PACIFIC JOURNAL OF MEDICAL SCIENCES

{Formerly: Medical Sciences Bulletin}

ISSN: 2072 – 1625

Pac. J. Med. Sci. (PJMS)

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ASSESSMENT OF ANTIBIOTICS PRESCRIBED TO PATIENTS WITH PERIPHERAL LYMPHADENOPATHYREFERRED FOR FINE NEEDLE ASPIRATION BIOPSY AT PORT MORESBY GENERAL HOSPITAL, PAPUA NEW GUINEA

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Runny title: Use of antibiotics amongst patients with peripheral lymphadenopathy

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ABSTRACT:
The pattern of antibiotics prescribed to patients with peripheral lymphadenopathy was assessed and compared with existing standard treatment guidelines (STGs) manual in Papua New Guinea (PNG). Information was obtained from patients referred to the Port Moresby General Hospital (PMGH) for fine needle aspiration biopsy by interviewing patients and reviewing patients' clinic attendance record books and referral letters. Of the 107 patients recruited for the study, 51 (47.7%) were prescribed antibiotics. Prescription data was obtained from 40 (78.4%) of the 51 patients. Amoxicillin which is recommended as a first line antibiotic for peripheral lymphadenopathy in PNG STGs was the preferred antibiotic by 18 (45.0%) of the 40 prescribers. There was high variability in the second line antibiotic selection, antibiotic combinations and treatment duration. The results highlight the need for on-going training on rational antibiotic prescribing by prescribers in Port Moresby.

Keywords: peripheral lymphadenopathy, Papua New Guinea, antibiotic prescribing, standard treatment guidelines
Submitted October, accepted November 2018

INTRODUCTION:

Peripheral lymphadenopathy is a common presentation at the primary healthcare setting and in most cases careful clinical examination reveals the primary pathology. The pathological causes are determined by disease epidemiology varying between tropical and non-tropical countries as well as between children and adults [1 – 5]. Mycobacterium tuberculosis infection (MTB) is a common

cause for peripheral lymph node enlargement in Papua New Guinea (PNG)where MTB is endemic [6,7] but lymph node enlargement can also be caused by skin infections, lymphoma, sexually transmitted infections (STIs) and dental infections [8,9]. The common causes for peripheral lymphadenopathy amongst children in PNG include acute infections, tuberculosis and malignancy [8]. In adults the frequent causes are MTB, Human Immunodeficiency Infection (HIV), skin or other soft tissue infections, filariasis, STIs, lymphoma and other malignancies [9]. In non-tropical countries acute viral infections and malignancies are a frequent cause for peripheral lymphadenopathy [5,10,11].

Empirical antibiotic treatment of peripheral lymphadenopathy is guided by local epidemiology of diseases. In PNG standard treatment guidelines (STGs) have been published to guide primary healthcare workers [8,9]. The guidelines are aimed at assisting primary healthcare workers (Community Health Workers, Nurses, Health Extension Officers) to treat common conditions before referral to a physician for further evaluation [12].Although the STGs are widely used by primary healthcare workers in PNG [13,14], Joshua et al [14]assessed the appropriateness of prescribing medicine using PNG STG sand found inappropriate prescribing to be 39.9% in children and 33.4% in adults involving both drug selection and dosage. The study also showed Amoxicillin was the common medicine prescribed across the three health facilities studied [14]. An observation by Samiak and Vince [13] also showed that 77% of health workers in urban clinics and rural health centres in PNG used the paediatric STGs for all conditions but only 51% followed the guidelines.

Despite increased antibiotic resistance there is arise in global antibiotic consumption. Klein et al [15] examined the pharmaceutical sales data of 76 countries and showed the antibiotic consumption (defined daily doses, DDD) increased by 65% and antibiotic consumption rate (DDDs per 1000 inhabitants) increased by 39% between 2000 and 2015. More importantly, the rise was driven by low- and middle-income countries (LMICs)where there was 114% increase between 2000 and 2015 [15,16].However, Abat et al [16] have argued that the increased antibiotic consumption in LMICs can be justified because the highest burden of infectious diseases is in these countries although antibiotics must be used with care. Laing et al [17] reviewed interventions proven effective in guiding medicine use in developing countries and listed 10 recommendations; one of these recommendations is the use of STGs. Standardising treatment approaches for infectious diseases also promotes judicious antibiotic prescription which reduces antibiotic resistance [17,18]. In PNG the paediatric STGs

have been in use throughout the health facilities for over 30 years and currently the manual is in its tenth edition [19,8]. The PNG Adult STG manual was last updated in 2012 and is in its sixth edition [9]. This paper describes the pattern of antibiotics prescribed to patients with peripheral lymphadenopathy referred to Port Moresby General Hospital (PMGH) for fine needle aspiration biopsy(FNAB). The observed prescribing patterns were also compared with the existing guidelines in the PNG STGs manual.

PATIENTS AND METHODS:

PMGH is the only tertiary referral hospital in PNG and is also the teaching hospital for the University of Papua New Guinea (UPNG) School of Medicine and Health Sciences (SMHS). It also serves as the referral hospital serving primary healthcare clinics and small private clinics in the National Capital District (NCD) in Port Moresby, PNG's capital city. The PMGH Pathology Department conducts FNAB clinics three times a week and processes patients referred for investigation. It is the only routine FNAB clinic within a public health facility in PNG.

Within the framework of a pilot project comparing diagnostic performance of the GeneXpert® tuberculosis system and microscopy in diagnosing tuberculous lymphadenitis [7], information on antibiotic use was obtained from patients referred for FNAB between November 2014 and August 2015.

The patients were recruited during one clinic day every week. Every third consecutive patient was selected. Both in-patients and out-patients with peripheral lymphadenopathy referred for FNAB were eligible for participation in the study. Verbal and written consent were requested from each of the selected patients or parents of children. Eligible consenting patients were clinically examined and interviewed using a pre-tested questionnaire. Basic demographic data, clinical history, site of lymphadenopathy and information on antibiotic prescribed were recorded. Patients' clinic attendance books and the referral letters were also reviewed and antibiotic name(s), dosage, frequency and treatment duration were recorded. Following accepted clinical practice in PNG, the paediatric population was defined as equal to or below 13 years of age and adult population as 14 years of age or above.

Ethical clearance and approval were obtained from the UPNGSMHS Research and Ethics Committee and from the PNG National Department of Health Medical Research Advisory Council (NDOH MRAC File No 54-6-2). The data obtained were tabulated in Microsoft Excel and analysed using the Excel data pack.

RESULTS:

Total of 1080 patients attended the PMGH FNAB clinic during the study period and information was obtained from 107 (9.9%) consenting eligible subjects.

Referring health facility:

A total of 13 health facilities were included in this study. Gerehu hospital had the highest referrals (29.9%) followed by referrals from PMGH wards (23.4%) and PMGH tuberculosis clinic (TBC) (11.2%). The other 10 referrals were from primary healthcare clinics and private practitioners (Table 1).

Demographic data:

Of the 107 patients there were 45 (42.1%) males and 62 (57.9%) females. Further analysis shows that there were 24 (22.4%) children, age range 1.9-13 years with mean age of 7.7±3.2 years and 83 adults, age range 16-70 years with mean age 31.5±11.7 years.

Duration of lymphadenopathy:

Among the 107 patients 58 (54.2%) had lymph node swelling for six months, 33 (30.8%) had lymph node swelling for more than six months before seeking medical attention and 16 (15.0%) presented to the clinic less than one month after lymph node enlargement.

Site of lymphadenopathy:

Cervical region was the commonly involved site among 88 (82.2%) patients, followed by inguinal among 7 (6.5%) patients, submandibular region among 3 (2.8%) patients. Other sites were axillary in 2 (1.9%) patients, preauricular in 2 (1.9%), supraclavicular in 2 (1.9%) and submental region also in 2 (1.9%) patients. One (0.9%) patient had a lump over the lumba-sacral region.

Antibiotic prescription pattern:

Among the 107 patients 51 (47.7%) had history of antibiotic use while 56 (52.3%) had no previous history of antibiotic use. Of the 51 patients given antibiotics, 11 (21.6%) revealed that they took antibiotics but there was no record in their clinic attendance books, the referral letter nor could they recall the name of the antibiotic they had taken. Hence, information on prescription pattern was obtained from 40 (78.4%) of the 51 patients. All 40 patients had antibiotic name recorded but dosage and frequency were not recorded in all of them. Only eight (20.0%) of the 40 patients had treatment duration recorded; of these, five days was the shortest antibiotic course (Co-trimoxazole 1 patient, Amoxicillin 2 patients, Erythromycin 1 patient), and two weeks was the longest treatment course (Chloramphenicol 1 patient).Two patients were on antibiotics for one week (Cefaclor, 1 patient, Chloramphenicol 1 patient) and one patient for 10 days (Chloramphenicol). Treatment duration was not obtained for 32 (80.0%) of the 40 patients.

Amoxicillin was the most common antibiotic prescribed (18/40; 45.0%), followed by Chloramphenicol (11/40; 27.5%), Co-trimoxazole (5/40; 12.5%), Flucloxacillin (3/40; 7.5%), Erythromycin (3/40; 7.5%), Cefaclor (2/40; 5%), Doxycycline (1/40; 2.5%) and Tinidazole (1/40; 2.5%). One patient was

commenced on tuberculosis treatment and referred for FNAB. Three patients (3/40, 7.5%) were prescribed two different antibiotics at the same time (Amoxycillin and Chloramphenicol, Chloramphenicol and Co-trimoxazole, Cefaclor and Tinidazole).Two patients were prescribed Amoxycillin initially and later prescribed Chloramphenicol after the completion of the initial treatment.

Table 1: Referring health facilities with number of referrals

REFERRING HEALTH FACILITIES	**N (%)**
Gerehu Hospital	32 (29.9)
PMGH wards	25 (23.4)
PMGH TBC	12 (11.2)
Six Mile PHC	9 (8.4)
Kaugere PHC	5 (4.7)
Badili PHC	4 (3.7)
Lawes Road PHC	4 (3.7)
Tokarara PHC	4 (3.7)
Kilakila PHC	3 (2.8)
Outside NCD	3 (2.8)
Private GP	3 (2.8)
PMGH specialist clinics	2 (1.9)
Nine Mile PHC	1 (1.0)
Total	**107 (100)**

TBC = TB clinic, PHC = primary healthcare clinic,
NCD = National Capital District, GP = general practitioner
.

DISCUSSION:

Evaluation of peripheral lymphadenopathy begins with detailed clinical history and careful physical examination and in most cases the primary pathology is usually identified from the clinical history and physical examination [20,21,10,11,5]. The history should contain age of the patient, onset and duration of lymphadenopathy, associated symptoms, drug history, occupation, place of residence and possible environmental exposures, sexual history, past medical history and family history. The physical examination characterises the anatomical features of lymphadenopathy such as anatomical location of lymph node enlargement, size, localised or generalised, single or multiple nodes, mobile or fixed, feature of overlying skin indicating possible inflammation, tender or non-tender, general consistency and end with careful examination of the primary draining site. Acute onset of lymphadenopathy associated with fever and a

sore throat may indicate infections whereas slow progressive non-tender enlargement suggests possible malignancy [11]. Head and neck region is a common site for peripheral lymphadenopathy so a careful inspection of the scalp and oral cavity should be done. Inguinal lymph node enlargement may suggest STIs or malignancies [10,11,5] but the lower limps including the toes and soles of the feet must be examined as well. An enlarged liver or spleen may suggest malignancy or chronic infections.

The PNG paediatric STG outlines a clear and concise management approach to lymph node enlargement in PNG children and broadly categorises possible causes as acute infections, tuberculosis and malignancy [8]. It also recommends careful visual assessment of the mouth, teeth and ears for evidence of infection if there are enlarged neck glands [8]. The recommended initial antibiotic is Amoxicillin for two weeks but if cellulitis is present Cloxacillin is the antibiotic of choice for two weeks [8]. An added benefit is that the paediatric STG has drug dosages calculated and presented in tables making it easy for fast and easy reference. There is also a brief description on the characteristics of lymphadenopathy that may be used to differentiate tuberculosis from possible malignancy [8]. These features ensure that the PNG Paediatric STG is able to be used by the lowest cadre of health workers in rural health facilities in PNG [13] and reflects over 30 years of experience developing the STG [19].

Lymphadenopathy management guidelines in the PNG Adult STG has more details compared to the PNG Paediatric STGs [8,9]. The additional information reflects the primary intended users in PNG and these are Doctors and Health Extension Officers. Indications for referral for further evaluation are suspected malignancy, no improvement after initial treatment and bleeding tendencies [8,9]. A notable difference between the adult and paediatric STGs is that the PNG Adult STG does not give antibiotic options. It is left to the health worker to make the appropriate antibiotic selection after identifying the primary pathology. The PNG Adult STG however, is more specific in the pathology investigation options, one of which is FNAB, an element missing in the paediatric STGs [8,9].

The results of this study demonstrate that the PNG STGs are useful in choosing initial antibiotic to treat patients with enlarged lymph nodes as indicated by Amoxicillin being the most common first choice antibiotic. It usually takes over one month for most patients to present to clinics in Port Moresby and this may reflect a lack of awareness among the public that MTB can start as a lymph node swelling. There may also be other barriers to accessing primary healthcare services in Port Moresby that need further investigation. Although Cloxacillin is mentioned as a second option antibiotic choice in the PNG Paediatric STG, only three patients were given this medicine, of which two had associated cellulitis. The other

antibiotics that were prescribed are not recommended in the STGs. Knowledge about local antibiotic susceptibility patterns are useful in deciding antibiotic choice but in PNG such data is scanty because of poor microbiology laboratory infrastructure [7]. A recent study done in Kundiawa hospital showed 79% of children from the community that had no prior history of antibiotic use and were diagnosed with osteomyelitis had Methicillin-Resistant Staphylococcus Areus (MRSA) suggesting community acquired MRSA [22]; indicating the need for on-going antibiotic susceptibility testing surveillance in PNG. Inappropriate use of antibiotics is increasing in developing countries [23,17]and this practice has been noted in PNG as well [22]. Although antibiotics recommended in PNG STGs are also influenced by cost of medicine, cadre of health worker prescribing, clinical experience and accessibility to the drug; future STGs revisions need to consider the drug susceptibility pattern of the local area. The wide choice of antibiotics prescribed with varying combinations is a cause for concern and highlights a need for on-going training of healthcare workers on the use of STGs and rational antibiotic prescribing in PNG.

CONCLUSIONS:

Amoxicillin appears to be a preferred first choice antibiotic for patients with peripheral lymphadenopathy by healthcare workers at primary healthcare clinics in Port Moresby. However, there is high variability in the second line antibiotic selection, antibiotic combinations and treatment duration. The results highlight the need for on-going training on the use of STGs in PNG and rational antibiotic prescribing.

ACKNOWLEDGMENTS:

The authors would like to acknowledge the assistance of all the technical and support staff at the Pathology Department, Port Moresby General Hospital, Papua New Guinea.

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