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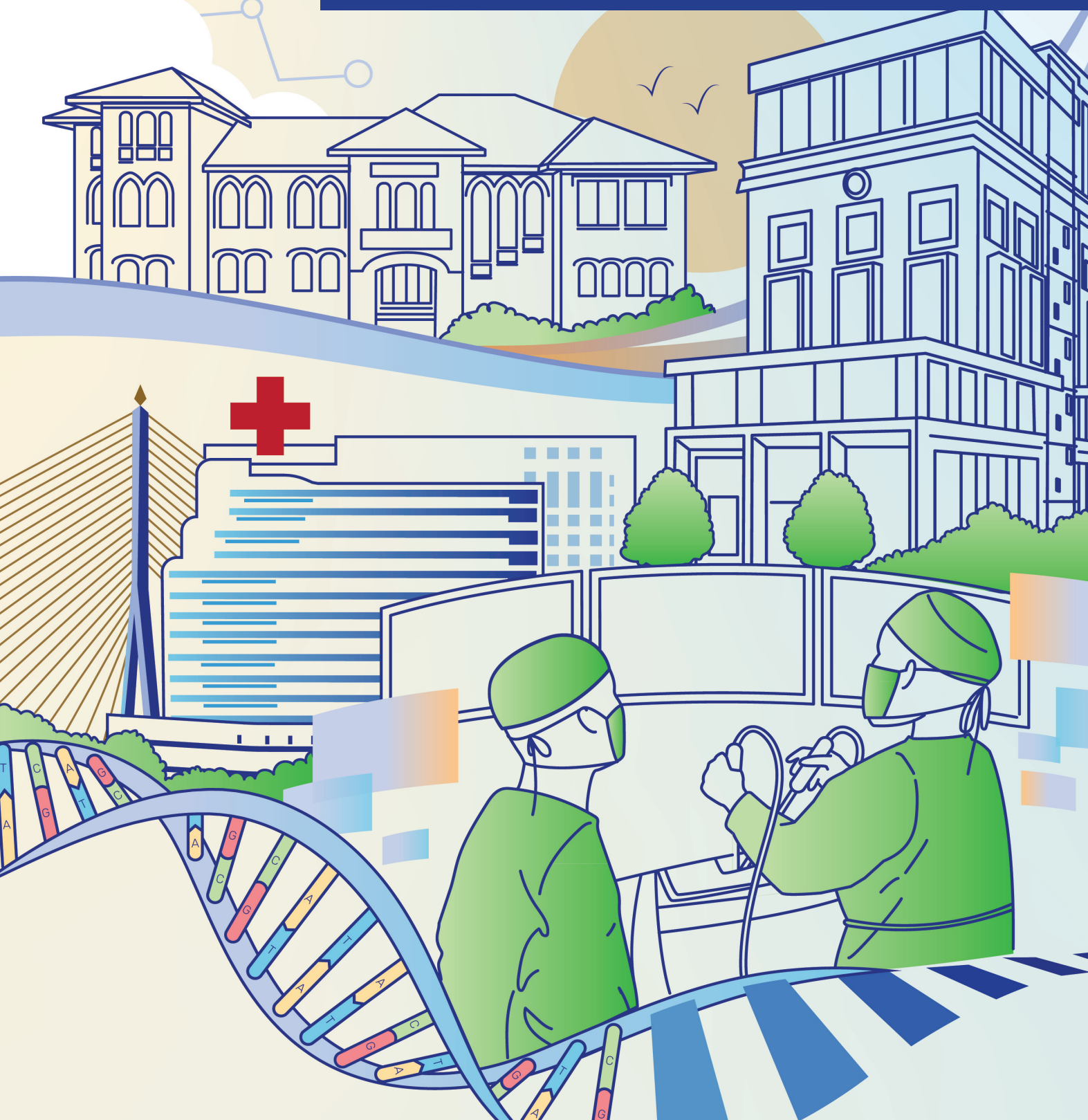

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ORIGINAL ARTICLES

Original Article

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Implementation Outcomes of Clinical Practice Guideline for Management of Acute Diarrhea in Children

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ABSTRACT

OBJECTIVE: To compare the length of stay and total charges for children with acute watery diarrhea admitted before and after the implementation of the 2021 clinical practice guideline for acute diarrhea in children.

METHODS: This was a descriptive study. We studied healthy children aged 1 month to 15 years with acute watery diarrhea who had been admitted for inpatient treatment at the Department of Pediatrics, Faculty of Medicine, Vajira Hospital. Independent sample t-test was used.

RESULTS: There were 51 patients in each group. Median age and IQR for the pre-implementation and post-implementation groups were 22 ± 39 and 27 ± 44 months, respectively (p = 0.403). Average length of stay in the post-implementation group was reduced by 5.9 hours with no statistical significance (63.18 hours vs 69.06 hours; p = 0.232). Average total charges after the CPG implementation were reduced significantly (7,752.31 THB vs 9,925.91 THB; p < 0.004) and average investigation costs were reduced (1,326.18 THB vs 2,397.98 THB; p < 0.001). There was no difference between the two groups in terms of post-admission complications and readmission proportion within 48 hours.

CONCLUSION: Using the 2021 clinical practice guideline for acute diarrhea was effectively helpful to reduce length of stay and total charges, with no difference in post-admission complications or readmission proportions.

KEYWORDS: acute diarrhea, antibiotics use, hospital charges, laboratory investigation, length of stay

INTRODUCTION

Acute diarrhea is defined as patient having loose or liquid stool 3 or more times within a 24-hour period, lasting 7 days or less[1]. A report by the US Centers for Disease Control and Prevention revealed 1.5 million pediatric out-patient visits and 220,000 admissions per year resulting from acute diarrhea[2]. In Europe, the incidence rate in children was 4-17%[3]. In 2018, the Department of Disease Control, Ministry of Public Health, Thailand[4] reported that the highest incidence rates were among children aged 0-4 years and 5-9 years (7,948.16 and 2,628.98 per 100,000 in the population, respectively).

Acute diarrhea is usually self-limited, and antimicrobial treatment is not necessary for disease recovery. Investigations to identify the etiologic agents and antibiotics are only required in some limited cases[1,5-6]. Inappropriate use of antibiotics in acute diarrhea results in drug-resistant

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bacteria. Besides, more prolonged carrier state and bacterial shedding via feces can be found in patients with *Salmonella* infections who have received inappropriate antimicrobial treatment[7]. For acute diarrhea resulting from Shiga-toxin producing *E. coli* or enterohemorrhagic *E. coli,* improper antibiotic prescription increases the risk of developing hemolytic uremic syndrome[8].

From previous studies, including several conducted in Thailand, it was found that the rates of unnecessary laboratory investigation and antimicrobial treatment were as high as 70%[9-12], resulting in longer lengths of stay and unnecessarily higher expenses. The most common unnecessary tests included stool culture, blood culture, stool viral antigen, and inflammatory markers such as C-reactive protein (CRP) and procalcitonin. In Italy Albano, et al. [13] conducted a randomized controlled trial in 2009 and showed that children who had received treatment based on the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines had significantly lower medical expenses and shorter durations of illness. In the US 2001-2006, Tieder, et al.[14] found that rational investigation and antimicrobial drug prescriptions for pediatric acute diarrhea, following the American Academy of Pediatrics-endorsed 2003 CDC recommendation, significantly reduced hospital expenses in the emergency departments and observation wards, while readmission proportion was not different between the groups.

At Vajira Hospital, the average length of stay among children with acute watery diarrhea in the 2017-2019 fiscal years was 3.43 days[15-17], which was much longer than that of other hospitals in Thailand in 2018-2019, which was only 2.3 days[16-17]. Similarly, a study by Tieder, et al. in the United States in 2009 found that the average length of stay was only 1.9 days[10] In addition, mean of hospital charges at Vajira Hospital was 9,695 Baht (THB) per case[15-17], although the reimbursement from National Health Security Office of Thailand was only 2,335 THB per case based on Diagnosis Related Groups (DRG)[17-18]. Excess unnecessary medical costs leaded to monetary problems and substantial budget losses.

As a result of the aforementioned, the Department of Pediatrics, Faculty of Medicine Vajira Hospital published the 2021 clinical practice guideline for acute diarrhea in children[19], adapted from the recommendations in Europe, the United States, and Thailand[1,5-6] to standardize treatment for children, in consideration of safety and reasonable price. This study was conducted to evaluate the effectiveness of the guideline by comparing the length of stay, medical expenses, complications, and readmission proportions between patients admitted before and after the implementation of the guideline.

METHODS

This was a descriptive study. We included children aged 1 month to 15 years who were diagnosed with acute diarrhea and admitted to Vajira Hospital before and after the implementation of the 2021 clinical practice guideline for acute diarrhea in children.

The exclusion criteria comprised patients with a history of gross bloody stools or visible bloody stool at admission, including cancer patients who received last chemotherapy session less than 3 months. The exclusion criteria included all patients with immunocompromised status namely patients with or using immunosuppressive agents or systemic corticosteroid, human immunodeficiency virus (HIV) infection, asplenia, inflammatory bowel disease, congestive heart failure, chronic kidney disease, chronic liver disease, current use of diuretics, suspected of sepsis at first presentation, regardless of gastrointestinal or extra-gastrointestinal cause, systemic infections (such as meningitis) requiring antibacterial treatment, surgical abdomen, COVID-19 infection, patients admitted after the implementation of the 2021 guideline with any poor adherence to the guideline.

The 2021 guideline-adherent practice was defined as rational submission of stool culture (indicated in infants aged less than 6 months,

suspected septicemia, alteration of consciousness, or shock, fever > 38 Celsius, mucous and/or bloody stool, severe abdominal pain or present abdominal tender point, patients with HIV, cancer, current use of immunosuppressive agents, inflammatory bowel disease, stool frequency more than 10 times/day, suspected infection from *Vibrio cholera*, diarrhea not improved within 7 days, or during the disease outbreak), blood culture (indicated in infants aged less than 6 months, suspected septicemia, alteration of consciousness, or shock, mucous bloody stool with high grade fever, patients with HIV, cancer, current use of immunosuppressive agents, inflammatory bowel disease), stool for viral antigen (only indicated during the disease outbreak), and inflammatory markers such as C-reactive protein and procalcitonin (indicated in septicemia, alteration of consciousness, or shock).

According to the guideline, empirical use of antibiotics is indicated for infants aged less than 3 months with mucous bloody diarrhea, or stool white blood cell (WBC) > 5 or stool red blood cell (RBC) > 10 cells/ high power field, or patients with fever > 38 Celsius and mucous bloody diarrhea, or stool WBC > 5 or stool RBC > 10 cells/ high power field, or patients with HIV, cancer, immunosuppressive agents, inflammatory bowel disease, suspected septicemia or severe clinical presentation, or compatible with other systemic infections, such as meningitis, surgical abdomen, or suspected infection due to *Vibrio cholerae* or *Shigella* spp. The criteria for discharge with safety were sufficient hydration status, or oral intake equals or exceeds losses, regardless of stool frequency, consistency, and complete cessation of diarrhea.

Post-admission complications were defined as septicemia and/or other systemic infections, such as to the central nervous system or bones and joints, of which the signs and symptoms do not manifest at admission, or readmission with severe diarrhea within 48 hours after discharge.

The study was conducted after receiving the approval from the Institutional Review Board of the Faculty of Medicine Vajira Hospital on May 6th, 2021 (COA 081/2564). This study was divided into 2 phases. The first pre-implementation phase was performed by the retrospective method. We recruited patients before the guideline implementation collecting the adequate number of calculated sample size (N =51). The post-implementation phase consisted of a retrospective part beginning on the day of guideline implementation to the day of protocol approval, and prospective part, starting on the day of protocol approval until a total of 51 eligible patients were recruited.

In the retrospective part, we collected and reviewed the medical records. Informed consent was applied to the patients and/or their parents in the prospective part. Data recording was computerized. All procedures were performed under confidentiality.

STATISTICAL ANALYSIS

We determined the sample size for comparing two independent means with the following equation:

$$n_1 = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 \left[\sigma_1^2 + \frac{\sigma_2^2}{r}\right]}{\Delta^2}$$
$$r = \frac{n_2}{n_1},\ \Delta = \mu_1 - \mu_2$$

where α (type I error) was 5%, ß (type II error) was 10%, μ_1 was the average length of stay in Vajira Hospital (3.43 days), μ_2 was the average length of stay in Thailand (2.3 days), and σ was 1.76 (standard deviation for length of stay among children with acute diarrhea admitted to Vajira Hospital during the 2017-2019 fiscal years). Ultimately, the sample size was 51 patients in each group.

Data were analysed using SPSS Version 28.0. Numerical data such as age, duration of diarrhea before admission, stool frequency, length of stay, and medical expenses were presented as mean with standard deviation, or median with interquartile range. These data were compared using the Mann–Whitney U test and independent samples t-test. Categorical data such as

sex, underlying diseases, gross stool appearance, and dehydration status were presented as frequency and percent. The Chi-square test or Fisher's exact test were used to compare these parameters. A p-value < 0.05 was considered statistically significant.

RESULTS

We eventually recruited eligible pre- and post-implementation groups, each of which consisted of 51 patients. The pre-implementation period was from February 4th, 2020 through January 24th, 2021, while the post-implementation period was from January 25th, 2021 through August 7th, 2022. Details about the inclusion and exclusion processes are shown in Figure 1.

Post-implementation participants were more predominantly male compared to the pre-implementation group with statistical significance (66.7% VS 47.1%, respectively). The post-implementation group had significantly more patients with mild dehydration than those of the pre-implementation group (62.7% VS 33.3%, respectively). We found no significant difference in age, underlying diseases, duration of diarrhea before admission, gross stool appearance, stool frequency, body temperature at admission or ward types between the two groups (table 1).

Pre-implementation and post-implementation participants who received guideline-adherent treatment were 2 out of 51 (3.9%) and 51 out of 51 participants (100%), respectively.

Investigation of the post-implementation participants showed significant decreases including in stool culture, blood culture, C-reactive protein and procalcitonin (table 2). When excluding pre-admission costs for COVID-19 screening during the pandemic in post-implementation participants, adherence to the guideline could significantly decrease the investigation cost with a mean decrease of 1,071.08 THB; and when adjusted with Thailand's medical care consumer price index[20] year 2020-2021, the adjusted mean decrease was 1,071.80 THB (p-value < 0.001).

Guideline-adherent practice could reduce the rate of empirical antibiotic use by 13.7%, despite having no statistical significance (p-value = 0.154), as shown in Table 2. The guideline insignificantly lowered total charges with a mean decrease of 304.78 THB (p-value = 0.693) and an adjusted mean decrease of 363.98 THB (p-value = 0.639). However, when excluding costs spent on COVID-19 preventive measures such as pre-admission COVID-19 screening, isolation ward, and personal protective equipment, adherence to the guideline could significantly cut down on total charges with a mean reduction of 2,114.39 THB (p-value < 0.004) and adjusted mean reduction of 2,173.59 THB (p-value < 0.004).

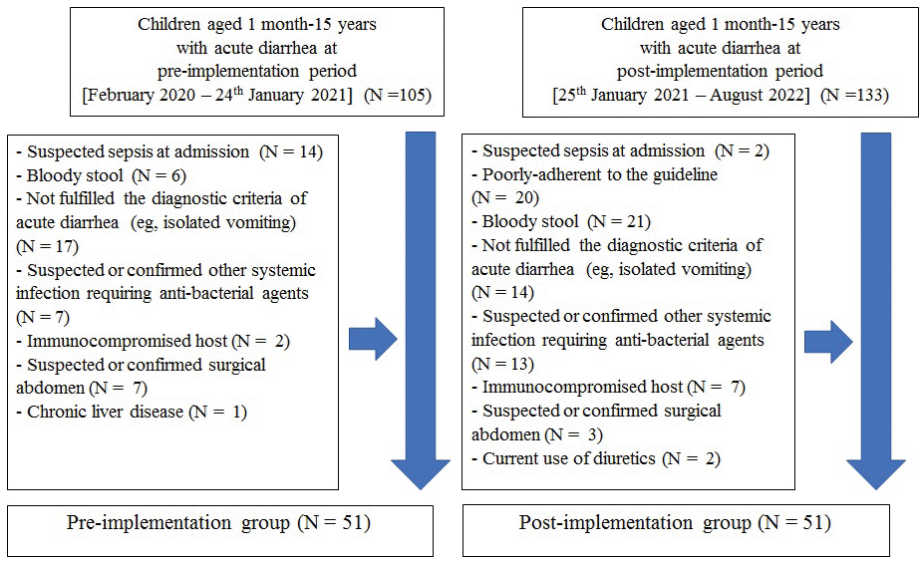

Figure 1 Inclusion and exclusion process

Table 1 Demographic data and baseline clinical characteristics of the participants

Factors	Pre-implementation group (N = 51)	Post-implementation group (N = 51)	P-value
Age (months)			
Median (IQR)	22 (12-51)	27 (14-57)	0.403
Sex			
Male, N (%)	24 (47.1)	34 (66.7)	0.046*
Underlying diseases			
Present, N (%)	7 (13.7)	13 (25.5)	0.135
Duration of diarrhea before admission (days)			
Median (IQR)	1 (1-2)	1 (1-2)	0.283
Gross stool appearance			
Watery, non-mucous stool, N (%)	39 (76.5)	37 (72.5)	0.650
Body temperature at admission			
Temperature > 38˚c, N (%)	30 (58.8)	32 (62.7)	0.685
Degree of dehydration, N (%)			
Mild dehydration	17 (33.3)	32 (62.7)	0.005*
Moderate dehydration	33 (64.7)	19 (37.3)	
Severe dehydration	1 (2)	0 (0)	
Ward type, N (%)			
General ward	32 (62.7)	40 (78.4)	0.082
Private ward	19 (37.3)	11 (21.6)	

Abbreviation: IQR, interquartile range; N, number

Table 2 Comparison of the laboratory investigation and empirical antibiotics use between two groups

Factors	Pre-implementation group (N = 51)	Post-implementation group (N = 51)	Difference of proportion (95% CI)	P-value
Stool culture (%)	42 (82.4)	28 (54.9)	-0.275 (-0.435, -0.094)	0.003*
Blood culture (%)	49 (96)	23 (45.1)	-0.51 (-0.638, -0.343)	< 0.001*
C-reactive protein and/ or procalcitonin (%)	15 (29.4)	6 (11.8)	-0.176 (-0.323, -0.016)	0.028*
Empirical antibiotics use (%)	23 (45.1)	16 (31.4)	-0.137 (-0.316, 0.052)	0.154

Abbreviation: CI, confident interval

In spite of having no statistical significance, the post-implementation group had a shorter average length of stay compared to that of the pre-implementation group with a mean reduction of 5.9 hours (p-value = 0.232). We found that none of the participants from either group developed post-admission complications, such as central nervous system infection, bone and joint infection or septicemia. Similarly, no participants were readmitted with more severe diarrhea within 48 hours after discharge (table 3). Rates of positive stool culture in the pre- and post-implementation groups were 9.5% and 17.8%, respectively. All the identified causative organisms in stool were *Salmonella* spp. None of the blood culture specimens from the two groups were found to have pathogenic bacteria.

Table 3 Comparison of investigation costs, hospital charges, length of stay, and complications between two groups

Factors	Pre-implementation group (N = 51)	Post-implementation group (N = 51)	Mean difference (95% CI)	P-value
Investigation costs, excluding pre-admission COVID-19 screening [THB, mean (SD)]	2,397.25 (1,434.44)	1,326.18 (764.34)	-1,071.08 (-1,522.63, -619.53)	< 0.001*
Adjusted investigation costs, excluding pre-admission COVID-19 screening [THB, mean (SD)]	2,397.98 (1,434.87)	1,326.18 (764.34)	-1,071.80 (-1,523.45, -620.15)	< 0.001*
Total charges [THB, mean (SD)]	9,866.71 (3,794.53)	9,561.92 (3,983.80)	-304.78 (-1,833.23, 1,223.66)	0.693
Adjusted total charges [THB, mean (SD)]	9,925.91 (3,817.29)	9,561.92 (3,983.80)	-363.98 (-1,896.80, 1,168.83)	0.639
Total charges, excluding costs for COVID-19 preventive measures [THB, mean (SD)]	9,866.71 (3,794.53)	7,752.31 (3,521.99)	-2,114.39 (-3,552.66, -676.12)	< 0.004*
Adjusted total charges, excluding costs for COVID-19 preventive measures [THB, mean (SD)]	9,925.91 (3,817.29)	7,752.31 (3,521.99)	-2,173.59 (-3,616.51, -730.68)	< 0.004*
Length of stay [hours, mean (SD)]	69.06 (26.04)	63.16 (23.42)	- 5.90 (-15.63, 3.83)	0.232
Post-admission complications (%)	0 (0)	0 (0)	N/A **	N/A **
Readmission with acute diarrhea within 48 hours (%)	0 (0)	0 (0)	N/A **	N/A **

Abbreviations: CI, confidence interval; N, number; SD, standard deviation THB, Thai Baht
** Calculated by difference of proportion

DISCUSSION

The post-CPG implementation group had a shorter length of stay by 5.9 hours compared to that of the pre-CPG implementation group, but without statistical significance. The 2021 clinical practice guideline for acute diarrhea in children by the Department of Pediatrics, Faculty of Medicine Vajira Hospital helped lessen unnecessary tests, such as for stool culture and blood culture, which previously prolonged the length of stay to wait for the results to become negative. The 2021 guideline, as well as the 2014 ESPGHAN guidelines, recommends the criteria for timely but safe discharge from hospital, such as when sufficient rehydration is achieved, and oral intake equals or exceeds losses, regardless of complete cessation of diarrhea. Meanwhile, the reason behind statistical insignificance could be the COVID-19 pandemic. The post-implementation period in this study occurred simultaneously with the delta and omicron variant era. During that chaotic period, all patients with signs and symptoms compatible with COVID-19, including fever, loose stool, and vomiting, would be sent to isolation wards to wait for pre-admission COVID-19 screening results, of which the running time lasted for 8-24 hours. When it became negative, a patient could be transferred to a general ward or private ward. These additional processes required in the post-implementation period could also potentially prolong the length of stay.

After the implementation of the guideline, when the expenses spent on COVID-19 preventive measures were excluded, adjusted total costs and investigation costs were reduced significantly, consistent with the study by Tieder, et al.[14] due to a decrease in unnecessary testing and use of antimicrobial drugs, especially injections which usually necessitate other medical equipment in the process.

Since the difference in degree of dehydration between two groups could be the potential

confounder to the results of our study, subgroup analysis was done on patients with mild dehydration in both phases. We found that any improvement in terms of length of stay, investigation costs and total charges in the post-implementation group were similar to findings in primary analysis.

Post-admission complications and readmission proportion between the two groups were not different, similar to the study by Tieder, et al.[14] The most common cause was virus, especially in immunocompetent children. Despite high mortality rates in young children without treatment, the clinical course was usually benign and self-limited with proper management. With thorough history-taking and physical examination to identify high-risk patients, it is safe to limit investigation and antibiotic use as necessary according to the guideline for otherwise healthy children with acute watery diarrhea.

A strength of our study was that there have been very few studies[13-14] demonstrating the association between guideline-adherent laboratory investigation and empirical antibiotics prescription in pediatric acute diarrhea and the length of stay and medical expenses. In addition, we analysed the adjusted hospital charges, using Thailand's consumer price index, published by the Ministry of Commerce, which made our findings more reliable and consistent with economic principles.

This study had some limitations. We gathered pre-CPG implementation group information in a retrospective manner using data collected from past medical records. Thus, some of the data may be incomplete or have information inaccuracies due to recording errors. The COVID-19 pandemic, during the post-implementation period, led to a substantial reduction in numbers of in-patients with acute diarrhea and could prolong the length of stay. Due to this barrier and the limited time frame for study, we could not perform random sampling to select the participants and decided to recruit the patients prospectively until a total of 51 patients were recruited.

CONCLUSION

In conclusion, the 2021 clinical practice guideline for acute diarrhea in children by the Department of Pediatrics, Faculty of Medicine Vajira Hospital helped reduce length of stay and hospital charges among previously healthy children with acute watery diarrhea, with no difference in post-admission complications or readmission proportions.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ACKNOWLEDGEMENT

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DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Original Article

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Risk Factors of Lymphangitis in Patients with Lymphedema at Vajira Hospital

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ABSTRACT

OBJECTIVE: Lymphangitis is a complication often found in lymphedema. It affects patient's quality of life, morbidity, cosmetic, and functional ability. Potential risk factors of lymphangitis were studied in lymphedema patients of Vajira Hospital.

METHODS: This study is a retrospective study. That is, data of lymphedema patients of Vajira Hospital from January 2007 to December 2018 were collected. Demographic data of patients' gender, age, underlying diseases, BMI, symptoms, site, onset, stages, causes, and types were analyzed to address risk factors using the SPSS program.

RESULTS: There were 140 patients participating, consisting of 12 males and 128 females, 78 of which had lymphangitis while the other 62 patients did not have lymphangitis. The average age of patients was 60.09±12.05 years and the average body mass index (BMI) was 28.73±7.81 kg/m^2. There were 75 patients having arm lymphedema and 65 patients having leg lymphedema. Additionally, 11 patients had primary lymphedema and 129 patients had secondary lymphedema. The most common complication of lymphedema was lymphangitis ($p < 0.001$). There was a higher chance for Campisi stages 3, 4 rather than Campisi stages 1, 2 ($p < 0.01$). The significant presence of wounds was a risk of infection ($p < 0.044$) in lymphedema patients. The average body weight of patients who had infection was estimated at 74.26 kg, which was higher than that of the non-infected patients, which was at 66.16 +/- 14.67 kg ($p = 0.037$).

CONCLUSION: It is suggested to treat lymphedema since the initial stage, before the symptom reaches its late stage, to reduce the chance of lymphangitis. Besides, patients should be advised to beware of wounds and immediately receive wound treatment to lessen the rate of lymphangitis. Moreover, patients with lymphedema and higher weight are of major concerns as they have more chance to get infected.

KEYWORDS: cellulitis, lymphangitis, lymphedema, risk factors

INTRODUCTION

Lymphedema, which is a result from the abnormality of lymphatic vessels, is divided into two categories: primary and secondary lymphedema. For primary lymphedema, it is considered a rare disease which is normally found in young children. It is supported by the prevalence rate of 1.2 cases per 100,000 persons among people aged lower than 20 years old[1]. For secondary lymphedema, it can be found in more than 90% of the whole lymphedema patients[2-3].

Lymphedema can be caused by various factors: infection, malignant tumor, radiation, and surgery. This disease has a huge effect on the

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patient's quality of life [4-5], cosmetic and functional ability. The patients who received gynecologic cancer and breast cancer treatment[6] have suffered from lymphedema. They also have more chances to get complications of lymphedema which are lymphangitis and lymphangiosarcoma[7].

Lymphangitis is a result of the infection of bacteria or bacteria toxin that spreads into skin and subcutaneous tissue in lymphedema patients. The main cause of skin infections is β-hemolytic streptococci which is found in 75-90% of cellulitis cases[8-13]. For the typical symptoms of lymphangitis, there are erythema, swelling, hot sensation, and tenderness at the affected site[14-15]. The severe conditions are tachycardia and hypotension. Lymphangitis is the frequent complication in lymphedema, which is found at around 40-50% in Asian patients with lymphedema[16]. The common risk factors for lymphangitis are overweight, damage to the cutaneous barrier, wound, venous insufficiency, and swelling of the lower extremity[17-18]. Former research points out that lymphedema is a risk factor of the occurrence of cellulitis in which a lymphoscintigraphy study has shown the abnormality of lymphatic supply on leg, which occurs around 50-77% in patients with cellulitis[19-20]. There is a systematic review and meta-analysis research that finds risk factors of getting cellulitis on leg. It is found that patients with previous cellulitis, wound, current leg ulcer, lymphedema, and body mass index of > 30 kg/m^2 [21], have a chance for recurrent infection of up to 57%, compared to patients with post cellulitis in lymphedema[22-23]. Therefore, the lymphatic system plays an important role in interstitial fluid balance and immunological function[24]. Each episode of cellulitis will destroy the lymphatic system, which can increase the risk of recurrent infection that leads to the possibility of lymphedema. For the diagnosis of lymphedema by performing lymphoscintigraphy, it is suggested to do with patients who have recurrent cellulitis [25-26]. This study presents risk factors of lymphangitis in patients with lymphedema at Vajira Hospital.

METHODS

Study Design

This research is a retrospective study. To illustrate, the studied data were derived from all patients with lymphedema who had received treatment in Vajira Hospital from January 1, 2007, to December 31, 2018. There were 150 subject patients, 10 of which were excluded due to uncompleted data. Thus, our subjects remained 140 patients and 78 patients had lymphangitis. In this regard, the study protocol had been approved by the Ethical Review Committee, Vajira Hospital, for research involving human subjects.

Data Collection

The data were categorized into patient characteristics (gender, age, body mass index), underlying diseases (diabetes mellitus, hypertension, cardiovascular disease), cancer stage, and characteristics of lymphedema (duration of lymphedema, Campisi clinical staging, primary lymphedema, secondary lymphedema, upper extremity lymphedema, lower extremity lymphedema). Inclusion criterias are; (1) patients aged 18 years and older; (2) patients who received diagnosis of lymphedema at arms and legs from two factors, congenital and complication from cancer surgery, in Vajira Hospital, from January 1, 2007, to December 31, 2018; (3) patients who received diagnosis of lymphangitis, had a history of admission with antibiotic use, had symptoms of redness, swelling, warm, and fever. Exclusion criterias are; (1) patients who had incomplete data recorded in Vajira Hospital; (2) death; (3) unreachable. This study was approved by research ethics committee; the COA number is 111/2561.

Statistical Analysis

The statistical analysis was done using the SPSS program for window version 22.0. The program was used for analyzing risk factors that increased the chance of lymphangitis in patients with lymphedema. Furthermore, it was also used for the multiple logistic regression analysis. The analytical results were presented using odds

ratio (OR), confident interval of 95%, and p-value (p-value < 0.05 refers to a significant value).

RESULTS

Based on 140 patients with lymphedema who received treatment in Vajira Hospital from January 1, 2007, to December 31, 2018, there were 78 patients who had lymphangitis.

According to the demographic data of **Table 1**, there were 12 males and 128 females patients with lymphedema. The average patients' age was 60.09±12.05 years. The average age of 78 patients who had lymphangitis was 60.13±12.15 years. For 62 non-infected patients, their age was 60.03±12.02 years. From all 140 patients, there were 11 patients who had primary lymphedema while the rest of 129 patients had secondary lymphedema. In case of BMI ≥ 30 kg/m^2, the infection group consisted of 30 patients, while the non-infection group was 15 patients (p = 0.075). The average weight of all patients was 70.70±23.79 kg. The average weight of the infection group was 74.26±28.6 kg while the non-infection group was 66.16±14.67 kg (p = 0.037).

Table 2 for patients with underlying diseases of diabetic mellitus, hypertension, coronary artery disease, chronic kidney disease, and dyslipidemia, there were 55 infected patients while 36 patients were not infected (p = 0.125).

In addition, **Table 3** reveals that the average period of lymphedema was 5 years. For the patients who had lymphedema for more than 5 years, there were 27 patients who had lymphangitis. The number of patients with lymphedema for less than 5 years who had lymphangitis were 37 patients (p = 0.267). We based our research on Campisi stage 2010[27] (**table 4**). **Table 5** portrays the number of patients with lymphangitis in stages 1 to 4. There were 3, 7, 38 and 30 patients, respectively. **Table 6** reflects when Campisi staging is used to compare between early stage (stages 1, 2) and late stage (stages 3, 4). It can be statistically accounted as p < 0.001 by late stage. It had an odd ratio of 19.39 when compared between the early stage and the late stage.

The major complication of lymphedema (**table 7**) that risked lymphangitis were wound, pain, heaving, limit of motion, doing activities, abnormal skin, and difficulties in wearing clothes. Among these, the significant symptom was the occurrence of wound (p = 0.044).

Table 1 Demographic data of lymphedema patients

Characteristic	Total (n = 140)	Lymphangitis	No lymphangitis	P-value*
Age (years)	60.09 +/- 12.05	60.13 +/- 12.15	60.03 +/- 12.02	0.963
Male	12	12	0	0.001
Female	128	66	62	
Primary lymphedema	11	6	5	0.377
Secondary lymphedema	129	72	57	
Height (cm)	155.89 +/- 7.53	156.49 +/- 8.57	155.14 +/- 5.95	0.288
BMI (kg/m^2)	28.73 +/- 7.81	29.77 +/- 9.07	27.45 +/- 5.73	0.097

Abbreviations: cm, centimeter; kg, kilogram; m, meter
* P-value < 0.5 = statistically significant

Table 2 Underlying diseases of lymphedema patients

Diagnosis	Total (n = 129)
Breast cancer	74
Cervical cancer	26
Endometrial cancer	11
Ovary cancer	8
Scar contracture	1
Bladder cancer	1
Inflammation (local dermatitis)	4
Chronic venous insufficiency	2
Obesity	2

Table 3 Duration of lymphedema

Years	Lymphangitis	No lymphangitis	OR	95% CI	P- value*
< = 5	37	34	1.00		
> 5	41	28	1.55	(0.72-3.36)	0.267

* P-value < 0.5 = statistically significant

Table 4 Campisi staging 2010

Campisi stage	Features
1A	No edema but presence of lymphatic impairment; no difference in volume/consistency of edema between limbs
1B	Mild edema that is reversible with appropriate limb position
2	Persistent edema that is partially reversible with appropriate limb position
3	Persistent edema that continually becomes more severe; recurrent acute lymphangitis
4	Fibrotic lymphoedema with lymphostatic warts, column-shaped limbs
5	Elephantiasis with severe limb deformation, scleroindurative pachydermatitis, widespread lymphostatic warts

Table 5 Number of lymphedema patients with lymphangitis in stages 1 to 4

Staging of lymphangitis	Number (78)
Stage 1	3
Stage 2	7
Stage 3	38
Stage 4	30

Table 6 Comparison of Campisi stages

Staging	Lymphangitis	No lymphangitis	OR	95% CI	P- value*
Stages 1,2	8	49	1.00		
Stages 3,4	70	13	19.39	(7.31-51.40)	< 0.001

* P-value < 0.5 = statistically significant

Table 7 Complication of lymphedema

Complication	Total 140 (%)	Lymphangitis		P-value*
		Infection 78 (%)	Non-infection 62 (%)	
Cellulitis/lymphangitis	78 (55.7)	77 (98.7)	1 (1.6)	< 0.001
Wound	18 (12.9)	14 (17.9)	4 (6.5)	0.044
Pain	38 (27.1)	22 (28.2)	16 (25.8)	0.751
Heaviness	67 (47.9)	40 (51.3)	27 (43.5)	0.363
Difficulties in living	27 (19.3)	17 (21.8)	10 (16.1)	0.399
Abnormal skin	26 (18.6)	12 (15.4)	14 (22.6)	0.277
Wearing clothes problem	22 (15.7)	15 (19.2)	7 (11.3)	0.200

* P-value < 0.5 = statistically significant

DISCUSSION

This research explored the risk factors of lymphangitis in patients with lymphedema. Our study found out that hypertension, diabetes mellitus, body mass index, treatment, and duration of the occurrence of lymphedema were not associated with the risks of lymphangitis.

The subject patients were 128 females and 12 males who had the infection. The result showed that all males with lymphedema had the infection (p = 0.001). However, there were more females with lymphedema due to breast

cancer surgery and oncological conditions. For male subjects, all of them had lymphedema from a groin node dissection procedure.

The ages with high incidence of cellulitis were 45-64 years[28]. In this research, the patients with lymphedema were aged approximately 60.09 +/-12.05 years.

According to J. Dobner's study conducted in Austria in 2018, with respect to body weight that affects the risk of infection in children and adults, both low weight and obesity heighten the risk of infection[29]. They state that there are other confounding factors namely malnutrition, hygienic status, and underlying diseases. However, our research found that obesity did not increase the risk of infection (p = 0.097). Yet, in comparison, the body weight of the infected patients, which is approximately 74.26±28.6 kg, is higher than the non-infection group, which is 66.16 +/- 14.67 kg (p = 0.037). Thus, patients with lymphangitis have more weight.

The study of Teerachisakul done in 2013 states that the duration of the occurrence of lymphedema of more than 5 years means the risk of lymphangitis[30]. Nevertheless, our research on 'nonsignificant duration' showed that the number of sample size was too low to address the significantly different value.

We found that the risk factor of highest odd ratio was Campisi stages 3,4 [OR 19.39]. According to research on leg edema, overweight and obesity are common predictive factors of cellulitis in the normal population[31-33]. For our study, we used a multiple logistic regression analysis to confirm the statistic result; high weight and Campisi staging had a significantly higher risk for infection, while lymphoscintigraphy, staging of cancer, treatment, and duration of the occurrence of lymphedema could not be concluded as a significant risk of infection due to the small number of subject patients. This can lead to further study in the future.

In this research, we observed the relation between cellulitis or lymphangitis and the underlying diseases namely hypertension, diabetes mellitus, coronary artery disease, chronic kidney disease, and dyslipidemia. We have found out that when comparing the lymphangitis group of patients who had underlying disease to the group without lymphangitis and did not have underlying disease, the value we got was not significantly different (p = 0.125) even though there was some former research finding the stated relation and mentioning that diabetes mellitus was associated with cellulitis[34-36]. According to our finding, there was a possibility of cellulitis in the patients with diabetes mellitus which delayed wound healing especially at the lower limbs, increasing the chance for getting skin and soft tissue infection. Yet, there is former research opposing the stated hypothesis. It claims that chronic lymphedema is the factor of delayed wound healing. Also, there is a study about hypertension, stating that it is not related to the occurrence of cellulitis, but the patients with lymphedema are hypothesized to be related to hypertension[37-38].We have noticed in our research that the condition of diabetes mellitus (p = 0.767) and hypertension (p = 0.171) had no relation to the risk of lymphangitis. From our study, cellulitis could be provoked by how the cutaneous barrier was disrupted, in which it could be a passage for germs to enter and colonize the area[39]. For the clinical aspect of cellulitis, it is mostly caused by local contamination of infection[40-41]. The treatment of risk factor for interdigital maceration, fungal nail infection, skin ulceration, and dry skin are really essential to prevent recurrent infections[42-43]. Skin care can prevent wounds. As accumulation of dermal and subdermal fluid and disruption of lymphatic channels are risks of the infection. The remedy of lymphedema is vital in blocking the occurrence of recurrent infections.

This study has potential limitations. Some of the data collection are based on retrospective medical records. Therefore, there cloud be data errors.

CONCLUSION

The goal of lymphedema's treatment is to prevent or lower the progression of the disease. Our research shows that there is the need to immediately cure the symptoms since the initial stage to forbid the disease to reach its end stage and to lower the infection.

CONFLICT OF INTEREST

None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this article.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to patients' privacy.

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Original Article

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Factors Affecting Dental Health Behaviors in Patients Using Removable Partial Dentures

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ABSTRACT

OBJECTIVE: To study the dental health behaviors and factors affecting the dental health behaviors of patients using removable partial dentures (RPDs).

METHODS: A cross-sectional descriptive study was conducted with 650 patients that wore RPDs and visited the dental department at Vajira Hospital, Thailand from July 2021 to October 2022. Data were collected using a structural questionnaire which consisted of four parts: demographic information, health status, dental health, and dental health behaviors. Data were analyzed using descriptive statistics and multiple logistic regression analysis at a significance level of 0.05.

RESULTS: Most of the patients brushed their teeth twice a day (72.2%) and used dental care tools (67.5%) such as mouthwash, dental floss, and proxabrush. Regarding denture care, most of the patients cleaned their dentures twice a day (51.2%), brushed with toothpaste (69.4%), and soaked their dentures in water at night (80.5%). Half of the patients visited dentists only when they had dental problems (52.5%). No statistically significant difference between the study variables and the frequency of brushing teeth or the methods of cleaning dentures was found. The application of dental care tools was significantly related to gender and the number of remaining teeth ($p < 0.001$). Further, the frequency of denture brushing was significantly associated with gender and educational level. The behavior of storing dentures appropriately at night was significantly associated with marital status, occupation, the position of dentures ($p < 0.001$), and their experience with wearing dentures. Additionally, the frequency of dental visits differed significantly depending on educational level, income per month, health insurance, the frequency of medical visits, the number of systemic diseases, and the number of remaining teeth.

CONCLUSION: Most of the patients wearing RPDs that attended Vajira Hospital did not follow dental care guidelines and irregularly visited the dentist. The demographic information, health status, and dental health had a correlation with dental health behaviors.

KEYWORDS: dental health behavior, dental health care, removable partial denture

INTRODUCTION

According to the 8th National Oral Health Survey of Thailand, tooth loss was the most common oral health problem among adults and seniors[1]. The average tooth loss for adults of ages ranging from 35 to 44 years was 3.6 teeth per person. The older persons aged 60-74 and 80-85 years had averagely 18.6 and 10 remaining teeth, respectively. This small number of remaining teeth affected masticatory efficiency. Therefore, dentures were frequently used to improve occlusion, pronunciation, and appearance, which also affected the physical and mental health as well as the quality of life of the edentulous persons[2-3]. According to the national oral health survey, only 5.2% of adults wore dentures, but 72.3% needed to wear removable partial dentures (RPDs).

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Most partially edentate patients prefer receiving RPD treatment because it is simple and more cost-effective than with fixed dental prosthesis. However, the post-insertion problems with RPDs are discomfort, denture pain, food impaction under the denture base, dental caries, and periodontitis[4-5]. Since RPDs require clasps that attach to the abutments in order to keep dentures stable when chewing, the area under the clasp and the rough acrylic surface of the dentures become areas for plaque accumulation, resulting in dental caries and periodontitis[6]. Previous studies have found that wearing RPDs resulted in increased risk of dental caries[5,7], and also gingivitis and periodontitis, particularly on the abutment teeth[8]. Therefore, in order to prevent dental problems, such as dental caries and tooth loss, denture wearers should have proper dental health behaviors and regularly dental check-ups[9-10].

Proper dental health behaviors and denture care practices are crucial and are key factors for good dental health in order to prevent tooth loss[11]. The suggested practices for good dental health and denture care are brushing teeth and dentures after every meal, brushing dentures with soap or denture cleaning solution, always removing dentures at night, and storing dentures in a container with water. However, many studies have found that denture wearers did not follow these practices[12-14]. In addition, a regular dental check-up every six months or at least annually is important for detecting early dental problems and for preventing severe dental diseases. Previous studies have analyzed the factors influencing patients' dental visits, such as sex[15-17], age[15-16], number of remaining teeth[15], and systemic disease[18]. However, a lack of studies regarding dental health behaviors has been conducted on denture wearers in Thai population.

Therefore, the objectives of this study were to examine the dental health behaviors and to evaluate the association between the factors and the dental health behaviors among patients wearing RPDs that received dental service in the dental department at Vajira Hospital, Bangkok, Thailand. The hypothesis was that several factors, including demographic information, health status, and dental health, affected the dental health behaviors.

METHODS

This cross-sectional descriptive study was conducted among patients wearing RPDs that visited the dental department at Vajira Hospital in Thailand from July 2021 to October 2022. Before conducting the study, the research was approved by the Ethical Committee of Navamindradhiraj University (COA 093/2564). The sample size was calculated using the following formula[19]:

$$n_1 = \left[\frac{z_{1-\frac{\alpha}{2}} \sqrt{\bar{p}\bar{q}\left(1+\frac{1}{r}\right)} + z_{1-\beta} \sqrt{p_1 q_1 + \frac{p_2 q_2}{r}}}{\Delta} \right]$$

$$r = \frac{n_2}{n_1}, q_1 = 1 - p_1, q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + p_2 r}{1+r}, \bar{q} = 1 - \bar{p}$$

In this formula, the symbol "n_1" represented the sample size for group 1. The symbol "p_1" and "p_2" were the proportion of outcomes occurring in group 1 and group 2, respectively. The symbol "r" was the ratio between the sample size in group 2 and group 1. The data from the study of Szalewski et al.[20] were represented in the formula. The significance level and the power level were set at 5% and 80%, respectively. According to this formula, the result of the sample size was 613 persons and consisted of at least 196 and 417 men and women, respectively. The dropout rate was set at 5%, so the total sample size was 650 persons. The patients that met the inclusion criteria and that did not meet any exclusion criteria were included in the study. The inclusion criteria were as follows: a patient aged over 18 years that is wearing RPDs or is wearing a RPD with an upper or lower full denture and that is receiving dental services in the dental department at Vajira Hospital; and a patient that has full consciousness, can communicate well in the Thai language, that has no hearing problems, and a patient that consents to and cooperates in answering the questionnaire. The exclusion criteria were as follows: a patient that has no remaining teeth; a patient that is wearing an immediate RPD; and a patient that has dementia and cannot cooperate in answering the questionnaire.

Before participating in the study, the patients were informed about the objectives of the study and were asked for consent. The questionnaire used in the study was designed and developed by reviewing many previous studies[12,15,20]. The questionnaire consists of four parts: demographic information (gender, age, marital status, address, educational level, occupation, and monthly income); health status (health insurance, frequency of medical visits, number of systemic diseases, physical capability, smoking, and drinking); dental health (number of remaining teeth, position of dentures, experience with wearing dentures, and having denture problems); and dental health behaviors (frequency of brushing teeth, using dental care tools, frequency of cleaning dentures, method of cleaning dentures, storing dentures at night, and frequency of dental visits). The content validity of each question in the questionnaire was evaluated by three specialists using the index of item objective congruence (IOC) developed by Rovinelli and Hambleton[21]. The IOC for each question was in the range between 0.67 and 1.00.

Data analysis was carried out using descriptive statistics and multiple logistic regression analysis. Descriptive statistics were used to analyze the frequency and percentages of the categorical data, and multiple logistic regression analysis was performed in order to analyze the factors associated with dental health behaviors. For the multiple logistic regression analysis, each dental health behavior was classified into binary outcomes by using Vajira's denture care guidelines (table 1). The cut-off point for the frequency of brushing teeth and dentures in this study was three times per day because we assumed that everyone had three meals a day. The significant factors ($p < 0.20$) in the univariate analysis were subjected to multivariate analysis in order to determine the independent predictive factors. The data were analyzed using IBM SPSS Statistics for Windows, Version 28.0 (IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY, USA: IBM Corp.). The statistical significance was set at 0.05.

RESULTS

A total of 650 patients, consisting of 196 males and 454 females aged 21 to 98 years, participated in this study. The majority of the patients belonged to the age group of 60 to 80 years. Most were married, lived in Bangkok, had a bachelor's degree, were unemployed or retired, and had an income lower than 10,000 baht/month. Most of the patients had government or state enterprise officers' medical benefits, visited physicians at least once a year, and had one systemic disease. Moreover, they were independent, non-smoking, and non-drinking. Most of the patients had 10 to 19 remaining teeth, wore upper and lower dentures, had been wearing dentures for more than 10 years, and did not have denture problems. The descriptive statistics on the demographic information, health status, and dental health are presented in Table 2.

Table 1 Classification of dental health behaviors by using Vajira's denture care guidelines

Dental health behaviors	Binary outcome	
	Following Vajira's guidelines	Not following Vajira's guidelines
Frequency of brushing teeth	3 times/day, more than 3 times/day	None 1 time/day 2 times/day
Using dental care tools	Yes	No
Frequency of brushing dentures	3 times/day, more than 3 times/day	1 time/day 2 times/day
Methods of cleaning dentures	Brushing with soap Using denture cleaning solution	Rinsing or brushing with water Brushing with toothpaste
Storing dentures at night	Storing dentures in water	Wearing dentures while sleeping Storing dentures in a dry container
Frequency of dental visits	Every 6 months Once a year	More than 1 year When having dental problems

Table 2 Demographic information, health status, and dental health

Variable type	Study variables	Factors	Frequency (%)
Demographic information	Gender	Male	196 (30.2)
		Female	454 (69.8)
	Age group	Less than 60 years old	158 (24.3)
		60-80 years old	421 (64.8)
		More than 80 years old	71 (10.9)
	Marital status	Married	343 (52.8)
		Never married	151 (23.2)
		Divorced/Widowed/Separated	156 (24.0)
	Address	Bangkok	492 (75.7)
		Suburb (e.g. Nonthaburi, Suphanburi)	158 (24.3)
	Educational level	Never attended school/Elementary school	142 (21.8)
		High school	130 (20.0)
		Diploma	72 (11.1)
		Bachelor's degree	232 (35.7)
		Postgraduate	74 (11.4)
	Occupation	Unemployment/Retirement	430 (66.2)
		Government employee	90 (13.8)
		Merchant/Personal business	77 (11.8)
		Other	53 (8.2)
	Income (per month)	Less than 10,000 baht	231 (35.5)
		10,000-19,999 baht	112 (17.2)
		20,000-29,999 baht	131 (20.2)
		30,000-39,999 baht	88 (13.5)
		40,000 baht or more	88 (13.5)
Health status	Health insurance	Government or state enterprise officers' medical benefits	384 (59.1)
		Universal health coverage	153 (23.5)
		Social security scheme	65 (10.0)
		None	48 (7.4)
	Frequency of medical visits	Having medical problem/more than 1 year	157 (24.2)
		At least once a year	493 (75.8)
	Number of systemic diseases	None	126 (19.4)
		1 disease	203 (31.2)
		2 diseases	161 (24.8)
		More than 2 diseases	160 (24.6)
	Physical capability	Independence	610 (93.8)
		dependence	40 (6.2)
	Smoking	No	625 (96.2)
		Yes	25 (3.8)
	Drinking	No	615 (94.6)
		Yes	35 (5.4)
Dental health	Number of remaining teeth	1-9 teeth	152 (23.4)
		10-19 teeth	262 (40.3)
		20 teeth or more	236 (36.3)
	Position of dentures	Upper	212 (32.6)
		Lower	123 (18.9)
		Upper and lower	315 (48.5)
	Experience with wearing dentures	1-5 years	194 (29.8)
		6-10 years	168 (25.8)
		More than 10 years	288 (44.3)
	Having denture problems	No	366 (56.3)
		Yes	284 (43.7)

Most of the patients brushed their teeth twice a day and used dental care tools such as mouthwash, dental floss, and proxabrush. Regarding denture care, the patients mostly brushed their dentures twice a day, brushed with toothpaste, and stored their dentures in water at night. Furthermore, they visited dentists only when having dental problems. The descriptive statistics on their dental health are presented in Table 3.

The results of the associations between the study variables and dental health behaviors using multiple logistic regression analysis are shown in Table 4. No statistically significant difference was found between the study variables and the frequency of the patients brushing their teeth or the methods of cleaning their dentures. The application of dental care tools was significantly higher among the females and the patients that had more than 20 teeth. The frequency of the patients cleaning their dentures three times or more per day was significantly associated with females and those that had attended high school. The association of inappropriate denture storage at night with the patients that were divorced, widowed or separated, merchants or those that had a personal business, the patients that wore only upper dentures, and the patients that wore dentures six years or more was statistically significant. Regular dental check-ups were significantly associated with a bachelor's degree, earning 20,000 baht per month or more, having no health insurance, visiting physicians at least once a year, and having 20 teeth or more. Furthermore, those having more than two systemic diseases significantly tended to visit the dentist more than one year or when having medical problems more than those having no systemic disease. A summary of the associations between the study variables and dental health behaviors is shown in Table 5.

Table 3 Dental health behaviors

Behaviors	Factors	Frequency (%)
Frequency of brushing teeth	None	1 (0.2)
	1 time/day	20 (3.1)
	2 times/day	469 (72.2)
	3 times/day	133 (20.5)
	More than 3 times/day	27 (4.2)
Using dental care tools	No	211 (32.5)
	Yes	439 (67.5)
	Mouthwash	249 (38.3)
	Dental floss	237 (36.5)
	Proxabrush	140 (21.5)
	Other	6 (0.9)
Frequency of brushing dentures	1 time/day	100 (15.4)
	2 times/day	333 (51.2)
	3 times/day	148 (22.8)
	More than 3 times/day	69 (10.6)
Methods of cleaning dentures	Rinsing with water	33 (5.1)
	Brushing with water	73 (11.2)
	Brushing with toothpaste	451 (69.4)
	Brushing with soap	39 (6.0)
	Using denture cleaning solution	131 (20.2)
	Other	3 (0.5)
Storing dentures at night	Wearing dentures while sleeping	81 (12.5)
	Storing dentures in a dry container	46 (7.1)
	Storing dentures in water	523 (80.5)
Frequency of dental visits	Every 6 months	140 (21.5)
	Once a year	125 (19.2)
	More than 1 year	44 (6.8)
	When having dental problems	341 (52.5)

Table 4 Showing the associations between the study variables and dental health behaviors

Study variables	Using dental care tools			Frequency of brushing dentures			Storing dentures at night			Frequency of dental visits		
	Crude OR	Adjusted OR (95%CI)	P-value	Crude OR	Adjusted OR (95%CI)	P-value	Crude OR	Adjusted OR (95%CI)	P-value	Crude OR	Adjusted OR (95%CI)	P-value
Gender												
Male	1.00	1.00 (Reference)		1.00	1.00 (Reference)		1.00			1.00		
Female	1.70	1.73 (1.13-2.66)	0.013	1.53	1.50 (1.01-2.22)	0.042	1.29			0.97		
Age group												
Less than 60 years old	1.00	1.00 (Reference)		1.00			1.00	1.00 (Reference)		1.00	1.00 (Reference)	
60-80 years old	1.07	1.25 (0.71-2.21)	0.435	1.00			1.39	0.78 (0.42-1.45)	0.433	0.81	0.84 (0.48-1.48)	0.554
More than 80 years old	0.50	0.93 (0.42-2.07)	0.854	0.70			1.73	0.96 (0.38-2.39)	0.923	0.33	0.57 (0.24-1.36)	0.202
Marital status												
Married	1.00	1.00 (Reference)		1.00			1.00	1.00 (Reference)		1.00	1.00 (Reference)	
Never married	1.07	0.86 (0.53-1.39)	0.538	1.27			0.87	0.80 (0.48-1.33)	0.379	1.12	1.06 (0.67-1.68)	0.796
Divorced/Widowed/ Separated	0.75	0.87 (0.54-1.37)	0.538	1.07			0.72	0.52 (0.32-0.87)	0.012	0.61	0.95 (0.59-1.52)	0.824
Address												
Bangkok	1.00			1.00			1.00			1.00		
Suburb	1.28			0.83			1.17			0.99		
Educational level												
Never attended school/ Elementary school	1.00	1.00 (Reference)		1.00	1.00 (Reference)		1.00			1.00	1.00 (Reference)	
High school	1.31	1.04 (0.61-1.77)	0.901	1.66	1.76 (1.01-3.05)	0.045	0.90			1.80	1.31 (0.70-2.42)	0.398
Diploma	2.96	1.95 (0.94-4.05)	0.072	1.09	1.03 (0.51-2.07)	0.937	1.36			2.20	1.24 (0.60-2.59)	0.563
Bachelor's degree	2.17	1.26 (0.71-2.25)	0.426	1.52	1.36 (0.76-2.43)	0.302	1.08			4.71	2.21 (1.19-4.10)	0.012
Postgraduate	3.62	1.97 (0.87-4.47)	0.105	2.05	1.75 (0.84-3.64)	0.136	0.82			5.11	2.09 (0.95-4.59)	0.066
Occupation												
Unemployment/ Retirement	1.00	1.00 (Reference)		1.00			1.00	1.00 (Reference)		1.00	1.00 (Reference)	
Government employee	1.29	1.03 (0.48-2.19)	0.947	0.88			0.56	0.51 (0.25-1.06)	0.071	1.81	0.98 (0.48-1.99)	0.948
Merchant/ Personal business	0.82	0.92 (0.50-1.67)	0.777	1.05			0.55	0.41 (0.22-0.78)	0.007	0.69	0.63 (0.34-1.17)	0.141
Other	0.66	0.86 (0.43-1.72)	0.660	0.84			1.00	0.90 (0.39-2.08)	0.806	0.99	0.99 (0.48-2.02)	0.974
Income (per month)												
Less than 10,000 baht	1.00	1.00 (Reference)		1.00	1.00 (Reference)		1.00			1.00	1.00 (Reference)	
10,000-19,999 baht	1.56	1.38 (0.81-2.37)	0.236	1.09	1.09 (0.64-1.84)	0.753	0.89			1.27	0.94 (0.53-1.68)	0.832
20,000-29,999 baht	2.02	1.66 (0.94-2.93)	0.083	1.39	1.35 (0.79-2.32)	0.276	1.20			2.92	2.03 (1.15-3.57)	0.014
30,000-39,999 baht	2.51	1.53 (0.74-3.15)	0.250	1.74	1.48 (0.78-2.82)	0.229	0.78			3.67	2.10 (1.05-4.21)	0.036
40,000 baht or more	2.21	1.39 (0.66-2.93)	0.384	1.18	1.07 (0.55-2.10)	0.845	0.78			4.03	2.16 (1.05-4.45)	0.036
Health insurance												
Government or state enterprise officers' medical benefits	1.00	1.00 (Reference)		1.00	1.00 (Reference)		1.00			1.00	1.00 (Reference)	
Universal health coverage	0.54	0.82 (0.49-1.35)	0.425	0.80	0.97 (0.60-1.56)	0.896	0.85			0.39	0.94 (0.54-1.64)	0.830
Social security scheme	0.63	0.70 (0.37-1.34)	0.279	0.59	0.61 (0.32-1.17)	0.139	1.29			0.83	1.09 (0.57-2.12)	0.790
None	1.19	1.53 (0.71-3.29)	0.278	0.99	1.18 (0.61-2.31)	0.623	0.79			1.08	2.52 (1.20-5.26)	0.014

Table 4 Showing the associations between the study variables and dental health behaviors (continued)

Study variables	Using dental care tools			Frequency of brushing dentures			Storing dentures at night			Frequency of dental visits		
	Crude OR	Adjusted OR (95%CI)	P-value	Crude OR	Adjusted OR (95%CI)	P-value	Crude OR	Adjusted OR (95%CI)	P-value	Crude OR	Adjusted OR (95%CI)	P-value
Frequency of medical visits												
Having medical problem/ more than 1 year	1.00			1.00			1.00			1.00	1.00 (Reference)	
At least once a year	1.08			0.73			1.25			2.92	4.88 (2.93-8.13)	< 0.001
Number of systemic diseases												
None	1.00			1.00	1.00 (Reference)		1.00	1.00 (Reference)		1.00	1.00 (Reference)	
1 disease	1.04			0.58	0.65 (0.40-1.07)	0.092	1.29	1.19 (0.68-2.08)	0.543	1.02	0.70 (0.40-1.21)	0.199
2 diseases	0.94			0.68	0.77 (0.45-1.33)	0.353	1.78	1.81 (0.96-3.43)	0.068	0.89	0.63 (0.34-1.15)	0.131
More than 2 diseases	0.77			0.64	0.77 (0.44-1.33)	0.344	1.41	1.32 (0.71-2.46)	0.387	0.59	0.42 (0.22-0.79)	0.007
Physical capability												
Independence	1.00	1.00 (Reference)		1.00			1.00			1.00	1.00 (Reference)	
dependence	0.37	0.58 (0.27-1.24)	0.162	0.65			0.97			0.15	0.37 (0.11-1.17)	0.090
Smoking												
No	1.00			1.00			1.00			1.00	1.00 (Reference)	
Yes	0.60			0.62			0.76			0.55	0.43 (0.16-1.14)	0.090
Drinking												
No	1.00	1.00 (Reference)		1.00			1.00			1.00		
Yes	0.49	0.55 (0.26-1.16)	0.117	1.04			1.49			0.75		
Number of remaining teeth												
1-9 teeth	1.00	1.00 (Reference)		1.00	1.00 (Reference)		1.00			1.00	1.00 (Reference)	
10-19 teeth	2.03	1.66 (1.06-2.58)	0.027	1.35	1.23 (0.78-1.95)	0.371	1.00			1.49	1.20 (0.73-1.98)	0.474
20 teeth or more	3.53	2.38 (1.42-3.98)	< 0.001	1.38	1.13 (0.70-1.85)	0.616	0.92			3.38	1.97 (1.16-3.35)	0.012
Position of dentures												
Upper	1.00	1.00 (Reference)		1.00			1.00	1.00 (Reference)		1.00	1.00 (Reference)	
Lower	1.64	1.47 (0.85-2.55)	0.171	0.86			1.44	1.47 (0.85-2.55)	0.170	1.59	1.13 (0.67-1.92)	0.642
Upper and lower	0.85	0.98 (0.65-1.49)	0.933	0.85			2.51	2.67 (1.66-4.28)	< 0.001	0.84	1.01 (0.66-1.54)	0.970
Experience with wearing dentures												
1-5 years	1.00	1.00 (Reference)		1.00	1.00 (Reference)		1.00	1.00 (Reference)		1.00		
6-10 years	1.19	1.24 (0.76-2.02)	0.392	1.17	1.14 (0.71-1.82)	0.585	0.70	0.48 (0.27-0.85)	0.012	0.87		
More than 10 years	1.38	1.35 (0.87-2.10)	0.177	1.46	1.39 (0.92-2.10)	0.124	0.72	0.51 (0.30-0.86)	0.012	0.82		
Having denture problems												
No	1.00			1.00			1.00	1.00 (Reference)		1.00		
Yes	1.07			0.83			1.35	1.37 (0.91-2.08)	0.134	0.82		

Abbreviations: CI, confident interval; OR, Odds Ratio

Variable was included in the multivariable model due to having a p-value < 0.200 in the univariable analysis.

Table 5 The summary of the associations between dental health behaviors and study variables

Dental health behaviors	Study variables
Frequency of brushing teeth	-
Using dental care tools	Gender Number of remaining teeth
Frequency of brushing dentures	Gender Educational level
Methods of cleaning dentures	-
Storing dentures at night	Marital status Occupation Position of dentures Experience with wearing dentures
Frequency of dental visits	Educational level Income per month Health insurance Frequency of medical visits Number of systemic diseases Number of remaining teeth

DISCUSSION

Denture care guidelines vary among countries. In this study, each dental health behavior was classified into binary outcomes according to the denture care guidelines at Vajira Hospital. These guidelines suggest brushing teeth and cleaning dentures after each meal, using dental care tools, cleaning dentures with soap or denture cleaning solution, removing dentures at night and storing them in water, and visiting the dentist one to two times per year. The results of this study revealed that no study variables affected the frequency of brushing teeth or the methods of cleaning dentures, but statistically significant differences between the study variables and the other dental health behaviors were found. Therefore, the null hypothesis was rejected.

In a cross-sectional study, an adequate sample size is needed in order to estimate the population prevalence. We used the data from the study of Szalewski et al.[20] to estimate the sample size because we found that representing the formula with the proportion of males and females that did not visit the dentist yielded a maximum sample size. So, we used the gender factor in order to calculate the sample size in our study. Moreover, the ratio between males and females in previous study was 0.47, and this might be the reason that the number of females in this study was twice that of the males.

Most of the patients brushed their teeth two times a day. Only a quarter of the patients followed Vajira's guidelines. There was no statistically significant association between the study variables and the frequency of brushing teeth. This result differed from previous studies[16,22]. For example, Olusile et al.[16] found that age, gender, marital status, educational level, and occupation were significantly related to the frequency of brushing teeth. Moreover, Kim et al.[22] found that patients with higher income and educational level were more likely to brush their teeth more than three times per day.

Using dental care tools is recommended for denture wearers because wearing RPDs increases plaque formation and poses higher risks of dental diseases. Therefore, denture wearers should pay special attention to cleaning their teeth. In this study, the percentage of patients that used dental care tools was higher than in other previous studies. According to the 8th National Oral Health Survey of Thailand, about half of the elderly (60-74 years old) used dental care tools[1]. The dental care tools that were mostly used were toothpicks (28.6%) and mouthwash (20.3%). Only 6% of the elderly used dental floss or proxabrush. A study of adult Nigerians reported that only 10.5% of the participants used dental floss or other dental care tools[16]. Moreover, Cakan et al.[13] discovered that only 4.8% of RPD wearers in a university hospital

used dental floss. This study also found a significant relationship between using dental care tools and gender and the number of remaining teeth. This finding is similar to Wang et al.'s study[23], which indicated that using extra dental care tools such as dental floss and mouthwash was associated with having more remaining teeth. However, we did not find an association between using dental care tools and income or educational level, which is not in line with Kim et al.'s study results[22].

Half of the patients in the present study cleaned their dentures two times a day. According to the interviews with the patients, they usually cleaned their dentures while brushing their teeth. Nevertheless, Barreiro et al.[24] found that 74.9% of denture wearers cleaned their dentures three times or more a day, whereas Cakan et al.[13] and Saha et al.[25] found that more than half of the denture wearers cleaned their dentures only once a day. The association between the frequency of brushing dentures and gender was significantly found in this study. This confirmed the finding of previous studies[12,13,26]. Further, we discovered a relationship between the frequency of brushing dentures and educational level, but not with smoking. These findings were opposite those of Cakan et al.'s study[13].

Cleaning dentures with a denture cleaning solution, toothpaste, or soap is commonly recommended by dentists[27]. However, the available toothpaste in Thailand contains ingredients that could abrade and scratch the surface of dentures[28-29]. The surface roughness of dentures results in increasing biofilm accumulation, microbial colonization, and discomfort of wearers[29]. Therefore, Vajira's denture care guidelines recommend using a denture cleaning solution or soap to clean dentures instead of toothpaste. In this study, most of the patients used toothpaste to clean their dentures, which could imply that most of the patients did not have correct knowledge about how to clean their dentures. Furthermore, we found that three patients used dishwashing liquid to clean their dentures. From the study of Sudswad et al.[29], dishwashing liquid could be used to clean dentures in the same way as using soap; however, dishwashing liquid is not widely recommended by dentists[27]. The study of Shankar et al.[26] on complete denture wearers found a correlation between denture cleaning method and gender. However, no statistical significance was found between the study variables and the methods that the patients used to clean their dentures in our study.

About 80% of the patients followed the dental recommendation of storing their dentures in water at night. However, 12.5% of the patients wore their dentures while sleeping, and 7.1% of the patients kept their dentures in dry containers. The percentage of the patients wearing dentures overnight was lower than in previous studies[13-14,24]. In this study, appropriate denture storage at night differed significantly depending on marital status, occupation, the position of dentures, and the patient's experience with wearing dentures. There was no significant difference between appropriate denture storage at night and age or educational level, which is similar to Cakan et al.'s study[13]. On the other hand, Szalewski et al.[20] found that educational level statistically significantly affected the practice of wearing dentures overnight. Moreover, Cakan et al.[13] also found that the removal of dentures at night was significantly lower among the participants that used their second dentures or more. This is in accordance with our study's results that the patients that had worn dentures for more than five years tended to store them at night incorrectly. The esthetic concern, lacking knowledge, and individual experience could be a reason why the patients wore their dentures or kept them in dry containers at night; so, dentists should inform the patients about proper storage denture at night because wearing dentures at night increases the risk of fungal infection and denture stomatitis[30].

More than half of the patients visited dentists only when having dental problems. This finding was similar to that of previous studies[20,24,31].

For example, Barreiro et al.[24] revealed that most of the participants visited dentists only when there was a complaint, and Namrata et al.[31] and Szalewski et al.[20] found that only 10% and 3.7% of the patients went for regular check-ups. No significant difference between gender and the frequency of dental visits was found in this study or in other studies[16-17]. This result differed from Szalewski et al.'s study[20]. The result in the present study that income and educational level significantly affected the frequency of dental visits supported Kim et al.'s study[22]. Further, Olusile et al. [16] found that patients with a higher educational level reported significantly more utilization of dental health services. This study also confirmed the association between the frequency of visiting physicians and visiting dentists; the patients that visited physicians at least once a year were more likely to visit dentists regularly. Surprisingly, the patients without health insurance tended to have regular dental visits. This result was in contrast to the study of Lutfiyya et al.[15]. Moreover, the patients that had more than two systemic diseases tended to have fewer dental check-ups. Therefore, a system should be created for determining if individuals have many systemic diseases because they have higher risks for loss of follow-ups. The patients that had lost more teeth also had a significantly higher chance of visiting the dentist only when having dental problems. This might reflect patients' unawareness of their oral health care.

Many researches have studied dental health behaviors and the factors that affect dental health behaviors in patients using RPDs[12-13,20,24,31]. The results of the researches were heterogenous. This could be due to demographic differences and the varied denture care guidelines and dentists' recommendation among countries[27,32]. This study was conducted with patients wearing RPDs in only one dental hospital setting in Thailand, so the generalizability of the findings may be limited to partially edentulous people living in urban areas of Thailand. Furthermore, since the grouping of each dental health behavior was classified using dental guidelines in Thailand, the results of this study might differ from those of other countries where dental guidelines are different. In future studies, dental diseases such as dental caries, periodontitis, and oral candidiasis should be assessed in denture wearers. In addition, the association among dental diseases and dental health behaviors should be investigated.

CONCLUSION

Most of the patients wearing RPDs at Vajira Hospital did not follow the denture care guidelines and irregularly visited the dentist. Dentists should be reminded to advise and motivate patients to realize the importance of regular dental visits and of expected dental behaviors. Further, appointments for dental check-ups should be regularly scheduled. In addition, gender, educational level, marital status, occupation, income per month, health insurance, the frequency of medical visits, the number of systemic diseases, the number of remaining teeth, the position of dentures, and the experience of wearing dentures were key factors in the present study that were correlated with dental health behaviors. The results of this study provided useful information for dental health education and health care system to create optimal patient follow-up processes for patients wearing dentures in the future.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

All of the data generated and analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Original Article

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Clinical Characteristics and Outcomes of Non-Neutropenic Fever in Children with Cancer: An Urban-Single Institution Experience

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ABSTRACT

OBJECTIVE: To evaluate the clinical characteristics and outcomes of pediatric cancer with non-neutropenic fever (NNF) in pediatric cancer patients in the absence of a central venous catheter.

METHODS: This single-center retrospective cohort study enrolled pediatric patients with cancer (age < 18 years) who received chemotherapy treatment at the Department of Pediatrics, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand, from January 2016 to July 2020. Clinical characteristics and outcomes of NNF episodes were described. Descriptive statistics were analyzed.

RESULTS: Fifty-one patients were reviewed, but the 97 NNF episodes were documented from 32 patients. Only One (of the 51 patients) had subcutaneous port. The most frequent cancer diagnosis was acute lymphoblastic leukemia (51%). NNF occurred in 3.8 per 1,000 days of chemotherapy period (95% confidence interval [CI] 3.1–4.6). The most frequently clinically documented infections were respiratory tract infection (35%), urinary tract infection (11%), and gastrointestinal infection (10%). The causative pathogens could not be demonstrated in 67.1% of NNF episodes. The commonly identified pathogens were viruses (12.3%), gram-negative bacteria (10.3%), and gram-positive bacteria (5.2%). Empiric treatment with antibiotic was initiated in 92.8% of the total episodes. Ceftriaxone was the most common antibiotic of choice. Only one episode had a positive hemoculture. Four (4.1%) episodes required intensive care unit admissions, and only one NNF-related mortality due to the human Bocavirus pneumonia and multi-organ failure occurred. The mortality rate of NNF was 3.1%.

CONCLUSION: NNF episodes are common and life-threatening complications among pediatric cancer patients and generally lead to hospitalization. The incidence of NNF was 3.8 per 1,000 days of chemotherapy (95% CI 3.1–4.6). The causative pathogen in 67% of NNF episodes was unknown, and the commonly identified pathogens were viruses. However, many patients did not identify any causative bacteria, and they received intravenous antibiotics and were hospitalized. The results of our study suggest that patients with severe symptoms may indicate early evaluation and prompt management for viral infection, especially in a patient with a negative bacterial culture and poor respond to antibiotic treatment. This study reveals baseline information for future cohorts to provide guideline management of this common complication during cancer treatment.

KEYWORDS: cancer, chemotherapy, fever, non-neutropenic fever, pediatric

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INTRODUCTION

Over the past few decades, there has been progress in the treatment of pediatric patients with cancer, including chemotherapy regimens, radiation and hematopoietic stem cell transplantation, to improve the treatment outcomes and survival rates of childhood cancer[1-2]. However, these treatment options are associated with immunosuppression caused by multiple factors such as neutropenia, hypogammaglobulinemia, T-cell dysfunction, and mucosal barrier injury[3]. Infection is an important cause of treatment-related mortality in these patients[4]. Febrile illness in children with cancer is a common complication that requires urgent evaluation and management during treatment[5]. Several consensus clinical practice guidelines are established for the management and predictive factors of severe adverse events of fever with neutropenia (absolute neutrophil count [ANC] < 500 cells/mm^3)[6-7]. In 2017, the International Pediatric Fever and Neutropenia Guideline Panel, a group of experts in pediatric oncology and infectious diseases, formulated evidence-based recommendations and classified febrile neutropenia (FN) into groups with low and high risks for the develop of poor outcomes using multiple factors and suggest that the low-risk FN group may consider outpatient management, careful monitor and follow-up[8]. Regardless, cancer patients without neutropenia are also immunocompromised. One study[9] reported a significant greater incidence of bacteremia in pediatric patients with non-neutropenic fever (NNF) than in patients with FN (23.6% vs. 9.4%, respectively), particularly associated with the presence of central venous catheter exit site infection. However, there is no standard evidence-based recommendation guideline for the management approach in patients with fever with an ANC ≥ 500 cells/mm^3. Recently, a meta-analysis that evaluated fever episodes with ANC ≥ 500 cells/mm^3 in pediatric cancer patients revealed that the pooled-average bacteremia rate was 8.2% among total 4,106 NNF episodes, and the management of febrile non-neutropenic patients differed across studies[10]. The authors also addressed a relatively risk factors of bacteremia included type of central venous catheter, ill appearing patients, and higher body temperature. A recent study[11] on developing the possible risk prediction model for bloodstream infection in febrile pediatric cancer patients who had central venous catheters with ANC ≥ 500 cells/mm^3 suggested that the low-risk group may consider outpatient care without antibiotics. In contrast, the high-risk group may be hospitalized for broad-spectrum antibiotics. Studies on the incidence, outcome, and consensus management guidelines among pediatric patients with NNF are limited, especially in Thailand.

This study was designed to provide additional information on this patient population. This urban single-institution retrospective study aimed to analyze the incidence, clinical manifestations, management, and outcomes of pediatric cancer with NNF.

METHODS

Study population

All pediatric patients with cancer aged < 18 years who received chemotherapy treatment at an urban-tertiary hospital in Bangkok, Thailand, from January 1, 2016, to July 31, 2020, were eligible for inclusion. The study was approved by the Ethical Clearance Committee on Human Rights Related to Research to Research Involving Human Subjects, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Thailand (COA 180/2563).

NNF episode was defined as fever reported from home or body temperature recorded in the hospital at least 38°C for 1 hour or > 38.3°C once and ANC ≥ 500 cells/mm^3 [11].

Recurrent fever episodes during a 7-day period of treatment were counted as a single episode. Fever episodes in patients who received treatment or antibiotics for a previous documented infection or discontinued antibiotics for < 24 hours or ANC declined to < 500 cells/mm^3 within 24 hours were excluded from this study.

Data collection

The cohort included 51 consecutive pediatric patients with cancer who had been treated between study periods. All medical records were retrospectively reviewed to identify all NNF episodes encountered in both outpatient and inpatient settings. For eligible patients, demographic data, including age, sex, and cancer diagnosis, were collected. Treatment-related data regarding treatment protocol, catheter, or device type were recorded. For all the identified NNF episodes, fever characteristics, including vital signs, sepsis based on the 2005 International pediatric sepsis consensus conference criteria[12], choice of antibiotics administered, laboratory data, culture results (blood, urine, and other cultures), and clinical outcomes were collected.

Statistical Analysis

Data analyses were performed using the PASW Statistical Software version 28 (SPSS, Chicago, IL, USA) and STATA version 11 (College Station, TX, USA). Descriptive statistics were expressed as mean ± standard deviation, median (range), or percent. Categorical data were analyzed using Fisher's exact test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Fifty-one patients were reviewed, but the 97 NNF episodes over 25,506 days of chemotherapy were documented from 32 patients. Nineteen patients (37.2% of patient population) had occurrence of fever episodes while neutropenic (ANC < 500 cells/mm^3) or undertreatment of the previous document of infection. NNF occurred in 3.8 per 1,000 days of chemotherapy (95% confidence interval [CI] 3.1–4.6). Patient characteristics are summarized in Table 1. The most common cancer diagnosis was acute lymphoblastic leukemia. The mean patient age was 7.7 years (range, 0.3–15.3 years). Almost all patients did not use any central venous catheters (CVCs). Only one (of the 51 patients) had subcutaneous port. All patients received trimethoprim-sulfamethoxazole as *pneumocystis jirovecii* pneumonia (PJP) prophylaxis.

Table 1 Patient characteristics

Characteristics	Results (N=51)
Age at baseline, years, mean±SD	7.7 ± 3.7
Male:Female	27:24
Cancer diagnosis, n (%)	
Acute lymphoblastic leukemia	26 (51.0)
Solid tumor	10 (19.6)
Osteosarcoma	3 (5.9)
Rhabdomyosarcoma	2 (3.9)
Hepatoblastoma	2 (3.9)
Germ cell tumor	1 (2.0)
Neuroblastoma	1 (2.0)
Ewing sarcoma	1 (2.0)
Medulloblastoma	4 (7.8)
Lymphoma	4 (7.8)
Acute myeloid leukemia	4 (7.8)
Langerhans cell histiocytosis	2 (3.9)
Chronic myeloid leukemia	1 (2)
Type of CVC, n (%)	
No	50 (98.0)
Subcutaneous port	1 (2.0)
Patients with any NNF episodes, n (%)	32 (62.8)

Abbreviations: CVC, central venous catheter; N, number; NNF, non-neutropenic fever; SD, standard deviation

The characteristics of the 97 NNF episodes are demonstrated in Table 2. The median body temperature was 38.6°C (range, 38–41°C). Fifty-six NNF episodes (57.7%) occurred in the inpatient setting. Most of the patients with NNF episodes (80.5%) present in outpatient settings, including clinics and emergency departments, were admitted. Patients with high presenting fever were more likely to be admitted. The mean temperature was higher in hospitalized patients (38.98°C, SD=0.73) compared with patients who were treated in outpatient settings (38.33°C, SD=0.17) (p = 0.01). The most frequently clinically documented diagnoses were respiratory tract infection (33%), urinary tract infection (UTI) (11.3%), and gastrointestinal tract infection (10.3%). However, 28% of NNF episode causes were unknown, and 32 (32.9%) febrile episodes were caused by identified microorganisms including virus (n=12), gram-negative bacteria (n=10), gram-positive bacteria (n=5), and mycoplasma (n=5). In over 30% of NNF episodes,

Table 2 Clinical characteristics of 97 non-neutropenic fever episodes

Characteristics	Results	
Median time to last chemotherapy, days (range)	6	(0-110)
Location of presentation, n (%)		
Inpatient	56	(57.7)
Pediatric clinic	26	(26.8)
Emergency department	15	(15.5)
Episode with absence of central line using, n (%)	97	(100)
Presenting signs or symptoms, n (%)		
URI symptoms	25	(25.8)
GI symptoms	15	(15.5)
Skin	12	(12.4)
LRI symptoms	8	(8.2)
Urinary tract infection symptoms	2	(2.1)
Seizure	1	(1.0)
No source on exam	34	(35.1)
Sepsis, n (%)	9	(9.2)
Hemoglobin (g/dl), median (range)	10.2	(5.0-13.7)
White blood cell count (cells/mm^3), median (range)	5,979	(1,000-22,500)
Platelet (cells/mm^3), median (range)	25,6500	(78,000-524,000)
Absolute neutrophil count (cells/mm^3), n (%)		
500-999	7	(7.2)
1000-5000	50	(51.5)
> 5000	40	(41.2)
Identified pathogens, n (%)		
Virus*	12	(12.3)
Gram negative bacteria	10	(10.3)
Gram positive bacteria	5	(5.2)
Mycoplasma species	5	(5.2)
Hemoculture		
Positive	1	(1)
No growth	84	(86.6)
Not done	12	(12.4)
Initial empiric antibiotics, n (%)		
Ceftriaxone	29	(29.9)
Ceftazidime plus amikacin	13	(13.4)
Piperacillin/Tazobactam	9	(9.3)
Antiviral agents	9	(9.3)
Meropenem	6	(6.2)
No antibiotic	7	(7.3)
Others	21	(24.6)
Median time to antibiotic, minutes (range)	82.5	(5-250)

Abbreviations: g/dl, grams per deciliter; GI, gastro-intestinal; LRI, lower respiratory traction infection; mm3, cubic millimeter; n, number; URI, upper respiratory tract infection

*influenza virus, varicella-zoster virus, respiratory syncytial virus, human bocavirus

patients reported presenting signs or symptoms of respiratory tract infection. Among the episodes with respiratory tract symptoms (n=33), nasopharyngeal swab for rapid diagnostic tests to identify influenza virus and respiratory syncytial virus (RSV) and multiplex polymerase chain reaction (PCR) test of qualitatively detecting of viral pathogens were done in 39.4% and 6.1% of episodes. The most common identified viruses were influenza virus (n=5), RSV (n=3), varicella-zoster virus (n=3), and human bocavirus (n=1). Blood culture was taken in 87 NNF episodes (89.7%). Only one blood culture-positive specimen was documented, and *Acinetobacter baumannii* was the only microorganism isolate identified, and the bacteremia rate was 1.03%. No episodes of gram-positive septicemia or fungemia occurred in this cohort. Fifteen bacteria were isolated from different sites including urine culture (n=10), stool or rectal swab culture (n=3), hemoculture (n=1), and sputum culture (n=1). The most commonly identified bacterial pathogens were *Salmonella spp.* (n=3), *Escherichia coli* (n=2), *Proteus mirabilis* (n=2), and *Enterococcus faecalis* (n=2). An empirical antibiotic was given in 92.8% of the NNF episodes. The most common initial empiric treatment with ceftriaxone monotherapy was administered in 29.9% of the total events, followed by ceftazidime plus gentamycin (13.4%). Additional antiviral agents were used in some patients with identified viral pathogens. The analysis suggests that only 20.6% (15/97) of NNF episodes were caused by the identified bacterial pathogens, and approximately 70% of identified gram-negative bacteria showed ceftriaxone susceptibility. We found that there was no significant association of antibiotic administration with mortality, needed of intensive care service or delay of the next chemotherapy cycle.

Among the hospitalized patients, the median length of stay was 5 days (range, 1–14 days). In this cohort, four patients who required ICU admission had septic shock (n=3) and pneumonia with respiratory failure (n=3). The clinical data of the patients with a severe condition that needed ICU admission are shown in Table 3. Viruses, including respiratory syncytial virus (n=2) and human bocavirus (n=1), were commonly identified pathogens in patients with severe pneumonia. One of the 32 patients who experienced NNF died, so the mortality rate was 3.1%. The NNF-related cause of death occurred in a 5-year-old boy with acute lymphoblastic leukemia who had severe human bocavirus pneumonia with multi-organ failure (table 3).

Table 3 Clinical courses of NNF patients with severe feature needed intensive care

	Case 1	Case 2	Case 3	Case 4
Age (year)	12.4	5.4	8	14
Sex	Male	Male	Female	Female
Diagnosis	ALL	ALL	ALL	ALL
Treatment protocol/ phase of treatment	TPOG ALL1301/ maintenance	TPOG ALL1302/ maintenance	TPOG ALL1303/ maintenance	TPOG ALL1302/ augmented consolidation
Comorbid	Down syndrome	None	Relapsed ALL	None
Type of central line	None	None	None	None
Presenting place	Inpatient	Outpatient	Emergency room	Inpatient
Day from latest CMT	9	27	18	6
Clinical presentations	Respiratory distress, wheezing	Oral ulcer	Respiratory distress	Severe abdominal pain
Sepsis	None	Yes	Yes	Yes
Initial ANC (cells/mm^3)	6,512	9,555	1,181	10,649
Lowest ANC (cell/mm^3)	6,512	9,555	599	1,400
Empirical antibiotics	IV Cefotaxime	IV Cefotaxime plus cloxacillin	IV Ceftazidime plus amikacin	IV Meropenem

Table 3 Clinical courses of NNF patients with severe feature needed intensive care (continued)

	Case 1	Case 2	Case 3	Case 4
Additional treatment	None	IVIg	None	
Reason for ICU	Respiratory failure	Progressive respiratory failure with shock	Respiratory failure	Septic shock
Identified pathogen	Yes, RSV	Yes, human bocavirus	Yes, RSV	No
Hemoculture	No growth	No growth	No growth	No growth
Final Diagnosis	RSV pneumonia	Human bocavirus pneumonia with multi-organ failure	RSV pneumonia	Severe necrotizing pancreatitis
Outcome	Discharge, full recovery	Dead	Discharge, full recovery	Discharge, full recovery

Abbreviations: ALL, acute lymphoblastic leukemia; ANC, absolute neutrophil count; CMT, chemotherapy; ICU, intensive care unit; IV, intravenous; IVIg, intravenous immunoglobulin; mm3, cubic millimeter; NNF, non-neutropenic fever; RSV, respiratory syncytial virus; TPOG, Thai pediatric oncology group

DISCUSSION

Fever is a common event among children with cancer during chemotherapy. Our cohort reports that NNF occurs in 3.8 per 1,000 days of chemotherapy in the absence of CVCs in children with cancer. NNF was common among patients aged 5–10 years, similar to previous studies[11,13].

The International Pediatric Fever and Neutropenia Guideline Panel reported the evidence-based clinical practice guideline for patients with FN[8]. It recommended considering initial or step-down outpatient management with a capable infrastructure to ensure safe outpatient monitoring and follow-up in patients with low-risk or severe adverse outcomes. However, specific management guideline of the patient with non-neutropenic fever is still unclear, and it varies across institution[14]. In multicenter retrospective review study by Esbenshade et al.[11] bacteremia occurred in 4.2% over 937 NNF episodes in pediatric oncology patients with central venous catheter, with 77.6% of episodes were outpatient at presentation. Overall 42% of NNF episodes (409/937) were received antibiotics. Following the approach to risk-stratified management of NNF in the study, there were 22/937 episodes (2.3%) of fever with high blood stream infection risk recommended to be admitted on broad spectrum antibiotics. Our study shows that the vast majority of patients with NNF presenting to the outpatient settings were hospitalized (80.5%). A high admission rate in our cohort may be caused by the providers' concern about the family's ability to observe and return to hospital service, and lack of risk-stratified approach management during the study period.

In this study, the causative pathogen could not be identified in 67.1%. The most common microbiologically proven infections were bacterial infections (gram-negative and gram-positive bacteria), followed closely by viral infections. Contrary to a previous study on children with cancer who had central line catheters[15], bacterial infection was greater than the fever of unknown origin, viral infection, and fungal infection in fever episodes with and without neutropenia. Additionally, this study documents a rate of bacteremia as low as 1.03% of NNF episodes, whereas a previous study reported 3.1%–8.2% [10-11, 16]. The lower rate of bacteremia may result from the lack of central line use in the study population. Although the bacteremia rate in our study population is relatively low, it was found that patients with severe symptoms were commonly caused by viral infection. Among our patients with severe symptoms requiring treatment in intensive care, 75% presented with viral pneumonia. Previous studies[17-18] reported that respiratory viral infections increase morbidity and mortality in children with cancer, which was similar to our study's patients.

Regarding the initial antibiotic therapy, ceftriaxone monotherapy constituted the most common antibiotic of choice. A similar finding was reported in a simple meta-analysis by Allaway et al. that empirical antibiotics therapy with ceftriaxone

is commonly prescribed in patients with NNF with a central line[10]. However, there was no significant association of antibiotic administration with mortality, intensive care admission or delay of the next chemotherapy cycle in our cohort.

In the present study, NNF-related mortality occurred in one out of thirty-two (3.1%). Fatal human bocavirus pneumonia with multi-organ failure in a boy with ALL was associated leading cause of death. Recent studies[19-20] showed that severe human bocavirus infection was rare. However, it could occur in patients with underlying chronic conditions, such as congenital heart disease, chronic lung disease, premature birth, cancer, and immune deficiency. A previous study evaluating NNF in children with cancer found a favorable outcome of NNF with an absence of NNF-related deaths[10]. The difference reported may be because of population differences or differences in specific clinical management across countries. NNF mortality among children with cancer may be unrecorded in Asian population.

As study limitations, the retrospective design may lead to incomplete data collection. Testing for potential causative pathogens may differ among NNF presenting episodes. More comprehensive information is more likely collected in inpatients than in outpatients. In addition, with a small sample size, single-center patients may not be representative of patients in other centers. Therefore, to obtain more accurate data, prospective multicenter research is warranted.

CONCLUSION

In conclusion, fever and infection are important and life-threatening complications among pediatric cancer patients with non-neutropenia and commonly lead to hospitalization. This study shows clinical characteristics and incidence of NNF in pediatric cancer in the absence of CVCs. In children with cancer, NNF occurs in 3.8 per 1,000 days of chemotherapy. A lower rate of bacteremia was registered in our study population. Viral infections are common among NNF episodes. However, many patients did not identify any causative bacteria; they received intravenous antibiotics and were admitted. The most clinically severe NNF episodes that required intensive care were caused by respiratory viral pathogens. The mortality rate was 3.1%, with human bocavirus pneumonia with multi-organ failure being the cause of death. The results of our study suggest that patients with severe symptoms may indicate early evaluation and prompt management for viral infection, particularly in a patient with a negative culture and poor respond to antibiotic treatment. Our study reveals clinical practice information, local distribution of pathogens, and significant effect of respiratory viral infection on pediatric patients with NNF in the absence of CVCs.

CONFLICT OF INTEREST

None

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DATA AVAILABILITY STATEMENT

Data available within the article or its supplementary materials

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Original Article

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Incidence of Percutaneous Nephrostomy Tube-Associated Urinary Tract Infections in Vajira Hospital

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ABSTRACT

OBJECTIVE: To study the incidence of percutaneous nephrostomy tube-associated urinary tract infection (PCNI), changes in urinary characteristics, and factors associated with PCNI.

METHODS: A chart review was performed to retrospectively collect data on patients who underwent percutaneous nephrostomy (PCN) insertion for the first time. The eligibility criteria were met by 103 patients. PCNI incidence and correlation, changes in urinary characteristics and infectious events following insertion, bacterial characteristics, and the relationship between the type of bacteria and the presence of symptoms were all investigated.

RESULTS: The incidences of PCNI, sepsis, pyuria, and bacteriuria after insertion were 25.2%, 14.5%, 61.1%, and 48.5% within 76, 67, 25, and 46 days, respectively. The most common bacteria were multi-drug-resistant *Escherichia coli* (MDR *E. coli*) (16.2%), *Pseudomonas aeruginosa* (*P. aeruginosa*) (11.7%), *Escherichia coli* (*E. coli*) (10.3%), and *Enterococcus faecalis* (*E. faecalis*) (10.3%), which were susceptible to carbapenem, piperacillin/tazobactam, and amikacin. The bacterial type and PCNI demonstrated no correlation. However, the frequency of PCN change, indwelling period, pyuria, and bacteriuria in chronic kidney disease was significantly correlated with PCNI ($p < 0.05$).

CONCLUSION: Quarter of patients with a PCN catheter develops PCNI. More than half of patients with PCN indwellers had pyuria or bacteriuria. *E. coli* has the most significant ratio. Carbapenem, piperacillin/tazobactam, and amikacin all had benefits but should be adjusted in terms of culture results, especially in the multi-drug resistance group. The incidence of PCNI may decrease with early diagnosis, drainage, and the shortest period before specific treatment in the future.

KEYWORDS: bacteriuria, percutaneous nephrostomy, pyuria, upper urinary tract obstruction, urinary tract infection

INTRODUCTION

Upper urinary tract obstruction is an obstruction from the renal pelvis to the distal ureter. Permanent renal failure or infection may occur if no immediate action is taken, which can be fatal. Goodwin et al.[1] invented percutaneous nephrostomy (PCN) that can address urinary obstruction, hydronephrosis, and infection in the upper urinary tract[2], and renal function is renormalized[3]. However, a risk of complications exists from tube insertion to long-term use.

Urinary tract infection (UTI) is a common and serious complication of indwelling drainage tubes[4], including PCN. Severe infections, such as sepsis, may require more complicated treatment,

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with an increased risk of patient death[5]. The current standard treatment guidelines for catheter-associated UTI are clear[6], but these guidelines exclude PCN patients whose definition varies among studies[7-8]. Previous studies have reported the incidence of percutaneous nephrostomy tube-associated urinary tract infection (PCNI) to be between 14-38%.[4,8-11]. Among cancer patients, there is an increased risk of PCNI associated with a history of UTI or neutropenia. However, for other patient groups, the risk factors for PCNI remain unclear. Academically strong clinical evidence still needs to be improved, and developing clear diagnosis and treatment guidelines because of the differences in patient characteristics in each area and common microorganisms is impossible despite numerous studies on these populations[8]. We believed that studying the incidence of infection and microbiological characteristics would help us plan treatment and improve the quality of patient management while providing reference data for future studies.

METHODS

Data collection

This retrospective cohort study collected data via outpatient and inpatient department chart reviews of patients in Vajira Hospital. The first PCN insertion occurred from January 2016 to June 2022, with 154 patients. The types of tubes used in the study included a suction tube (10 Fr) or a pigtail catheter (10 Fr) with ultrasound-guided insertion. Routine changing of the tubes in the study was performed using the under-guidewire lead technique with changing times of 30 days and 90 days, respectively. Patients with PCNs inserted at other hospitals and those with a follow-up time of < 60 days were excluded. 103 patients met the eligibility criteria.

The collected patient data included sex, age, comorbidity, indication for insertion, and urinalysis profiles specifically collected from PCN, which diagnosed pyuria as having > 5 white blood cells per high-power field in urine. The type of bacteria found in culture was recorded if bacteriuria (≥ 10^5 CFUs/ml) was present, along with antibiotic susceptibility. The duration from PCN insertion to changes in urine characteristics and the presence of signs of infection were also noted. Bacteriuria, together with symptoms such as fever of > 37.8°C or costovertebral angle tenderness, was identified as a UTI (PCNI in this study) or sepsis if positive hemoculture was also present. Patients who had their first PCN catheter inserted due to infection were not counted as having PCNI, and changes in urine output and infection status were recorded after successful treatment and negative urine culture results. The hospital length of stay in the PCNI population, number of sides of tube insertion, and frequency of tube change until September 2022 or tube removal were also recorded.

The Institutional Review Board approved this study, Faculty of Medicine Vajira Hospital, Navamindradhiraj University (COA 214/2565).

Statistical analysis

Qualitative data were reported as frequency distributions and percentages. Quantitative data were reported as mean and standard deviation, or median and interquartile range, regarding data appropriation. The frequency distribution and percentage with a 95% confidence interval were used to report the incidence and prevalence rates of pyuria, bacteriuria, PCNI and sepsis. Frequency distribution, percentage analysis, crude analysis, and the chi-squared test were used to report the correlation between the type of microorganism and PCNI. Frequency distribution, percentages, Spearman rank-order correlation, and pairwise correlation coefficients were used in the correlation analysis for patients with PCNI. SPSS for Windows, version 28.0 (IBM Corp., Armonk, NY, USA), was used for analysis. All statistical tests were considered statistically significant at a p-value of < 0.05.

RESULTS

This study involved 103 patients, primarily female (66%), with a mean age of 59.1 years and cancer as the main comorbidity (89.3%). Chronic kidney disease was also common among these patients (44.6%). The main indication for insertion was acute kidney injury (85.4%), and the leading cause was urinary tract obstruction due to cancer (80.5%). Unilateral insertion (68.9%) was more common than bilateral insertion, and the median number of tube changes was four with a 143-day indwelling period (table 1).

The prevalence of pyuria was 61.1% (n = 63), and the incidence of bacteriuria was 48.5% (n = 50) during the entire period of PCN indwelling, with 23.3% being asymptomatic (n = 24), 25.2% being PCNI (n = 26), and 14.5% having sepsis (n = 15) (table 2). The median duration from PCN insertion to the presence of pyuria and bacteriuria was 25 and 46 days, respectively. The mean duration from PCN insertion to the presence of PCNI and sepsis was 76 and 67 days, respectively. The median length of stay for UTI treatment was 17 days. (table 3).

During the entire period of PCN indwelling in 51 patients with positive urine cultures, we analyzed 68 specimens. We found gram-negative bacteria in 59 specimens (86.7%), and 61% of the gram-negative bacteria were drug-resistant. Gram-positive bacteria were present in 8 specimens (10.2%), and only 1 (12.5%) was drug-resistant. The most common microorganisms detected were multi-drug-resistant *Escherichia coli* (MDR *E. coli*) (16.2%), *Pseudomonas aeruginosa* (*P. aeruginosa*) (11.7%), *Escherichia coli* (*E. coli*) (10.3%), and *Enterococcus faecalis* (*E. faecalis*) (10.3%) (table 4).

Table 1 Demographic data for the study population

Variables	Mean (SD)/Median (IQR)/Count (%) (N=103)
Mean Age (year), SD	59.1 (13.9)
Gender	
Male	35 (34%)
Female	68 (66%)
Comorbidity	
Diabetic mellitus	11 (10.7%)
Chronic kidney disease	46 (44.6%)
Immunocompromised[a]	20 (19.4%)
Cancer	92 (89.3%)
Genitourinary tract cancers	23 (22.3%)
Gastrointestinal cancers	19 (18.4%)
Gynecologic cancers	45 (43.7%)
Others cancer	5 (4.9%)
Stone	10 (9.7%)
Indication	
Acute kidney injury	88 (85.4%)
Infection	9 (8.7%)
Pain	3 (2.9%)
Others[b]	3 (2.9%)
Cause	
Malignant disease	83 (80.5%)
Stone	11 (10.7%)
Ureteric stricture	8 (7.8%)
Ureteric Injury	1 (1%)
Side	
Unilateral	71 (68.9%)
Bilateral	32 (31.1%)
Changed time (times), Median (IQR)	4 (2-7)
Indwelling time (days), Median (IQR)	143 (82.5-257.5)

Abbreviations: IQR, interquartile range; N, number; SD, standard deviation
[a] = Patients who received chemotherapies or immunosuppressive drug within 1 year of PCN insertion
[b] = Others indication included ureteric injury, ureteric stricture

Table 2 Prevalence of inflammatory and incidence of PCNI

Variables	Count (%), N=103
Pyuria	63 (61.1%)
Bacteriuria	50 (48.5%)
Asymptomatic bacteriuria	24 (23.3%)
Symptomatic: PCNI	26 (25.2%)
Sepsis	15 (14.5%)

Abbreviations: N, number; PCNI, percutaneous nephrostomy tube-associated urinary tract infections

Table 3 Mean time to develop pyuria and infectious conditions

Variables	Median time (day), (IQR)
Time from insertion to pyuria	25 (6-64)
Time from insertion to bacteriuria	46 (19-126.8)
Time from insertion to PCNI	76 (38.75-144.25)
Time from pyuria to PCNI	16 (2.25-48.6)
Time from bacteriuria to PCNI	4 (0-23)
Time from insertion to sepsis event	67 (44-91.5)
Length of stay for infection treatment	17 (7.3-30.5)

Abbreviation: IQR, interquartile range; PCNI, percutaneous nephrostomy tube-associated urinary tract infections

Table 4 Microbiological characteristics in PCN indwellers

Variables	Total Count (%) N=68 (%)	Symptomatic Count (%) N=39/68	Asymptomatic Count (%) N=29/68	P-value
Gram negative	23 (33.8%)	14 (35.9%)	9 (31%)	0.29
Klebsiella pneumoniae	4 (5.9%)	3 (7.7%)	1 (3.5%)	0.32
Escherichia coli	7 (10.3%)	5 (12.9%)	2 (6.8%)	0.26
Pseudomonas aeruginosa	8 (11.7%)	4 (10.3%)	4 (13.7%)	1.00
Acinetobacter baumannii	1 (1.5%)	0 (0%)	1 (3.5%)	-
Stenotrophomonas maltophilia	2 (2.9%)	1 (2.5%)	1 (3.5%)	1.00
Proteus mirabilis	1 (1.5%)	1 (2.5%)	0 (0%)	-
Gram positive	7 (10.3%)	4 (10.3%)	3 (10.3%)	0.71
Enterococcus faecalis	7 (10.3%)	4 (10.3%)	3 (10.3%)	0.71
Drug-resistant gram negative	36 (52.9%)	20 (51.3%)	16 (55.2%)	0.51
MDR *Klebsiella pneumoniae*	4 (5.9%)	3 (7.7%)	1 (3.5%)	0.32
MDR *Escherichia coli*	11 (16.2%)	5 (12.9%)	6 (20.7%)	0.76
MDR *Pseudomonas aeruginosa*	5 (7.3%)	3 (7.7%)	2 (6.8%)	0.66
MDR *Acinetobacter baumannii*	6 (8.8%)	5 (12.9%)	1 (3.5%)	0.10
MDR *Chryseobacterium indolgenes*	1 (1.5%)	0 (0%)	1 (3.5%)	-
MDR *Citrobacter frundii*	2 (2.9%)	1 (2.5%)	1 (3.5%)	1.00
MDR *Enterobacter Cloacae*	6 (8.8%)	2 (5.1%)	4 (13.7%)	0.41
MDR *Proteus mirabilis*	1 (1.5%)	1 (2.5%)	0 (0%)	-
Drug-resistant gram positive	1 (1.5%)	1 (2.5%)	0 (0%)	-
MRSA	1 (1.5%)	1 (2.5%)	0 (0%)	-
Fungal	1 (1.5%)	0 (0%)	1 (3.5%)	-
Candida albican	1 (1.5%)	0 0 (0%)	1 (3.5%)	-

Abbreviations: MDR, multi-drug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; N, number

Non-drug-resistant gram-negative bacteria, including *E. coli*, *P.aeruginosa*, and *Klebsiella pneumonia* (*K. pneumonia*), are susceptible to amikacin (100%, 100%, and 75%, respectively), carbapenem (100%), and piperacillin/tazobactam (100%, 87.5%, and 100%, respectively). Additionally, *E. coli* and *K. pneumonia* were susceptible to cotrimoxazole at 71.4% and 75%, respectively, but fluoroquinolone and cephalosporin were relatively low (0%–25% and 25%–28.6%, respectively), whereas *P. aeruginosa*, regarding fluoroquinolone, was susceptible to levofloxacin at 12.5% and ciprofloxacin at 62.5%, and only 75% for ceftazidime in cephalosporin group. The majority

of the multi-drug-resistant gram-negative bacteria showed the highest susceptibility to amikacin and cotrimoxazole (50%–81.8% and 27.8%–83.3%, respectively) while being minimally susceptible to cephalosporin and fluoroquinolone (0%–18.2% and 0%–9.1%, respectively), as well as piperacillin/tazobactam (0%–63.6%). Multi-drug-resistant *Pseudomonas aeruginosa* (MDR *P. aeruginosa*) was resistant to most antibiotics but showed some susceptibility to colistin (20%).

Only two types of microorganisms were found for gram-positive bacteria, including *E. faecalis* (10.3%), which was more common than methicillin-resistant *Staphylococcus aureus* (MRSA) (1.5%). Almost all types of the studied bacteria were resistant to amoxicillin/clavulanic acid and ampicillin, except *E. faecalis*, which was susceptible to ampicillin (85.7%). Among gram-positive bacteria, *E. faecalis* and MRSA were susceptible to vancomycin at 100% (table 5).

The type of microorganism and the presence of UTI demonstrated no correlation (table 4). A significant correlation was found between patients with PCNI and chronic kidney disease (CKD), number of tube changes, indwelling period, pyuria, and bacteriuria ($p < 0.05$) (table 6).

Table 5 Antibiotic susceptibility of isolated microorganisms from PCN cultures

Antibiotics / Organisms	*Escherichia coli*	MDR *Escherichia coli*	*Pseudomonas aeruginosa*	MDR *Pseudomonas aeruginosa*	*Klebsiella pneumoniae*	MDR *Klebsiella pneumoniae*	MDR *Enterobacter cloacae*	MDR *Acinetobacter baumannii*	*Enterococcus faecalis*	MRSA
	Counts (%) N=7/68	Counts (%) N=11/68	Counts (%) N=8/68	Counts (%) N=5/68	Counts (%) N=4/68	Counts (%) N=4/68	Counts (%) N=6/68	Counts (%) N=6/68	Counts (%) N=7/68	Counts (%) N=1/68
Amikacin	7 (100%)	9 (81.8%)	8 (100%)	R	3 (75%)	4 (100%)	3 (50%)	3 (50 %)	N/A	N/A
Gentamicin	5 (71.4%)	1 (9.1%)	4 (50%)	R	4 (100%)	3 (75%)	3 (50 %)	1 (16.7%)	3 (42.9%)	1 (100%)
Amoxi/clav	1 (14.3%)	N/A	N/A	N/A	1 (25%)	R	N/A	N/A	N/A	N/A
Ampicillin	R	R	N/A	N/A	R	R	R	N/A	6 (85.7%)	N/A
Ceftriaxone	2 (28.6%)	2 (18.2%)	N/A	N/A	1 (25%)	R	R	NA	N/A	N/A
Ceftazidime	2 (28.6%)	2 (18.2%)	6 (75%)	R	1 (25%)	R	R	1(16.7%)	N/A	N/A
Ciprofloxacin	R	R	5 (62.5%)	R	1 (25%)	R	R	R	N/A	N/A
Levofloxacin	R	1 (9.1%)	1 (12.5%)	R	R	R	N/A	R	N/A	N/A
Imipenem	7 (100%)	9 (81.8%)	8 (100%)	R	4 (100%)	3 (75%)	1 (16.7%)	R	N/A	N/A
Ertapenem	7 (100%)	8 (72.7%)	N/A	R	4 (100%)	2 (50%)	1 (16.7%)	N/A	N/A	N/A
Meropenem	7 (100%)	9 (81.8%)	8 (100%)	R	4 (100%)	3 (75%)	3 (50 %)	R	N/A	N/A
Pip/tazobactam	7 (100%)	7 (63.6%)	7 (87.5%)	R	4 (100%)	2 (50%)	R	R	N/A	N/A
Cotrimoxazole	5 (71.4%)	3 (27.8%)	N/A	N/A	3 (75%)	2 (50%)	5 (83.3%)	N/A	N/A	1 (100%)
Vancomycin	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	7 (100%)	1 (100%)
Colistin	N/A	N/A	2 (25%)	1 (20%)	N/A	N/A	2 (33.3%)	2 (33.3%)	N/A	N/A
Tigecycline	N/A	N/A	N/A	N/A	N/A	N/A	N/A	6 (100%)	N/A	N/A

Abbreviations: MDR, multi-drug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; R, resisted; N, number; N/A, susceptibility testing is not performed

Table 6 Correlation of percutaneous nephrostomy tube-associated urinary tract infections

Variables	Mean (SD)/Median (IQR)/Count (%) (N=26/103, 52%)		r	P-value
Age (year), Mean (SD)	59.7 (12.1)		0.04	0.70
Comorbidity				
Diabetic mellitus	2	(7.7%)	-0.06	0.57
Chronic kidney disease	16	(61.4%)	0.20	0.05*
Immunocompromised[a]	8	(30.7%)	0.17	0.09
Genitourinary tract cancer	9	(34.6%)	0.17	0.08
Gastrointestinal cancer	2	(7.7%)	-0.16	0.10
Gynecologic cancer	12	(46.1%)	0.03	0.77
Stone	3	(11.5%)	0.04	0.72
Changed time (times), Median (IQR)	6	(4-13.75)	0.26	0.01*
Indwelling time (days), Median (IQR)	256	(127.3-403.5)	0.28	0.00*
Pyuria	26	(100%)	0.45	0.00*
Bacteriuria	26	(100%)	0.56	0.00*

Abbreviations: IQR, interquartile range; r, correlation coefficient; SD, standard deviation

*$p < 0.05$ significant

[a], Patients who received chemotherapies or immunosuppressive drug within 1 year of PCN insertion

DISCUSSION

This study revealed a higher incidence of PCNI than in previous studies in the United States of America, with 14%, 19%, and 20%[8-11], but lower than 38% in Sweden[4]. The incidence of sepsis was higher than that of other studies, which were 3%[4] and 9%[8] but similar to the 12% reported in a Brazilian study[12]. The mean duration from PCN insertion to PCNI was both shorter and longer than that reported in previous studies (14 days[4], 42 days[10], and 100 days[8]) and longer than the duration from insertion to sepsis (67 days), demonstrating that patients with sepsis might have some factors that made them sensitive to more severe infection. Ramez et al.[9] reported a correlation between acute pyelonephritis and PCN in patients with cancer. This study revealed that 89.3% of patients had cancer, which was probably the cause of the high infection incidence. However, the study did not observe any correlation.

The present study revealed a correlation between pyuria and bacteriuria with PCNI because it is a diagnostic criterion for the infection. Moreover, pyuria can result from the body's response to PCN, with or without concurrent infection. However, the comparable prevalence of asymptomatic and symptomatic bacteriuria (23.3% vs. 25.2%) suggests that the observed correlation may not have significant clinical relevance. Furthermore, no previous study explained the relationship between pyuria and bacteriuria as infection risk factors, related to Cronan et al.'s study revealed that bacteriuria after tube insertion did not usually cause disease unless there was obstruction[13].

Pappas et al.[14] reported that 6% of patients still have no renal function improvement, although urinary drainage was already used in patients with acute renal failure. In addition, CKD might damage body immunity through decreased response to kidney-affecting medications, a factor in complicated UTIs[15-16]. In contrast, Maramara et al.[11], indicating no association between CKD in the population with PCN and UTI or bacteriuria. Even though it could not be interpreted as a risk factor for UTI, the correlation between PCNI and CKD was demonstrated in this study which may be explained by a higher proportion of the study population than other diseases. Besides the relatively high mean age of populations, other factors, such as delayed drainage time in some cases due to difficult medical treatment access or delayed diagnosis, may lead to permanent renal damage and restoration of function that was not as good as it should be.

The tube-indwelling period is another factor despite a lower urinary tract catheter[17]. A correlation was found between changing frequency, indwelling period, and PCNI, which was higher than that reported in previous studies[9-10]. This could be attribute to the necessity for frequent tube changes due to tube dislocation, tube obstruction, and the waiting time for specific treatment. Additionally, factors of personal hygiene, tube care, or delayed tube change might reinforce infection. However, timely replacement of PCN when indicated is crucial as delaying replacement beyond four days after symptom onset may increase the risk of recurrent infection[8].

The proportion of drug-resistant microorganisms in terms of microbiological characteristics was higher (61%) than in previous studies, which was 37.7%[11] and 47%[18]. However, no microorganism was significantly associated with the presence of the signs. The remarkable proportion of both types of *E. coli* might be due to environmental factors, common microorganism prevalence, inadequate treatment time, antibiotic administration in asymptomatic patients, or a long PCN indwelling period[19], which might lead to change in the biological properties of drug-susceptible strains *E. coli* in the urine of patients with PCN. Therefore, proper management should be considered to prevent changes to drug-resistant ones in the future due to the main proportion of organisms usually found in the symptomatic group. However, sepsis could be detected with the same or different microorganisms in the urine, and recurrent infection did not always require the same

microorganism as the previous culture[20]. The following most common microorganisms for gram-negative and overall organisms were similar to those in the previous study, which were *P. aeruginosa* and *E. faecalis*[18].

Non-drug-resistant *E. coli* and *K. pneumonia* were more susceptible to cotrimoxazole than fluoroquinolones regarding antibiotic susceptibility for the gram-negative group. The resistance rate of fluoroquinolones and cephalosporins was relatively high in almost every microorganism, but ciprofloxacin and ceftazidime could still be considered for treating *P. aeruginosa*. A previous study revealed that meropenem and amikacin are the most effective antibiotics against gram-negative bacteria[21]. Carbapenem and piperacillin/tazobactam remained susceptible to non-drug-resistant gram-negative microorganisms (87.5%–100%) in the study population, but susceptibility substantially decreased (0%–81.8%) in the drug-resistant group. Amikacin remains susceptible to more than half (50%–100%) of almost every group of gram-negative microorganisms, except MDR *P. aeruginosa*, which was resistant to nearly every antibiotic. Therefore, empirical treatment for nosocomial microorganisms, especially MDR *P. aeruginosa*, MDR *Enterobacter Cloacae* (MDR *E. cloacae*), and MDR *Acinetobacter baumannii* (MDR *A. baumannii*) must be primarily used with these drug groups that might partly affect specific results of culture so that the type of antibiotics could be appropriately adjusted. Vancomycin remains a good treatment choice for gram-positive bacteria because most bacteria in this group remain susceptible. However, ampicillin may be considered for the treatment of *E. faecalis*.

The statistical significance of the study may be lower than other studies due to the limited population size, and risk factors could not be analyzed despite finding a correlation between PCNI and certain factors. Additionally, the study did not compare the incidence rates of PCNI between patients who received unilateral or bilateral PCN insertion or between symptomatic and asymptomatic patient populations. Furthermore, this was a retrospective study, which means that certain data may not have been recorded, such as the type of PCN tube, simultaneous urethral catheter insertion, and urine collection from an old or new tube, which might be contaminated by colonization and treatment for symptomatic patients. Moreover, this study was conducted in a single institution, so the data may only be applicable to similar institutions in the same area and may not generalize to institutions with different patient characteristics.

CONCLUSION

Quarter of patients with a PCN catheter develops PCNI. More than half of patients with PCN indwellers had pyuria or bacteriuria. *E. coli* has the most significant ratio. Carbapenem, piperacillin/tazobactam, and amikacin all had benefits but should be adjusted regarding culture results, especially in the MDR group. Early diagnosis and drainage and the shortest period before specific treatment may decrease the incidence of PCNI in the future.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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None

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Original Article

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A 5-Year-Retrospective Review: The Clinical Outcome between Adequate and Inadequate of Initial Antibiotics Treatment in Pediatric Patients, Vajira Hospital

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ABSTRACT

OBJECTIVE: The results of adequate and inadequate empirical antibiotics remain unclear. This study aimed to evaluate the results of using adequate and inadequate empirical antibiotics.

METHODS: A retrospective cohort analysis that covered January 2017 and December 2021 was conducted. At Vajira Hospital, we enlisted pediatric patients with bacteremia and urinary tract infections (UTIs). Patient attributes, empirical antibiotics, therapeutic results, financial expenditures, and antibiotic susceptibility patterns were assessed.

RESULTS: In total, 286 pediatric patients were enrolled. There were 230 (80.4%), and 56 (19.6%) patients with UTIs and bacteremia, respectively. The organism that was found the most frequently was *Escherichia coli* (53.5%), while third-generation cephalosporin was the most often used empirical antibiotic (74.5%). Only 78.4% of *Escherichia coli* were vulnerable to third-generation cephalosporin. Of 220 patients (76.9%) were treated with adequate empirical antibiotics. The outcomes in the adequate empirical antibiotics group revealed better-improved symptoms than inadequate empirical antibiotics group (96.4% VS 84.8%, p = 0.002).

CONCLUSION: Clinical outcomes among pediatric patients from adequate initial antibiotics groups were reported the better outcomes. The mortality rates were not different. Nonetheless, appropriate empirical antibiotics are needed. In UTI patients, amikacin is preferable options for empirical antibiotics.

KEYWORDS: adequate, empirical antibiotics, inadequate, pediatrics

INTRODUCTION

Infections are to blame for one-third of all fatalities globally[1]. Bacteremia, and urinary tract infections (UTIs) each had in-hospital death rates of 23.4%, and 11.9%, respectively[2]. Bacteremia is linked to higher rates of morbidity, death, and costs[3]. Additionally, bacteremia has a mortality rate that ranges from roughly 28 to 55%[4]. In addition to bacteremia, major and frequent issues include UTIs. Each year, 8.1 million UTIs diagnoses were recorded in the United States. If the condition was not treated properly, renal failure would result[5-7]. In order to address and avoid complications from bacteremia, and UTI, appropriate antibiotics are required.

Antibiotic-resistant microorganisms are now more prevalent, which increases costs, lengthens hospital stays, and boosts fatality rates[8]. The World Health Organization promotes awareness of microbes that are resistant to antibiotics[8]. However, the use of inferior empirical antibiotics is rising. Information on adequate and

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inadequate empirical antibiotics varies. Inadequate empirical antibiotics have been shown to promote catastrophic outcomes in the past, but another investigation found there was no distinction in the results between inadequate and adequate empirical antibiotics[9-13]. In order to determine if appropriate empirical antibiotics are necessary, data on outcomes between adequate and inadequate empirical antibiotics as well as antimicrobial susceptibility patterns in the pediatric ward at Vajira Hospital require examination. The primary objective is to approve the mortality rate between adequate and inadequate initial antibiotics.

METHODS

We carried out a 5-year retrospective cohort analysis at a single location. When bacteremia and UTIs were determined to be caused by bacteria on hemoculture, and urine culture (≥ 10^5 CFU per milliliter of urine), respectively with the relevant symptoms, we enrolled pediatric patients under the age of 15 who had these diagnoses [14-15]. Therapy was determined to be adequate or inadequate empirical antibiotics treatment based on the in-vitro susceptibility of an isolated organism. Adequate empirical antibiotics are referred to as in-vitro susceptibility of the isolated pathogen to at least one of the antibiotics administered and inadequate empirical antibiotics are referred to as in-vitro resistance of the isolated pathogen to at least one of the antibiotics administered that administration in the first 24 hours[16].

We collected all data from 1 January 2017 to 31 December 2021 at the Pediatrics outpatient and inpatient departments at Vajira Hospital, Navamindradhiraj University. Vajira Hospital is a tertiary care facility that serves over 700,000 outpatient visits and 30,000 inpatient admissions per year. Demographic information, organisms, antimicrobial susceptibility patterns, treatment results between sufficient and inadequate empirical antibiotics, and expenditures were gathered. Institutional review board ethics clearance was received from the Faculty of Medicine at Vajira Hospital, Navamindradhiraj University.

The sample size for the comparison results between adequate and inadequate empirical antibiotics was determined using an unmatched cohort study. Kelsey et al. described the sample size formula for the present method.

$$n_1 = \frac{(Z_{\alpha/2}+Z_{1-\beta})2\bar{p}\bar{q}\,(r+1)}{r(p_1-p_2)^2}$$
$$n_2 = rn_1$$

where n_1 = amount of inadequate empirical antibiotics (exposed group), n_2 = amount of adequate empirical antibiotics (unexposed group), α = 0.05, 1-β = 0.8, p_1 = correlation between inadequate empirical antibiotics and death, p_2 = link between the segment of adequate empirical antibiotics and death.

According to an earlier study, inadequate empirical antibiotics resulted in 67.8% in-hospital mortality, whereas adequate empirical antibiotics resulted in 28.7% in-hospital deaths[17]. Additionally, data from a month at the pediatric department of Vajira Hospital showed that the number of patients receiving an appropriate course of empirical antibiotics was more than three times higher than that of the inadequate group. As a result, we aimed to gather samples from unexposed and exposed groups at a ratio of 3 to 1.

At least 66 participants in total, comprising at least 17 in the exposed group and 49 in the unexposed group, made up the overall sample size. This study was approved by the Institutional Review Board Faculty of Medicine (COA 069/2565).

Interquartile range (IQR) and percentage were used in descriptive statistics to determine the mean. The Independent Samples T-test, Mann-Whitney U Test, Chi-Square Test, or Fisher's Exact Test, as applicable, were correlated to the p-value. IBM SPSS Statistics 28.0 was used to examine the data.

RESULTS

From January 1, 2017, to December 31, 2021, we enrolled 286 pediatric patients who had been diagnosed with UTIs, and bacteremia. Age was 7.16 months on average (IQR 2.21-30.66).

159 (55.6%) of the patients were male. Furthermore, genitourinary tract illness was the most prevalent underlying condition in 90 (31.5%) patients (n = 39, 13.6%) such as vesicoureteral reflux, chronic kidney disease, and renal cysts. From the sample, 236 were inpatients (82.5%). UTIs, and bacteremia were identified in 230 (80.4%), and 56 (19.6%) patients, respectively. The most prevalent empirical antibiotic (74.5%) was third-generation cephalosporin. Septic shock was the most prevalent complication, occurring in 14 (4.9%) patients. Both adequate and inadequate empirical antibiotics can cause complications (10.5% vs. 16.7%, p = 0171). The improved clinical showed that 208 patients in adequate empirical antibiotics, and 60 patients in inadequate empirical antibiotics (p = 0.002). Still, 18 patients (6.3%) died, 12 patients received appropriate empirical antibiotics, and 6 patients received inadequate empirical antibiotics (p = 0.099). (table 1)

Table 1 Patient characteristics of adequate and inadequate empirical antibiotics

Patient profile	Total patients (N = 286)		Adequate empirical antibiotics (N = 220)		Inadequate empirical antibiotics (N = 66)		P-value
Age; months*	7.16	(2.21-30.66)	7.16	(2.11-34.06)	7.16	(2.41-19.66)	0.945
Sex							
Male	159	(55.6%)	116	(52.7%)	43	(65.2%)	0.075
Female	127	(44.4%)	104	(47.3%)	23	(34.8%)	
Underlying disease	90	(31.5)	65	(29.5%)	25	(37.9%)	0.201
Genitourinary tract	39	(13.6%)	25	(11.4%)	14	(21.2%)	0.041
Neurological	18	(6.3%)	11	(5.0%)	7	(10.6%)	0.143
Cardiovascular	17	(5.9%)	14	(6.4%)	3	(4.5%)	0.770
Hematological	13	(4.5%)	12	(5.5%)	1	(1.5%)	0.311
Respiratory	8	(2.8%)	6	(2.7%)	2	(3.0%)	1.000
Endocrine	6	(2.1%)	6	(2.1%)	0	(0.0%)	0.342
Gastrointestinal	6	(2.1%)	3	(1.4%)	3	(4.5%)	0.138
Delay development	1	(0.3%)	1	(0.5%)	0	(0.0%)	1.000
Type of care							
Inpatient care	236	(82.5%)	185	(84.1)	51	(77.3%)	0.201
Outpatient care	50	(17.5%)	35	(15.9%)	15	(22.7%)	
Diagnosis							
UTI	230	(80.4%)	176	(80%)	54	(81.8%)	0.739
Bacteremia	56	(19.6%)	44	(20%)	12	(18.2%)	
Initial antibiotics							
third-generation cephalosporin	213	(74.5%)	169	(76.8%)	44	(66.7%)	0.097
aminoglycosides	81	(28.3%)	70	(31.8%)	11	(16.7%)	0.017
carbapenems	28	(9.8%)	22	(10.0%)	6	(9.1%)	0.827
Complication	34	(11.9%)	23	(10.5%)	11	(16.7%)	0.171
septic shock	14	(4.9%)	9	(4.1%)	5	(7.6%)	0.325
seizure	11	(3.8%)	7	(3.2%)	4	(6.1%)	0.285
acute kidney injury	9	(3.1%)	8	(3.6%)	1	(1.5%)	0.690
respiratory failure	4	(1.4%)	2	(0.9%)	2	(3.0%)	0.229
others	4	(1.4%)	2	(0.9%)	2	(3.0%)	0.229
Transferred to ICU	25	(8.7%)	20	(9.1%)	5	(7.6%)	0.702
Length of stay; days*	81.5	(13-161)	88	(11-163)	58	(17-130)	0.609
Cost expenses; Baht*	26,230	(11,269-152,156)	25,898	(11,625-175,017)	31,128	(9,473-109,044)	0.723
Status of discharge							
Improved	268	(93.7%)	208	(94.5%)	60	(90.9%)	0.002
Death	18	(6.3%)	12	(5.5 %)	6	(9.1%)	0.099

Abbreviations: ICU, intensive care unit; N, number; UTI, urinary tract infection

*Data are presented as median (interquartile range)

Klebsiella pneumoniae and *Escherichia coli* were the frequent organisms in bacteremia, and UTI patients. (table 2)

Third-generation cephalosporin (84.8%) was the most often utilized empirical antibiotics for UTI patients. With adequate and inadequate empirical antibiotics, 175 patients (99.4%) and 53 patients (96.4%), respectively, recovered symptoms significantly in adequate empirical antibiotics (p = 0.001). However, 0.6% of patients receiving adequate empirical antibiotics and 3.6% receiving inadequate empirical antibiotics perished (p = 0.142) from UTIs. (table 3)

Table 2 Prevalence of pathogens by diagnosis

Pathogen	Total (N=286)		Adequate empirical antibiotic (N=220)		Inadequate empirical antibiotic (N=66)	
	N	(%)	N	(%)	N	(%)
Bacteremia	47	(100)	37	(78.7)	10	(21.3)
Klebsiella pneumoniae	8	(17.0)	7	(18.9)	1	(10.0)
Escherichia coli	6	(12.8)	4	(10.8)	2	(20.0)
Enterobacter cloacae	4	(8.5)	4	(10.8)	0	(0.0)
Pseudomonas aeruginosa	3	(6.4)	3	(8.1)	0	(0.0)
Staphylococcus epidermidis	3	(6.4)	2	(5.4)	1	(10.0)
Acinetobacter baumannii	2	(4.3)	0	(0.0)	2	(20.0)
Staphylococcus capitis	2	(4.3)	1	(2.7)	1	(10.0)
Staphylococcus hominis	2	(4.3)	1	(2.7)	1	(10.0)
Streptococcus agalactiae	2	(4.3)	2	(5.4)	0	(0.0)
Acinetobacter calcoaceticus complex	1	(2.1)	1	(2.7)	0	(0.0)
Acinetobacter pittii	1	(2.1)	1	(2.7)	0	(0.0)
Acinetobacter spp.	1	(2.1)	1	(2.7)	0	(0.0)
Aeromonas hydrophilia	1	(2.1)	1	(2.7)	0	(0.0)
Burkholderia cepacia	1	(2.1)	1	(2.7)	0	(0.0)
Burkholderia species	1	(2.1)	1	(2.7)	0	(0.0)
Enterococcus faecium	1	(2.1)	0	(0.0)	1	(10.0)
Pantoea species	1	(2.1)	1	(2.7)	0	(0.0)
Proteus mirabilis	1	(2.1)	1	(2.7)	0	(0.0)
Pseudomonas putida	1	(2.1)	1	(2.7)	0	(0.0)
Salmonella group D	1	(2.1)	1	(2.7)	0	(0.0)
Salmonella species	1	(2.1)	1	(2.7)	0	(0.0)
Serratia marcescens	1	(2.1)	1	(2.7)	0	(0.0)
Staphylococcus coagulase negative	1	(2.1)	1	(2.7)	0	(0.0)
Staphylococcus haemolyticus	1	(2.1)	0	(0.0)	1	(10.0)
UTI	231	(100)	176	(76.2)	55	(23.8)
Escherichia coli	144	(62.3)	112	(63.6)	32	(58.2)
Klebsiella pneumoniae	33	(14.3)	22	(12.5)	11	(20.0)
Enterococcus faecium	9	(3.9)	4	(2.3)	5	(9.1)
Pseudomonas aeruginosa	9	(3.9)	8	(4.5)	1	(1.8)
Enterococcus faecalis	8	(3.5)	7	(4.0)	1	(1.8)
Proteus mirabilis	8	(3.5)	7	(4.0)	1	(1.8)
Enterobacter cloacae	6	(2.6)	5	(2.8)	1	(1.8)
Morganella morganii	3	(1.3)	2	(1.1)	1	(1.8)
Staphylococcus haemolyticus	3	(1.3)	2	(1.1)	1	(1.8)
Kluyvera ascorbata	2	(0.9)	2	(1.1)	0	(0.0)
Streptococcus agalactiae	2	(0.9)	2	(1.1)	0	(0.0)
Enterobacter kobei	1	(0.4)	0	(0.0)	1	(1.8)
Pseudomonas putida	1	(0.4)	1	(0.6)	0	(0.0)
Staphylococcus hominis	1	(0.4)	1	(0.6)	0	(0.0)
Staphylococcus saprophyticus	1	(0.4)	1	(0.6)	0	(0.0)

Abbreviations: N, number; UTI, urinary tract infection

Table 3 Patient treatment and outcome in urinary tract infection patients

Patients	Total (N = 231)		Adequate empirical antibiotic (N = 176)		Inadequate empirical antibiotic (N = 55)		P-value
Initial antibiotic treatment							
third-generation cephalosporin	195	(84.4%)	152	(86.4%)	43	(78.2%)	0.144
aminoglycosides	58	(25.1%)	50	(28.4%)	8	(14.5%)	0.038
Piperacillin/tazobactam	15	(6.5%)	11	(6.3%)	4	(7.3%)	0.759
Complication	19	(8.2%)	13	(7.4%)	6	(10.9%)	0.406
Length of stay (days)*	65	(10-153)	71	(8-159)	51	(15-129)	0.959
Cost expenses (Baht)*	20,114	(8,569-45,946)	19,768	(9,342-46,193)	21,774	(2,246-44,536)	0.918
Status of discharge							
improved	228	(98.7%)	175	(99.4%)	53	(96.4%)	0.001
death	3	(1.3%)	1	(0.6%)	2	(3.6%)	0.142

Abbreviations: N, number

*Data are presented as median (interquartile range)

With respect to treatment and results, bacteremia did not differentiate between adequate and inadequate empirical antibiotics. (table 4)

The most often used empirical antibiotics were third-generation cephalosporin, although only *Acenitobacter spp., Burkholderia spp., Enterobacter spp., Escherichia coli, and Klebsiella pneumoniae* were susceptible to them, with respective susceptibilities of 60%, 50%, 45.5%, 78.4%, and 43.9%. Coagulase-negative *Staphylococcus* was shown to be sensitive to *trimethoprim/sulfamethoxazole* in 73.3%, but only 46.7% to vancomycin. (table 5)

Table 4 Patient treatment and outcome in bacteremia patients

Patients	Total (N = 56)		Adequate empirical antibiotic (N = 44)		Inadequate empirical antibiotic (N = 12)		P-value
Initial antibiotic							
aminoglycosides	23	(41.7%)	20	(45.5%)	3	(25.0%)	0.154
carbapenems	20	(35.7%)	14	(31.8%)	6	(50.0%)	0.460
third-generation cephalosporin	16	(28.6%)	15	(34.1%)	1	(8.3%)	0.131
vancomycin	3	(5.4%)	3	(6.8%)	0	(0.0%)	1.000
Complication	14	(29.8%)	9	(24.3%)	5	(50.0%)	0.137
Length of stay (days)*	97	(48-213)	97	(49-214)	100	(30-189)	0.582
Cost expenses (Baht)*	231,071	(118,561-530,180)	279,322	(128,619-619,972)	180,373	(103,221-260,005)	0.274
Status of discharge							
improved	45	(80.4%)	37	(84.1%)	8	(66.7%)	0.186
death	11	(19.6%)	7	(15.9%)	4	(33.3%)	0.186

Abbreviations: N, number

*Data are presented as median (interquartile range)

Table 5 Antimicrobial susceptibility pattern from urine, blood, and cerebrospinal fluid specimens

Pathogens	Penicillin	Third-generation cephalosporin	Carbapenems	Piperacillin/ tazobactam	Quinolones	Trimethoprim/ sulfamethoxazole	Aminoglycosides	Vancomycin	Macrolides
Acinetobacter spp.	0%	60%	60%	60%	60%	0%	60%	-	-
Aeromonas hydrophilla	100%	100%	100%	100%	100%	100%	100%	-	-
Burkholderia spp.	50%	50%	100%	50%	50%	100%	50%	-	-
Enterobacter spp.	0%	45.5%	100%	72.7%	63.6%	63.6%	90.9%	-	-
Enterococcus faecalis	88.9%	0%	0%	0%	22.2%	0%	66.7%	100%	-
Enterococcus faecium	0%	0%	0%	0%	8.3%	0%	16.7%	100%	-
Escherichia coli	13.1%	78.4%	98.7%	97.4%	60.1%	40.5%	88.9%	-	-
Klebsiella pneumoniae	2.4%	43.9%	97.6%	65.9%	53.7%	43.9%	75.6%	-	-
Kluyvera ascorbata	0%	100%	100%	100%	100%	100%	100%	-	-
Morganella morganii	0%	100%	100%	100%	100%	100%	100%	-	-
Pantoea species	0%	100%	100%	100%	100%	100%	100%	-	-
Proteus mirabilis	33.3%	88.9%	100%	88.9%	66.7%	44.4%	66.7%	-	-
Pseudomonas spp.	0%	92.9%	85.7%	85.7%	85.7%	7.1%	78.6%	-	-
Salmonella spp.	50%	100%	50%	50%	100%	100%	0%	-	-
Serratia marcescens	0%	100%	100%	0%	100%	100%	100%	-	-
Staphylococcus coagulase negative	20%	-	-	-	6.7%	73.3%	46.7%	40%	6.7%
Streptococcus spp.	100%	100%	-	-	-	-	40%	100%	-

(-) is not done for drug susceptibility

DISCUSSION

The results of adequate and inadequate empirical antibiotics differed according to past studies. According to previous research, using inadequate empirical antibiotics was linked to higher 28-day death rates, higher inpatient mortality rates, and increased treatment failure rates[9-13,17-20]. Other research on people with bacteremia found a lack of evidence of higher fatality rates and longer hospital stays due to inadequate empirical antibiotics[17,20-22]. Inadequate empirical antibiotics did not increase the risk of 30-day death or UTIs recurrence in UTI patients[23]. Adults made up the majority of the comparative results between adequate and inadequate empirical antibiotics. There was less indication of a correlation among children. Thus, the purpose of this study is to examine the results of groups of children who received adequate and inadequate empirical antibiotics. According to this analysis, pediatric patients responded much better to adequate empirical antibiotics compared to inadequate empirical antibiotics. Additionally, patients who received inadequate empirical antibiotics experienced more complications, higher costs, and more in-hospital deaths, although this did not provide any conclusive information on the effects of these treatments on outcomes for a large group of patients. The duration of stay and frequency of transfers to the ICU, however, were the same for both groups. In this study, the bacteremia subgroup had a higher rate of complications, a longer duration of stay, and in-hospital deaths, but there was no definitive proof. The UTIs category only had clinically meaningful improvements when receiving adequate empirical antibiotics. This grouping also experienced higher complications, financial hardships, and in-hospital deaths but lacked conclusive proof. Aminoglycosides were the suitable option for UTI patients with a narrow spectrum antibiotic and strong sensitivity to *K. pneumoniae* and *E. coli*, according to this study, which showed that adequate empirical antibiotics improved clinical outcomes in pediatric patients with UTIs.

The data gathered for bacteremia, and UTIs, which are serious and frequent illnesses, were the study's main strengths. In addition, this study found that the present knowledge of pediatric patients was scant. The study's main

drawback, though, was the small patient population, particularly in cases of bacteremia. Therefore, more research should be done to compare the outcomes of pediatric patients with each disease who are given adequate and inadequate antibiotics.

Furthermore, antimicrobial susceptibility patterns at the pediatric ward of Vajira Hospital had few different from antibiotic susceptibility patterns from the National Antimicrobial Resistance Surveillance Center, Thailand (NARST) [24] such as *Acinetobacter spp., Burkholderia spp., Enterobacter spp., E.coli, and Salmonella spp.* is susceptible to third-generation cephalosporin about 60%, 50%, 45.5%, 78.4%, and 100%, respectively in Vajira Hospital, but in NARST, is susceptible to third-generation cephalosporin 35-63%, 87-97%, 64-72%, 55-65%, and 87-89%, respectively. The dissimilar antimicrobial susceptibility patterns between Vajira Hospital and NARST can be attributed to the fact that this study solely gathered data from the pediatric ward, which exclusively represents a tertiary care hospital. Hence, antimicrobial susceptibility patterns should be collected in each hospital.

CONCLUSION

Clinical outcomes among pediatric patients from adequate empirical antibiotics groups were reported the better outcomes. The mortality rates were not different. Nonetheless, appropriate empirical antibiotics are needed. To choose the best empirical antibiotics, antimicrobial susceptibility trends in hospitals must be observed. In UTI patients, amikacin is preferable options for empirical antibiotics.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

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DATA AVAILABILITY STATEMENT

The data that support this study are available on request from the corresponding author, Thiraporn Kanjanaphan.

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