagnosed with an advanced stage CLL (Rai 3 or 4).<sup>17</sup>

None of previous studies reported symptomatic hypercalcemia as an initial presentation of CLL. J Eaudreuil et.al. found two CLL patients who progressed to Richter's syndrome and presented with symptomatic hypercalcemia. TNF- $\alpha$  levels were high whereas serum calcitriol levels were low in both cases. One case was checked for PTH level and that was suppressed. IL-6 was high in one case. The authors suggested that the increasing in TNF- $\alpha$  and IL-6 levels may correlate with hypercalcemia in terms of bone resorption. These circulating cytokines may interact synergistically with PTHrP to increase bone resorption.<sup>17</sup>

Hypercalcemia may correlate with an increased white blood cell count, lymph node enlargement and organomegaly among CLL patients.<sup>20</sup> A report showed relapsed-CLL patients with progression of hypercalcemia without evidence of Richter's syndrome.<sup>9</sup> These evidences suggested that hyper-

calcemia in CLL patient may imply high tumor burden or may develop Richter's syndrome. However, hypercalcemia is not indicated for a poor prognosis.<sup>17</sup>

General treatments of hypercalcemia in CLL are similar to the treatment for other causes of hypercalcemia. The treatments comprise of parenteral hydration with saline to promote calcinuria, and the administration of calcitonin and bisphosphonate to suppress bone resorption. Although general treatments of hypercalcemia could normalize calcium levels in most CLL cases, some studies showed little response until start chemotherapy.<sup>18</sup> In this case, we controlled serum calcium to normal range with hydrations and diuretics. Chlorambucil and prednisolone regimen was administered subsequently to this patient as it was a suitable treatment in the context of poor performance status and poor socio-economic status. Serum calcium level remain normalized since the therapy was given.

## Conclusion

We report an interesting case of CLL who was initially presenting with symptomatic hypercalcemia, caused by osteolytic bone lesion. Hypercalcemia might indicate high tumor burden, relapsed disease or transformed into severe form (Richter's syndrome). Therefore, we recommended to closely monitor serum calcium levels during their indolent period.

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