An-Najah National University
Faculty of Graduate Studies

Problems Associated with Reconstitution, Administration, and Storage of Antibiotic Suspensions for Pediatrics in Nablus City-Palestine

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Dedication

To my family

Specially my mother, father, husband, and my little daughter

Acknowledgement

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Thanks to my family with all my love, specially my mother, father, husband, and Uncle Mohamad Sbeeh, who stood with me throughout my study and provided me with psychological support and encouragement**.**

الإقرار

أنا الموقعة ادناه ، مقدمة الرسالة التي تحمل العنوان:

Problems Associated with Reconstitution, Administration, and Storage of Antibiotic Suspensions for Pediatrics in Nablus City-Palestine

المشاكل المتعلقة بحل واعطاء وتخزين معلقات المضادات الحيوية للأطفال في مدينة نابلس/فلسطين

أقر بأن ما اشتملت عليه هذه الرسالة إنما هو نتاج جهدي الخاص، باستثناء ما تمت الاشارة اليه حيثما ورد، و أن هذه الرسالة كاملة، أو أي جزء منها لم يقدم من قبل لنيل أي درجة أو لقب علمي أو بحثي لدى أي مؤسسة تعليمية أو بحثية اخرى

Declaration

The work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name:	.....	اسم الطالب:
Signature:	.....	التوقيع:
Date:	.....	التاريخ:

Abbreviations

Abbreviations	Meaning
MoH	Ministry of Health
CDC	Center of Disease Control
URTI	Upper Respiratory Tract Infection
USP	United States Pharmacopeia
EP	European Pharmacopeia
QC	Quality Control
OTC	Over The Counter
AOM	Acute otitis media
AAP	American Academy of Pediatric
AAFP	American Academy of Family Physicians
IM	Intramuscular
PCN	Penicillin
BID	Twice Daily
TID	Three Times Daily
PO	Orally
ICH	International Conference of Harmonization
BP	British Pharmacopeia
HPLC	Highly Performance Liquid Chromatography
NA	Not Available
PPI	Patient Package Insert

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Abstract

Pediatric infectious diseases either viral or bacterial remain a very common community health problem; in bacterial infection an antibiotic is the drug of choice, to achieve therapeutic effect and prevent treatment failure antibiotics must be properly used. The objective of this study is to evaluate the appropriateness of antibiotic suspensions use for pediatrics among Palestinian mothers including their reconstitution, dose administration, duration, and storage condition. This study was a questionnaire based cross sectional descriptive study. It was conducted at Ministry of Health (MoH) primary health care Al-Wosta clinic and a pediatric private clinic in Nablus city between 22 January, and 22 March 2013. A sample of400 mothers, 200 visited MOH, and 200 visited the private clinic were met and asked to answer a face to face questionnaire. The results showed that most common pediatric infections were bronchitis 110 (27.5%), throat infection (pharyngitis) 110 (27.5%), and otitis media 108 (27.0%), the most commonly prescribed antibiotic was amoxicillin, amoxicillin and clavulanic acid, and azithromycin. Regarding mothers'

practice 347 (86.8%) of mothers told that they read instructions, 311 (77.8%) could understand manufacturer instructions, and 176 (44.0%) of mothers asked pharmacists for advice if they didn't understand the instructions. In order to prepare antibiotic suspension 302 (75.5%) used boiled then cooled tap water, and 192 (84.4%) of mothers used syringe to measure the needed amount of water, and 304 (76.6%) of mothers added water in two steps, 392(98.0%) of mothers claimed that they shook the drug bottle before used. Regarding dose administration, 313 (78.2%) considered syringe as the most accurate tool for dose administration, most of mothers told that they gave drug dose with major meals when direction were to give three times daily. About use duration 6 (1.5%) of mothers claimed that they used antibiotic suspension after 2 weeks, and 26 (6.5%) gave left over antibiotic suspension to another child. One hundred seventy seven (44.2%) of mothers told they stored dry powder antibiotic in medicinal cabinet, while 226 (56.5%) of them stored suspension in refrigerator.

Although our results reflect good knowledge about antibiotic suspension use between Palestinian mothers there is a room for improvement. The pharmacists are recommended to explain directions to mothers and confirm on them by writing, to supply them with syringe with suitable calibration for dose administration, and to tell them about storage condition and duration of use.

Chapter one

Introduction

Chapter One

Introduction

1.1 Background

According to the Center of Disease Control (CDC) antibiotics are drugs that fight infections caused by bacteria by killing or inhibiting their growth. Alexander Fleming discovered the first antibiotic, penicillin, in 1928. After the first use of antibiotics in the 1940s, they transformed medical care and dramatically reduced illness and death especially among elderly and children from infectious disease. Antibiotic include penicillins, cephalosporins, macrolides, sulfa drugs, aminoglycosides, tetracyclines and quinolones. It is important to have rational approach to antibiotics use as improper use can cause bacterial resistance (Center of Disease Control, 2013).

Pediatric infectious diseases either viral or bacterial remain a very common community health problem with an average occurrence of 6-8 times a year, upper respiratory tract infections (URTI) represent the most common illnesses in pediatric outpatient setting. Most children have 4-6 acute URTI a year (Chan and Tang, 2006b), they include otitis media, pharyngitis, and sinusitis (Wells et al., 2009). When infection is caused by bacteria then antibiotic is the drug of choice, most of newborns, infants, and preschool children receive antibiotic in the form of dry powder for reconstitution to suspension before administration (McMahon et al.,

1997b). To achieve therapeutic effect, prevent treatment failure and bacterial resistance antibiotics must be properly used. Antibiotics prescribed for infants and young children are usually dispensed as oral suspensions because of children's inability to swallow tablets or capsules; unavailability of certain antibiotics in a chewable tablet form; and the discomfort, expense, and associated risk of antibiotic injections(Dusdieker et al., 2000). Appropriate use of antibiotic suspensions includes (i) the correct reconstitution, (ii) concentration, (iii) dose administration, (iv) duration of treatment course, and(v) storage conditions(Dusdieker et al., 2000).

Although oral suspension is an appropriate formulation for pediatric age group, dose measuring accuracy is the challenge. Dose accuracy of pharmaceutical suspension depends on homogeneity of the dispersion and dose delivery device, if the medicine comes in suspension form, it should be shaken well before use. Suspension disadvantage is physical instability and particles sedimentation resulting in lack of dose uniformity, this may lead to dosing error if the preparation is not completely re-suspended before measuring the dose (McMahon et al., 1997a). In fact, the United State Pharmacopeia (USP), European Pharmacopeia (EP), and other regulatory bodies require a number of quality control (QC) tests in order to assure the homogeneity of the produced suspension and accordingly uniformity of content and dose. Manufacturers carry out several trials during reformulation and formulation in order to satisfy these requirements.

Moreover they carry out several pharmacopeial and technological QC tests such as particle size of the active ingredient, sedimentation rate, sedimentation volume, viscosity, flocculation, and etc. The most important objective of these tests is to achieve homogenous suspension with dose uniformity (European Medicines Agency, 2000).

Accordingly oral liquid medications usually come with at least one of dose delivery devicessuch as; (i) medication cup,(ii) dropper, (iii) calibrated spoon, and (iv) syringe(Booth and Whaley, 2010, Ogden, 2007). Household silverware spoons should not be used for delivery of medications as they are not accurate. In fact these spoons are usually available in different size. Syringes have many advantages; they are accurate even for small volumes, they are easy to use, and more importantly they are easy to be cleaned. Regarding dosing cups dosing error are common with them, so as a general role they should not be used for doses less than 5 ml even if the cup has calibration less than 5 ml(Booth and Whaley, 2010, Kaneshiro, 2009).

Storage conditions are also important, manufacturer instructions should be followed exactly, manufactures' instructions recommend that some antibiotic suspensions need refrigerator, while for other antibiotic suspensions we need to avoid refrigerator. In addition climate condition should be taken in consideration for dry powder antibiotics, and antibiotic suspensions that don't need refrigerator.

Antibiotics are misused because many patients do not take them according to their doctor or pharmacist instructions. They may stop taking their antibiotics too soon, before their illness is completely cured. Some patients save unused medicine and take it later for another illness, or pass it to other ill family members or friends and some patients go to the pharmacy and take the antibiotics as an over the counter (OTC) drug (Al Khalil et al., 2005).

Mothers' knowledge and practice regarding antibiotic reconstitution, dose administration, and storage were assessed; results showed that too few mothers have a correct practice regarding to (i) reconstitution, (ii) dose administration, (iii) storage condition without assistance (Iornguru et al., 2010).

1.2 Oral pharmaceutical dosage forms:

Drugs are presented in wide variety of dosage forms, even same drug may be presented in several dosage forms. It is the role of pharmacists to know the different properties of these dosage forms in order to give patient the most appropriate formulation (Winfield and Richards, 2004).

The oral rout of drug administration is the most convenient for patients (Helliwell and Taylor, 1993). There are solid and liquid oral dosage forms, solid dosage form such as capsules, tablets, while syrup, elixir, and suspension are liquid oral dosage forms (Shargel et al., 2004).

1.2.1 Solid oral dosage form:

a- Tablets:

Tablets are the most commonly used solid dosage form (Shargel et al., 2004). There are several types of tablets such as (WHO Pharmacopeia, 2013):

1- Uncoated tablets:

The release of active ingredients from these types of tablets is unmodified. They are formed by compression and have no special coating.

2- Coated tablets:

In this type of tablets a core surrounded by continuous layer as sugar coated tablets or film coated tablets, such as Augmentin film coated tablet

3- Effervescent tablets:

Effervescent tablets are uncoated tablets generally containing acid substances and carbonates or hydrogen carbonates that react rapidly in the presence of water to release carbon dioxide. They are intended to be dissolved or dispersed in water before administration. Effervescent tablets, should be stored in tightly closed containers or moisture-proof packs and may require the use of separate packages containing water-adsorbent agents, such as silica gel.

4- Chewable tablets:

Chewable tablets are usually uncoated. They are intended to be chewed before being swallowed. Chewable tablets are especially useful in formulation for children, as they are commonly used for multivitamins and antibiotics such as Augmentin 125,200,250,and 400 mg chewable tablet (Shargel et al., 2004).

5- Tablets used in oral cavity:

Tablets for use in the mouth are usually uncoated. They are usually formulated to give a slow release and local action of the active ingredient(s) (for example, compressed lozenges) or the release and absorption of the active ingredient(s) under the tongue (sublingual tablets) or in other parts of the mouth (buccal) for systemic action.

6- Modified release tablets:

Modified-release tablets are coated, uncoated or matrix tablets containing excipients or prepared by procedures which, separately or together, are designed to modify the rate, the place or the time of release of the active ingredient(s) in the gastrointestinal tract. Modified release tablets include: (i) Sustained-release tablets that are designed to slow the rate of release of the active ingredient(s) in the gastrointestinal tract. (ii) Delayed-release tablets are intended to resist gastric fluid but disintegrate in intestinal fluid, such as Klacid XL tablet.

Tablets should be kept in well-closed containers and protected from light, moisture, crushing and mechanical shock.

b- Capsules.

Capsules are solid dosage forms with hard or soft shells. They are of various shapes and sizes and contain a single dose of one or more active ingredients. They are intended for oral administration. The different categories of capsule include :(i) hard capsules, (ii) soft capsules, (iii) modified-release capsules (including delayed-release capsules (gastro-resistant/enteric capsules) and sustained-release capsules (extended-/prolonged-release capsules).

Capsules should be kept in well-closed containers. They should be protected from light when required, and from excessive moisture or dryness, and should not be subjected to temperatures above 30 °C.

1.2.2 Liquid oral dosage forms:

a- Solutions:

Solutions are homogenous mixtures of solute/s dissolved in one or more solvents. Usually solid dissolved in liquid which is aqueous, oily, or alcoholic. Oral solutions have several advantages over solid dosage form as (i) easy to swallow, (ii) readily absorbed from gastrointestinal tract, (iii) preferred dosage form in children and elderly. In addition solutions have advantages over suspensions that the medication is dispersed homogenously throughout the formulations, so don’t need to shake the bottle before use. The dose usually administered as volume of multiple of 5 ml as “give the patient 5 ml medicine spoon” the term “teaspoonful” and

“tablespoonful” should not be used as expression for oral liquid dose as they are not accurate measures. Different forms of oral solutions such as (i) syrups, (ii) elixirs, (iii) tinctures, and (iv) oral drops (Kennedy, 2004a).

b- Suspensions:

Suspensions are dispersed system in which one substance (dispersed phase) is distributed in particulate form throughout another (continuous phase) (Kennedy, 2004b). Oral suspensions may show a sediment which is readily dispersed on shaking to give a uniform suspension which remains sufficiently stable to enable the correct dose to be delivered(WHO Pharmacopeia, 2013). So it is important to add label for suspension “Shake well before use” shaking the bottle will redisperse the medication and ensure that patient can measure an accurate dose. Another label needed to add “store in a cool place” as stability of suspensions may be adversely affected by temperature flocculation so suspension made from reconstitution of dry powders may need to be stored in refrigerator. In addition, reconstituted suspensions will have relatively a short shelf life so when used, patient be sure that it is freshly prepared (Kennedy, 2004b).

1.2.3 Pediatric dosage forms:

Pediatrics include: newborns, infants, toddlers, preschoolers, school age children, and adolescents. So for a given drug it may be necessaryto develop more than one formulation to provide access to all pediatric groups. Pediatric formulations include (i) liquid preparation as solutions

and suspensions, (ii) chewable tablets, (iii) fast dissolving tablets, and (iv) powders (Maldonhauado and Schaufelberger, 2011).

1.3 Common infections that require antibiotics in children:

1.3.1Otitis media:

Otitis media is an inflammation of the middle ear usually follows a viral upper respiratory tract infection that causes Eustachian tube dysfunction and mucosal swelling in the middle ear. The causative organisms are mainly Steptococcal pneumonia, Haemophilusinfluenzae, and Moraxella cataralis. Clinical presentation involves otalgia, fever, irritability, and hearing loss. These often follow cold symptoms of runny nose, nasal congestion, or cough. Treatment includes reduction in sign and symptoms, eradication of infection, and prevention of complications as hearing loss (Wells et al., 2009).

1.3.2Pharyngitis:

Pharyngitis is an acute infection of oropharynx or nasopharynx, viruses as rhinovirus, coronavirus, and adenovirus are the most common cause of acute pharyngitis, while Group A Streptococcus is the most causative bacterial microorganism. Clinical presentation includes sore throat, pain on swallowing, and fever (Wells et al., 2009).

1.3.3 Sinusitis:

Sinusitis is an inflammation or infection of paranasal sinus mucosa, the majority of these infections are viral in origin, bacterial sinusitis can be categorized into acute; disease lasts less than 30 days with complete resolution of symptoms caused by Streptococcal pneumonia and Haemophilusinfluenzae, and chronic; in which the episode of inflammation last more than 3 months with persistence of respiratory symptoms, caused by polymicrobials including anaerobes (Wells et al., 2009).

Although most URTI are caused by viruses antibiotics are frequently prescribed(World Health Organization, 1995). Inappropriate use of antibiotics leads to economically and clinically preventable negative consequences including unnecessary adverse effects, increase mortality and morbidity from treatment failure, wasting healthcare resources, and increase the emergency of bacterial resistance (Kenealy and Arroll, 2013).

When a child has bacterial infection then an antibiotic is the drug of choice. Selection of the proper anti-microbial therapy depends upon knowledge of the most likely causative organism and susceptibility patterns in a particular region. The most narrow spectrum antibiotic that covers the likely organisms is preferred. In addition, cost, taste, and dosing schedule should be taken into account. It is important to make sure the patient has no allergy or sensitivity to the class of antibiotics intended to use (Uchicago, 2006).

1.4 Treatment for common bacterial infections in children:

1.4.1 Acute otitis media treatment:

Based on CDC recommendations, treatment of acute otitis media (AOM) depends on whether the patient falls into the high or low risk category for resistant otopathogens. The primary risk factors for resistant bacteria are daycare attendance and antibiotic use in the preceding 30 days. For low risk patients, first-line therapy is low dose amoxicillin (40-45 mg/kg/day) or high dose amoxicillin/clavulanic acid (80-90/6.4mg/kg/day). For high risk patients (day care or antibiotics within 30 days), first line therapy is high dose amoxicillin/clavulanic acid, high dose amoxicillin (80-90 mg/kg/day), or cefuroxime. AAP/AAFP (American Academy of Pediatrics, American Academy of Family Physicians) guidelines advise that if the patient is 6 months – 2years and the diagnosis of AOM is uncertain, or > 2 years with mild symptoms or uncertain diagnosis, it is acceptable to treat symptomatically for 48-72 hours, and begin antibiotic therapy only if symptoms do not improve. Alternative therapies: For patients with true allergies to penicillin, first line therapy is azithromycin 10 mg/kg x 1 day, followed by 5 mg/kg x 4 days. For low risk patients who fail initial antibiotic therapy at 72 hours, the next line of therapy is high dose amoxicillin/clavulanic acid, cefuroxime, or ceftriaxone intramuscular (IM for 3 days). For high risk patients who fail initial therapy, the next line is clindamycin or 3 days of IM ceftriaxone. For treatment failures farther out, with recurrent symptoms from 10-28 days

after initial treatment, low risk patients can be treated with high dose amoxicillin/clavulanic acid, cefuroxime, or IM ceftriaxone. High risk patients can be treated with high dose amoxicillin/clavulanic acid, cefuroxime, or IM ceftriaxone. Tympanocentesis should be considered for high risk patients who have either early or late treatment failure(Lieberthal et al., 2013).

1.4.2 Group A Strep Pharyngitis treatment:

Penicillin V is the recommended treatment. For children < 27 kg (250 mg) three times daily (tid). For children > 27 kg (500 mg) twice daily (bid) or tid.

Alternative therapy: For patients allergic to penicillin (PCN), erythromycin 20-40 mg/kg divided in 2-4 doses is first line therapy. In patients with whom compliance is an issue, a onetime dose of IM penicillin G can be used, 600,000 unit for < 27 kg, 1.2 million unit for > 27 kg. Length of treatment: Ten days of treatment are necessary to prevent the development of rheumatic fever (Uchicago, 2006).

1.4.3 Acute bacterial sinusitis treatment*:*

First line therapy: For mild to moderate symptoms in a child without recent antibiotic therapy and not in daycare, first line therapy is amoxicillin 45-90 mg/kg/day divided bid. For children with severe symptoms (3-4 days of fever of > 102° and purulent nasal discharge), in daycare, or recently

treated with antibiotics, first line therapy is high dose (90 mg/kg/day amoxicillin., 6.4 mg/kg/day clavulanic acid) divided bid.Alternative therapies: For patients with allergies to penicillin, first line therapy is azithromycin 10 mg/kg kg x 1 day, followed by 5 mg/kg x 4 day, or clarithromycin 15 mg/kg/day divided bid. For patients who fail amoxicillin, high dose amoxicillin/clavulanic acid is the next step. If a patient is vomiting, a dose of IM ceftriaxone can be given, 50 mg/kg, and then PO antibiotics started in 24 hours if the patient has improved.

Length of treatment: There are a variety of recommendations for length of treatment for sinusitis, ranging from 10-28 days. Treating for 10-14 days is common, but there is no strong evidence for this (Wald et al., 2001, Uchicago, 2006).

Depending on signs, symptoms, and specific physical examination doctors decide if the child has bacterial or viral infection, which affect drug prescription patterns. When a child has bacterial infection then antibiotic is the drug of choice. To achieve therapeutic effect and prevent treatment failure, antibiotics must be properly used. The appropriate use includes correct reconstitution, dose administration, and storage condition (Dusdieker et al., 2000).Mothers should read and follow the manufacturer's instructions for antibiotic suspension reconstitution carefully including: type and amount of water that should be added, appropriate device for measuring the amount of water, and steps for water addition.

1.5 Significance of the study:

There are limited data about problems associated with the reconstitution, administration, and storage of antibiotic suspensions among pediatrics in Palestine. It is important to evaluate the appropriate use of antibiotics in pediatrics in order to prevent misuse and overuse of antibiotics that lead to therapeutic failure, bacterial resistance, hospital admission, use of intravenous antibiotics, and even death. Findings can help in developing educational programs and improve mothers' counseling to avoid improper use of antibiotics in pediatrics.

1.6 Objectives:-

1.6.1 General objective:

The aim of this study is to evaluate the problems associated with reconstitution of dry powder antibiotic, dose administration and storage condition for antibiotic suspensions used for pediatrics among Palestinian mothers.

1.6.2 Specific objectives:

1- To assess mothers' ability for dry powders antibiotics reconstitution.
2- To assess mothers' ability for1`2 dose administration of antibiotic suspensions.
3- To assess how and where mothers store reconstituted antibiotic suspensions.
4- To find any possible relationship between mothers' practices and a group of sociodemographic factors.

Chapter Two

Literature review

Chapter two

Literature review

2.1 Pharmaceutical solvents:

Solvent or vehicle is the medium which contains the ingredients of medicine. The type of solvents depends on properties of active ingredients. There are different types of vehicles including:

(i) Water:

Water is the vehicle for most pharmaceutical preparations as it is widely available, inexpensive, non-toxic, non-irritant, and it is a good solvents for many ionized drugs. There are different types of water:

a- Potable water is drinking water; its chemical composition may include mineral impurities which would react with drugs as calcium carbonate in hard water.

b- Purified water is prepared from suitable potable water with suitable treatment as distilled water that has been prepared by distillation.

c- Water for preparations is potable water that boiled then cooled, which can be used in oral or external preparations which are not intended to be sterile.

d- Water for injections is pyrogen- free distilled water, sterile for parenteral use.

(ii) Other vehicles:

a- Syrup BP is a solution of 66.7% v/v sucrose in water. It will promote dental decay and is unsuitable for diabetic patients. Sugar free solvents have replaced glucose solvent as sorbitol, mannitol, and xylitol.

b- Alcohol (ethanol) is rarely used for internal preparations but is useful for external preparations.

c- Glycerol may be used alone as a vehicle in some external preparations. It is viscous and miscible both with water and alcohol. It may be added stabilizerand sweetener in internal preparations. In concentrations above 20.0% v/v it acts as a preservative.

d- Propylene glycol is a less viscous liquid and better solvent than glycerol (Kennedy, 2004a).

2.2 Liquid medications measuring tools and accuracy:

Liquid medications usually come with dose measuring device as (i) medicine cup, (ii) dosing spoon, (iii) dropper, or (iv) syringe (Charles, 2008). One common error with liquid medications involves taking wrong dose too much or too little, this occurs due to confusion between different dose measurements (Institue for safe medication practice, 2013)**.** To avoid dose measuring error (i) the dosing device that comes with the medicine should be used. If dosing device doesn't come pharmacist should be asked to recommend one, (ii) household measuring device should never be usedas

they are inaccurate, (iii) users need to look carefully at the line on measuring tool (Institue for safe medication practice, 2013, Charles, 2008).

2.3 Studies related to the reconstitution of dry powder antibiotic, dose administration and storage conditions of antibiotic suspensions:

Patient misunderstanding of label instructions is common, that leads to medication error and less effective medication (Davis et al., 2009b). A Malaysian study: showed that patients did not follow the instruction because they did not understand them. Only 21.4% of 205 patients were able to comprehend complete antibiotic instructions(Hassan et al., 1994).

A Palestinian study that investigated utilization of antibiotics from a group of pharmacies in Nablus city showed that regarding antibiotic suspensions for children, 3.5% respondents said that the quantity of water added to prepare should not be a specific quantity, 10.1% could not decide or they had no idea whether it is specific or not (Al Khalil et al., 2005). In another study 25.5% of 107 mothers knew the crucial importance of viewing the lower meniscus of water at eye level to obtain the correct final volume of drug(Iornguru et al., 2010).

For optimal reconstitution, pharmacies use distilled or purified water to reconstitute powders for suspension. Tap water is unsuitable for pharmaceutical formulation due to its high content of calcium and other minerals that are incompatible with the components of suspension. The correct procedure is to tab the bottle few times first to loose the powder,

then to add approximately half volume of water, shake the bottle vigorously and finally to add the remaining volume of water, and shake well (Technician Training Tutorial, 2011).

In addition to optimal reconstitution, dose administration method should be taken into consideration to administer the right dose. Antibiotic dry powder products contain enclosed dosing devices as syringe, medicinal spoon, or medicine cup. It is important to use a suitable device to have the correct dose. In a study from Ghana, 95.0% of people used household spoons in dosing oral liquid medications, and 39.0% actually preferred the enclosed dosing devices, in that study oral syringe was the most common accurate dosing device, while the medicinal cup was relatively accurate if used correctly(Tbayor and Lkipo, 2010).

In another study 80.0% of 100 parents used household teaspoon to measure acetaminophen syrup dose. The volume of these spoons were measured using a syringe, the average volume was from 1.5-5 ml, 79.0% parents assumed that household teaspoon contains 5ml of acetaminophen (Hyam et al., 1989)

Proper use of antibiotic suspensions includes proper storage also. The storage condition of reconstituted antibiotic suspensions must be tightly controlled as drugs are chemicals that may react with external environment such as temperature, humidity, and light. This reaction may lead to change in physical properties as color, or drugs degradation that

results in reduction or loss of activity or cause adverse effects on patients' health(Obitte et al., 2009). In fact the International Conference on Harmonization (ICH) has set of guidelines for the studying of the stability of active ingredients of the pharmaceutical products. A study to evaluate storage, utilization and cost of drug products in Palestinian households showed places that 40.6% of drugs were stored in pharmacy cabinet, 16% were stored in the refrigerator, 43.4% were stored in several places around the house (kitchen and bed rooms), in addition 32.5% of drugs were stored not in original container and approximately 70% of the reconstituted suspensions were stored outside the refrigerator (Sweileh et al., 2010).

Another study from Durban showed that 49.0% of 100 patients stored medication in bedroom, 44.0% stored in common area in house, and 7.0% stored medication in car(Naidoo et al., 2006). Improper storage of suspension may affect their stability, for example antibiotic suspension as amoxicillin-clavulanic acid must be refrigerated at (2-8 **°C**) and should be used within 2 weeks to maintain its stability and antimicrobial activity. Validated HPLC (highly performance liquid chromatography) method showed that reconstituted amoxicillin-clavulanic acid suspension that was stored at room temperature (27-29 **°C**) was stable for 5 days only (Peace et al., 2012). The therapeutic effect of amoxicillin suspension decreased after 14days even if stored in refrigerator temperature (2-8 **°C**)(Naidoo et al., 2006). Others antibiotics should be stored out of the refrigerator, since cooling may affect the viscosity of the reconstituted formulation.

Dry powder antibiotics are also affected by storage conditions, in summer heat in some places can reach up to 50°C, this is higher than U.S Pharmacopeia's definition of room temperature (20-25**°C**) that affects dry powder antibiotic stability (Nwokoye et al., 2012).Accordingly, ICH divided the world into 4 stability zones, as shown in (table 1.1) (ICH, 2013)

Table (2.1): ICH stability zones

Zone	**Type of climate**	**Temperature**
Zone I	Temperate zone	21ºC ± 2ºC
Zone II	Mediterranean/subtropical zone	25ºC ± 2ºC
Zone III	Hot dry zone	30ºC ± 2ºC
Zone IV	Hot humid/tropical zone	30ºC ± 2ºC

2.4 Studies related to Patient Package Inserts (PPIs):

PPIs are the most readily available form of written information on drugs for patients. They should be clear, understandable to general population to achieve safe and effective use of medication and avoid medication error (AL-Ramahi et al., 2012).

A Palestinian study showed that 100 (45.0%) of 222 consumers reported that they always read information in the leaflet of the drug package, 65 (29.3%) said that they read PPI most of the time, 41 (18.5%) said that they read it sometimes, and only 16 (7.2%) of participants said that they rarely or don't read PPI. Regarding to find front size in PPIs suitable for reading 39.5% of consumers answered with yes. Arabic language for PPIs was preferred by most consumers (89.8%). In addition 94 (42.3%) of consumers found information in PPIs useful and enough.

While 167 (74.0%) of consumers thought that information in PPIs need to be improved (AL-Ramahi et al., 2012).

Another Palestinian study thatinvestigated the attitude of the Palestinian public to patient package insert PPI showed 51.7% of 371 participants said that they read PPI, but either find it vague or rise their fears and concerns(Sweileh et al., 2004).

Others studies have shown that symbols and pictograms in the patient package insert help the patient understand and use the drug correctly(Bernardini et al., 2000).In addition there is a need to review and re-write the language of most PPI in the Palestinian market to make them easily readable and not to contain unnecessary or over-estimated language especially in the side effect section. It should be emphasized that PPI should not replace patient-pharmacist communication (Sweileh et al., 2004).

Chapter Three

Methodology

Chapter three

Methodology

3.1 Setting:

This survey was carried out at a governmental primary healthcare center Al-Wosta clinicand a pediatric private clinic in Nablus city between 22, January2013 to 22, March2013.

3.2 Population of the study:

All mothers who visited the selectedAl-Wosta governmental primary healthcare centerand a pediatric private clinic in Nablus city during the study period and meet the inclusion criteria were asked to participate in the study.

Inclusion criteria: mothers who came in follow up visit for their childrenwho used reconstituted oral antibiotic suspension in the previous visit. Depending on Al-Wosta clinic registrations and computerized system in the private clinic.

3.3 Sample size:

The minimum sample size for this study was calculated to be 384 mothers based on Roasoft sample size calculatoras Nablus city population is around 200 000, margin of error that can be accepted is 5.0%, and confidence level is 95.0% . So the target was 400 mothers.

3.4 Data collection:

Data collection tool was a face to face questionnaire designed based on extensive literature review of similar studies (Al Khalil et al., 2005, Chan and Tang, 2006b, Bayor et al., 2010, Elberrya et al., 2012). The questionnaire included information about sociodemographic characteristics of study subjects, appropriate reconstitution, administration and storage of antibiotic suspensions (Appendix 1,2). The study protocol was authorized by the Institutional Review Boards (IRB) (Appendix 3) and Ministry of Health (Appendix 4) before initiation of this study.

To evaluate the mothers' practice, the manufactures’ instructions on drug box and package insert were reviewed as in (table 3.1) and were compared with mothers’ practice.

Table (3.1): Instructions for the most commonly prescribed antibiotic suspensions

	Antibiotic	How to reconstitute	Steps to add water	Storage of dry powder	Storage of reconstituted suspension
B lactam (penicillin)	Amoxitid 250 mg (Amoxicillin)	Add 44 ml of water	2 steps each step approximately half total amount	Store the drug at room temperature below 30°C	Keep the suspension refrigerated for 10 days
	Amoxitid 400 mg (Amoxicillin)	Add 46 ml of water	2 steps each step approximately half amount	Store the drug at room temperature below 30°C	Keep the suspension refrigerated for 10 days
B lactam (penicillin)	Curam312.5 (Amoxicillin+Clavulanic acid)	Add drinking water to the line	2 steps each step approximately half amount	Store at temperature below 25°C	Keep the suspension refrigerated for 7 days
	Moclav (Amoxicillin+Clavulanic acid)	Add drinking water to the line	2 steps each step approximately half amount	Store at temperature below 25°C	Keep the suspension refrigerated for 7 days
	Ogmin 400mg 70 ml (Amoxicillin+clavunic acid)	Add 60 ml of water	2 steps each step approximately half amount	Store the drug at room temperature below 30°C	Keep the suspension refrigerated for 7 days
	Clamoxin 400 (Amoxicillin+Clavulanic acid	Add 60 ml of distilled water	2 steps each step approximately half amount	Store at temperature below 25°C	Store at refrigerator for 7 days
	Augmentin 35ml (Amoxicillin+Cavulanic acid	Add 32 ml of distilled water	NA	Store at temperature below 25°C	Keep in refrigerator for 7 days
	Augmentin 70ml (Amoxicillin+Clavulanic acid	Add 64 ml of distilled water	NA	Store at temperature below 25°C	Keep in refrigerator for 7 days

B lactam (pencilli n)	Bepenvk (Penicillin V)	Add 68ml of water	2 steps each step approximately half amount	Store at temperature below 30°C	Store at refrigerator for 7 days
B lactam (cephalosporins)	Adcef250 mg(Cefdinir)	Invert bottle and shake the powder to become lose. Add 40ml of boiled and cooled water	2 steps each step approximately half amount	Store at temperature below 25°C	Store at temperature below 25°Cfor 10 days
	Jeflex 250 mg (Cefalexin)	Shake the bottle to loosen granules add distilled water to the line	2 steps each step approximately half amount	Store at temperature below 25°C	Store at refrigerator for 7 days
	Zinnat 250 mg (Cefuroxime)	Shake the bottle to loosen the powder add 19 ml of water	One step	Store at temperature below 30°C	Store at refrigerator not more than 10 days
Macrolides	Azenil15cm (Azithromycin)	Tap the bottle to loosen the powder add 9ml of distilled water	NA	Store at temperature below 25°C	Store at temperature below 25°Cfor 5 days
	Azenil 22.5cm (Azithromycin)	Tap the bottle to loosen the powder add 12ml of distilled water	NA	Store at temperature below 25°C	Store at temperature below 25°Cfor 5 days
	Azemix22.5cm (Azithromycin)	Add 12 ml of water	2 steps each step approximately half amount	Store the drug at room temperature below 30°C	Store the drug at room temperature below 30°Cfor 5 days
	Erythrocare 400 mg (Erythromycin)	. Add boiled and cooled water to line	2 steps each step approximately half amount	Store at temperature below 25°C	Store at refrigerator for 7 days
	Zitrocin15cm (Azithromycin)	Add 7ml of distilled water	NA	Store at temperature 15-30°C	Store at temperature 15-30°Cfor 5 days

Macrolides	Zitrocin22.5cm (Azithromycin)	Add 10.5 ml of distilled water	NA	Store at temperature 15-30**°C**	Store at temperature 15-30**°C**for 5 days
	Zitrocin 30cm (Azithromycin)	Add 14cm of distilled water	NA	Store at temperature 15-30**°C**	Store at temperature 15-30**°C**for 5 days
	Klacid (Clarithromycin)	Add water to the granules until the line	NA	Store at room temperature below 30**°C**	Store at room temperature below 30**°C**for 14 days
Sulfa	Sulprim (Trimethoprime+Sulfa methoxazole)	Already reconstituted	NA	Store at temperature below 30**°C**	Store at temperature below 30**°C**

- This information depending on patient package insert and manufacturers' information on drug box during the study period.

3.5 Statistical analysis:

Statistical analysis was performed by using Statistical Package for Social Sciences (SPSS version 16.0). Mean ± standard deviation was computed for continuous data. Frequencies (percentages) were calculated for categorical variables. Categorical variables were compared using Chi-square. A p-value of less than 0.05 was considered to be statistically significant for all analyses.

Chapter Four

Results

Chapter four

Results

4.1 Socio-demographic characteristics:

The study sample was 400 women. Women age was mainly between 20-30 years of age 258 (64.5%), with a mean age of 28.8±6.2 years, minimum age was 17 years, and maximum age was 52 years, 307 (76.8%) were from Nablus city, 236 (59.0%) of them had a child with age between 1-3 yearswith a mean age of 2.6±1.9 years, minimum age was 0.08years, and maximum age was 12 years, most of participants had high school or university degree (39.8% and 47.8% respectively), (70.8%) of mothers had medical insurance, (68.5%) of participants reported medium monthly income, and (79.2%)were not working (table 4.1).

Table (4.1): Socio-demographic characteristics of 400 mothers

Characteristics	Frequency	Percentage
Mothers age		
Less than 20 years	13	3.2%
Between 20-30 years	258	64.5%
Between 31-40 years	115	28.8%
Above 41 years	14	3.5%
Monthly income		
Low	63	15.8%
Medium	274	68.8%
High	63	15.8%
Educational level		
Elementary school	6	1.5%
Middle school	44	11.0%
High school	159	39.8%
Diploma/University degree and more	191	47.8%

Characteristics	Frequency	Percentage
Living place		
City	307	76.8%
Village	90	22.5%
Camp	3	0.8%
Working mother		
Yes	83	20.8%
No	317	79.2%
Child age		
Less than 1 years	63	15.8%
Between 1-3 years	236	59.0%
Between 3.1-5 years	64	16.0%
Above 5 years	37	9.2%

4.2 Prescribed antibiotics and indications

During the study period the diagnosis according to prescribers was mainly throat infection (pharyngitis) in 110 (27.5%) children, bronchitis in 110 (27.5%), and otitis mediain 108 (27%)(table 4.2), and the most commonly prescribed antibiotic was amoxitid (amoxicillin) in 161(40.2%)children then ogmin (amoxicillin + clavulanic acid) in 51 (12.8%) as shown in(table 4.3).

Table (4.2): Indications for used antibiotics

Indication	Frequency	Percentage
Throat infection (pharyngitis)	110	27.5%
Bronchitis	110	27.5%
Otitis media	108	27.0%
Tonsillitis	45	11.2%
Urinary tract infection	14	3.5%
Dental infection	4	1.0%
Pneumonia	4	1.0%
Skin infection	3	0.8%
Sinusitis	1	0.2%
Trauma	1	0.2%

Table (4.3): The most commonly prescribed antibiotics (N=400)

Prescribed antibiotic	Frequency	Percentage
Amoxitid(Amoxicillin)	161	40.2.%
Ogmin(Amoxicillin+Clavulanic acid)	51	12.8%
Azemix(Azithromycin)	33	8.2%
Moclav(Amoxicillin+Clavulanic acid)	30	7.5%
Azenil(Azithromycin)	28	7.0%
Erythrocare(Erythromycin)	25	6.2%
Jeflex(Cefalexin)	15	3.8%
Curam(Amoxicillin+Clavulanic acid)	14	3.5%
Augmentin(Amoxicillin+Clavulanic acid)	10	2.5%
Adcef(Cefdinir)	8	2.0%
Zitrocin(Azithromycin)	7	1.8%
Zinnat(Cefuroxime)	6	1.5%
Clamoxin(Amoxicillin+Clavulanic acid)	5	1.2%
Sulprim(Trimethoprim+sulfamthoxazole)	3	0.8%
Bepenvk(Penicillin V)	3	0.8%
Klacid(Clarithromycin)	1	0.2%

4.3 Reading and understanding the instructions:

Among the 400 mothers,347 (86.8%) claimed that they read the manufacturer instructions either on the box or in the package insert, 311 (77.8%) of them told that they could understand the instructions. In case of not understanding the instructions, 176 (44%) of participants asked for help from pharmacists, while 41 (10.2%) asked their doctors (table 4.4).

Table (4.4): Reading and understanding instructions to prepare antibiotic suspension (N=400)

Characteristics	Frequency	Percentage
Read instructions		
Yes	347	86.8%
No	50	12.5%
Understand instructions		
Yes	311	77.8%
No	45	11.2%
Pharmacist advise	176	44.0%
Doctor advise	41	10.2%
Others	180	45.5%

4.4 Reconstitution of antibiotic suspensions:

In order to reconstitute dry powder antibiotic, most mothers 302 (75.5%) used boiled and cooled tap water, 52 (13.0%) used mineral water, 31(7.8%) used tap water directly, 7(1.8%) used distilled water, and 5 (1.2%) of drugs were prepared by pharmacists(table 4.5).Fortunately the correct practice (use boiled then cold tap water, use distilled water, and one prepared by pharmacist) was done by 310 (77.8%). And there was no significant association between correct practice and socio-demographic characteristics.

Table (4.5): Water used to prepare antibiotic suspension (N=400)

Water used	Frequency	Percentage
Boiled and cooled tap water	302	75.5%
Mineral water	52	13.0%
Tap water directly	31	7.8%
Distilled water	7	1.8%
Prepared by pharmacists	5	1.2%
Already reconstituted	3	0.8%

Regarding the method of reconstitution, 192 (48.4%) of mothers used syringe as tool to measure the volume of water, while 179 (45.1%) of participants used line on drug bottle, 25 (6.3%) used enclosed medicinal cup, and 1 (0.3%) used baby bottle as shown in (figure 4.1) according to the instructions, the correct practice was followed by 344 (86.8%) of mothers.There was no significant association between correct practice and socio-demographic characteristics.

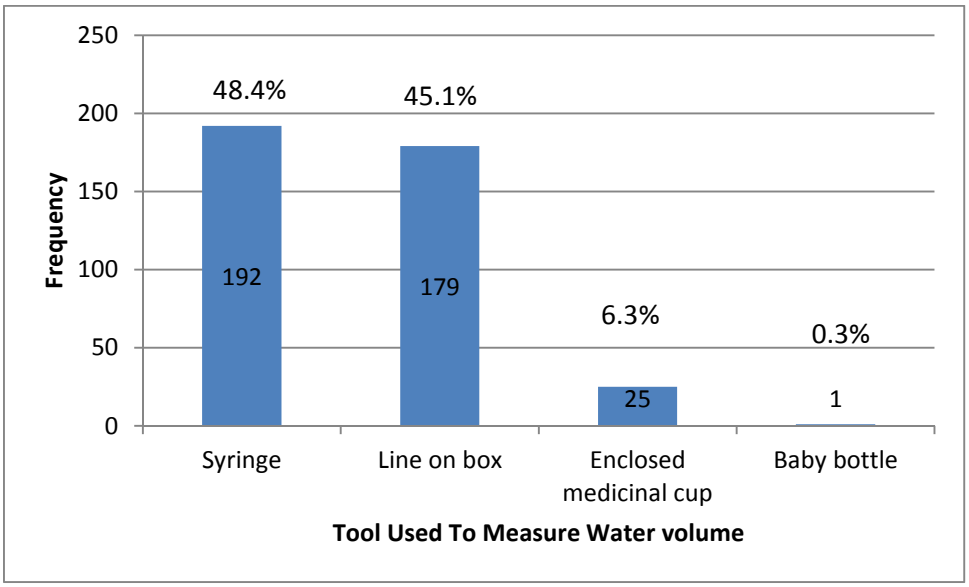

Figure (4.1): Tools used to measure water volume(N=397)

The water was added either in one step, two steps, or several steps. And the correct practice according to the instructions was done by 304 (76.6%) of mothers as shown in (table 4.6). There was no significant association between correct practice and socio-demographic characteristics.

Table (4.6) Water addition steps (N=397)

Addition steps	Frequency	Percentage
One step	48	12.1%
Two steps	304	76.6%
Several steps	45	11.3%

4.5 Administration of antibiotic doses:

Most of the mothers392 (98.0%) claimed to shake the drug bottle before use as shown in (figure 4.2) which means that 98.0% of mothers followed correctpractice.

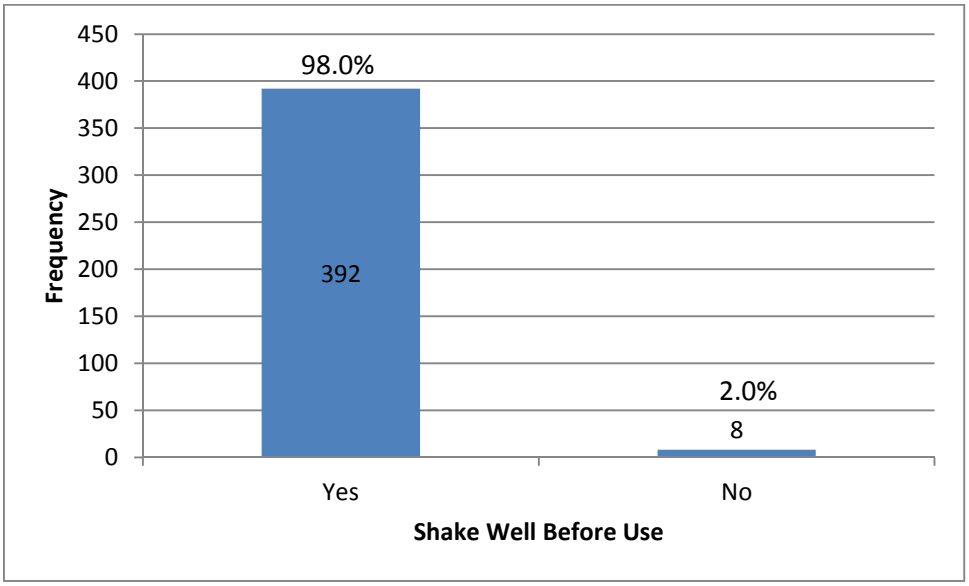

Figure (4.2): Mothers' practice regarding shaking antibiotic suspensions before use (N=400)

Among 400 mothers,313 (78.2%) of them considered syringe as the most accurate tool for drug administration, 57(14.0%), 20 (5.0%), and 10 (2.5%) of them considered household teaspoonful, medicinal spoonsful, and medicinal cup as the most accurate tool respectively, as shown in (table 4.7), the correct practice according to related studies was practiced by 313 (78.2%) of mothers. And there was no significant association between correct practice and socio-demographic characteristics.

Table (4.7): Drug administration (N=400)

Tool used to administer dose	Frequency	Percentage
Syringe	313	78.2%
Household teaspoon	57	14.3%
Medicinal spoon	20	5.0%
Medicinal cup	10	2.5%

The mothers were asked if the full medicinal cup equals drug dose always, 39 (9.8%) of mothers answered that enclosed medicinal cup is equal to the drug dose as shown in (table 4.8). And the correct answer was by 347 (86.8%) of mothers who said that the full cup is not always equal to the dose.

Table (4.8): Dose medicinal cup equal drug dose? (N=400)

Medicinal cup equal dose	Frequency	Percentage
Yes	39	9.8%
No	347	86.8%
Don't know	14	3.5%

The mothers were asked about their practice if the direction for antibiotic suspension is"use three times daily"; 224(56.0%)of mothers told that they administer the dose with major mealsas shown in (figure 4.3) the correct practice was done by 112 (28.0%) of mothers. And there was no significant association between correct practice and socio-demographic characteristics.

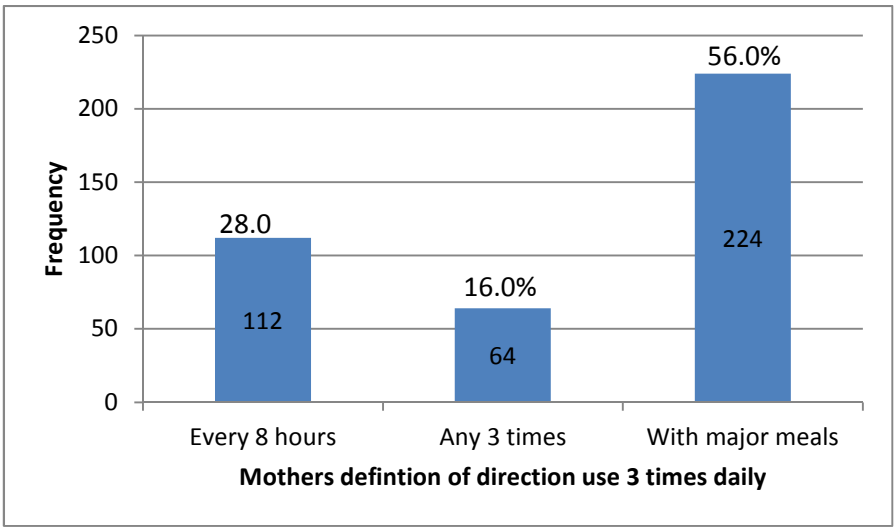

Figure (4.3) Mothers practice for direction" use 3 times daily"

Regarding the duration of administration; 394 (98.5%) of mothers didn't used suspension after two weeks of reconstitution (figure 4.4), and374 (93.5%) of mothers didn't use the leftover (remnant) for another child as shown in (figure4.5).Fortunately the correct practice according to manufacturer instructions was done by 394 (98.5%), 374 (93.5%) respectively. And there were no significant association between correct practices and socio-demographic characteristics.

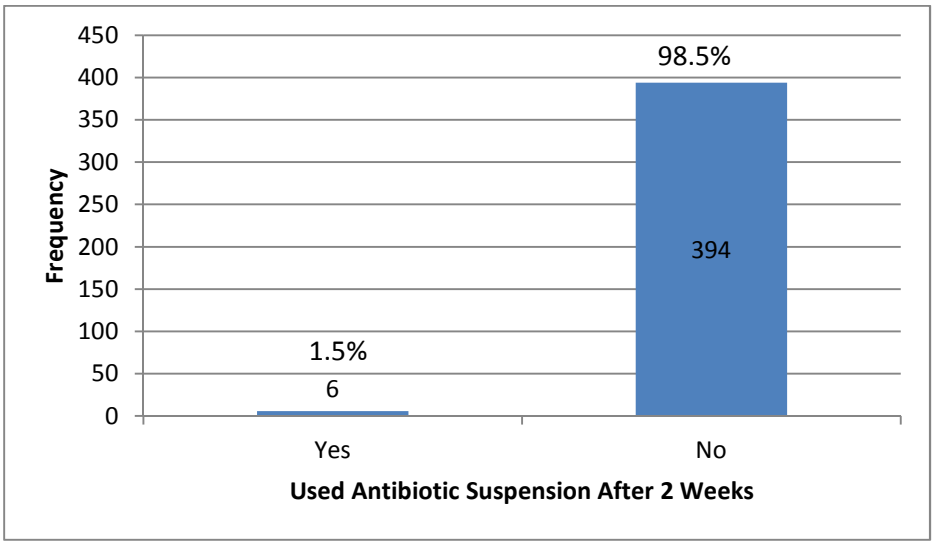

Figure (4.4): Mothers' practice regarding of the use antibiotic suspension after 2 weeks (N=400)

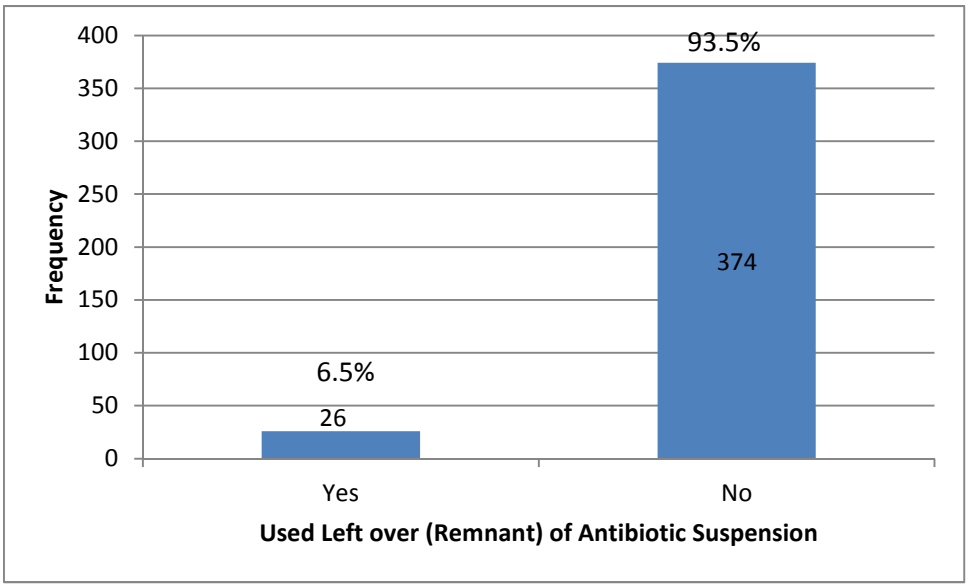

Figure (4.5): Mothers' practice regarding the use of remnant antibiotic suspension(N=400)

4.6 Storage conditions for antibiotic suspensions:

Regarding the storage of dry powder; 177 (44.2%) of mothers told that they stored dry powder antibiotic in medicinal cabinet, 72 (18.0%) in kitchen, 56 (14.0%) in refrigerator,48 (12.0%) in dining room, 22(5.5%) above refrigerator, and 25 (6.2%) of mothers used antibiotic directlyas shown in (figure 4.6), and the correct practice (store in medicinal cabinet, and used directly) was done by 202 (50.5%) of mothers. And there was no significant association between correct practice and socio-demographic characteristics.

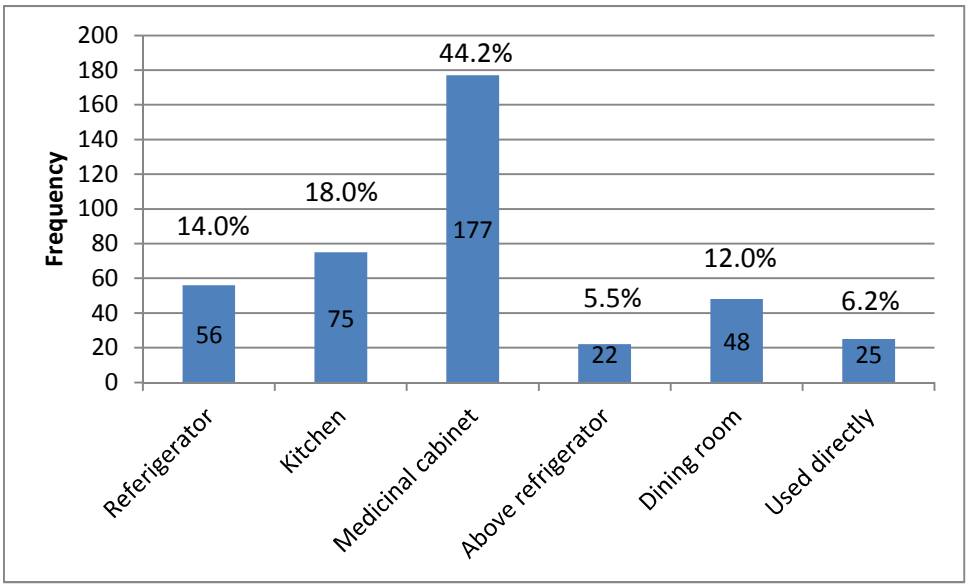

Figure (4.6): Storage condition of dry powder antibiotic (N=400)

Storage of suspension after reconstitution; 226 (56.5%) of mothers told that they stored antibiotic suspension in refrigerator, 71 (17.8%) in medicinal cabinet, 54 (13.5%) in kitchen, 31 (7.8%) indining room, and 18 (4.5%) above refrigeratorfigure (4.7), and the correct practice was done by 200(50.0%) of mothers. And there was no significant association between correct practice and socio-demographic characteristics.

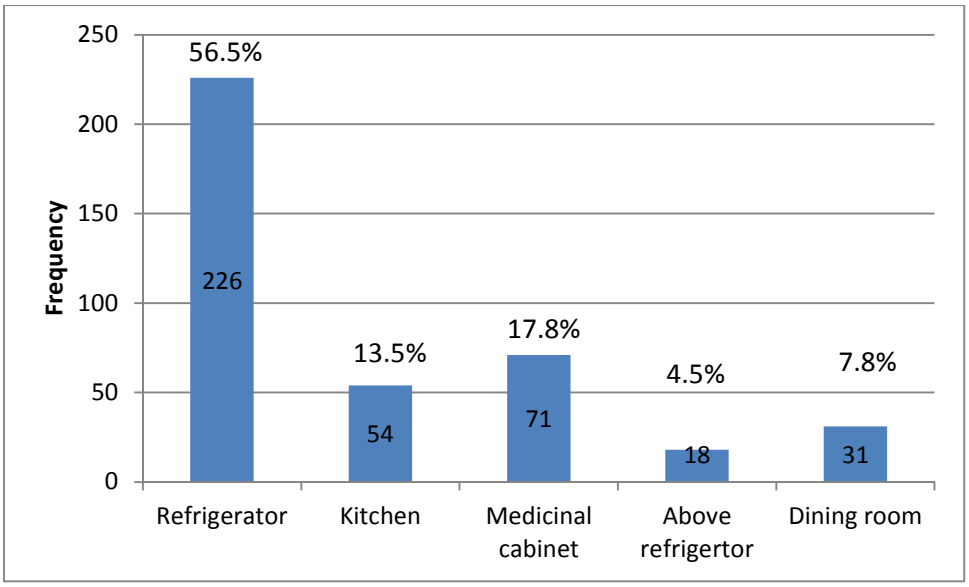

Figure (4.7): Storage condition of antibiotic suspension (N=400)

Mothers were asked about the meaning of “store in a cool place"; 164 (41.0%) of mother answeredwith refrigerator, 141(35.2%) answered with any temperature, 93 (23.2%) answered was medicinal cabinet, and 2 (0.5%) answered with freeze (figure 4.8). The correct practice was followedby 93(23.2%)mothers according to (BP), also we can consider refrigerator as suitable place in case of temperature above 8-15 **°C**to avoid temperature flocculation for suspensions (Winfield, 2004). And there was no significant association between correct practice and socio-demographic characteristics.

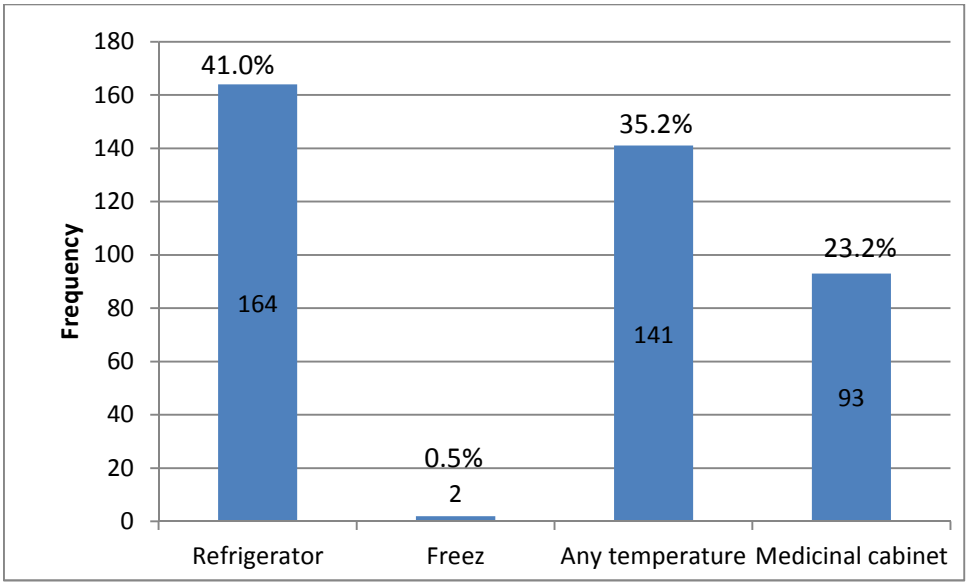

Figure (4.8): Mothers’ definition of a cool place (N=400)

Chapter Five

Discussion

Chapter five

Discussion

Most children have 4-6 acute URTI yearly when infection is caused by bacteria then antibiotic is the drug of choice(Chan and Tang, 2006b). To achieve therapeutic effect and prevent treatment failure, antibiotic must be properly used. Suitable dosage forms for pediatric use are usually available in pharmacy(Maldonhauado and Schaufelberger, 2011). Among these dosage form dry antibiotic suspension are most used(Cetinkaya, 2012). Most antibiotics are water sensitive; accordingly they should be formulated as dry suspension for reconstitution(Ogden, 2007). The reconstitution requires addition of suitable pharmaceutical solvent which is water. The appropriate use includes (i) correct reconstitution, (ii) dose administration, (iii) and storage conditions. This study demonstrates Palestinian mothers' practice regarding antibiotic dry powder reconstitution, dose administration, and storage conditions of antibiotic suspensions, and compares their practice to other mothers.

5.1 Reading and understanding instructions:

For optimal usefulness from antibiotic suspension manufacturer instructions should be followed exactly. This study showed that 347 (86.8%) of 400 mothers read the instructions either on box or package insert, and 311(77.8%) told that they understood the instructions.This is a good level of awareness and understanding compared to others Palestinian

studies,one showed that 100 (45.0%) of 222 consumers reported that they always read information in the leaflet of the drug package(AL-Ramahi et al., 2012), anothershowed that 51.7% of 371 participants said that they read PPI(Sweileh et al., 2004).One study showed that patient instructions understanding ranged from (53.0%) for least understood to (89.0%) for most commonly understood label(Davis et al., 2009b). It is recommended to make instructions clear and complete as much as possible, and to encourage patients or caregivers to read instruction always.

5.2 Dry powder antibiotic reconstitution:

Reconstitution of dry powder antibiotic depends on type of antibiotic and manufacturer instructions. Generally distilled or boiled then cooled tap water is used. First the bottle should be tabbed few times to loose the powder, then approximately half volume of water should be added, the bottle is shaken vigorously, the remaining of water should be added and shaken well(Technician Training Tutorial, 2011). One exceptionis zinnat (cefuroxime) where the recommended addition of water isin one step (zinnat manufacturer instruction).

In this study 302 (75.5%) of mothers used boiled then cooled tap water, 7 (1.8%) of mothers used distilled water, this follow the correct practice. While 52 (13.0%) used mineral water, and 31 (7.8%) used tap water directly, this follow wrong practice. As mineral water is usually rich in minerals, accordingly this practice may cause decomposition of drug,

and incompatibilities such as interactions with the drugs leading to complexion reactions(Kennedy, 2004a). And 304 (76.6%) of mothers followed correct practice in addition of water in two steps.Addition of water in one step makes difficult to get the lumps out(Ogden, 2007), while measuring volume of water several times toadd increases the percentage of error in measured volume(Ansel, 2010).

Regarding the volume of water, antibiotics as Amoxitid (amoxicillin), Curam, Moclav (amoxicillin+clavulanicaci), Erythrocare (erythromycin), and Jelex (cephalexin) have line as mark on bottle to which water should be added, while other antibiotics either have medicinal cup, or syringe to measure volume of water. Fortunately the correct practice was done by 344 (86.6%) of mothers. Despite this good practice of reconstitution, the addition of water up to the mark or using medicinal cup as measuring tool may result in inaccurate fluid volume due to the width of these tools. In fact in measuring volume, it is recommended to use narrow tools to achieve correct volume(Ansel, 2010).

A previous Palestinian study asked about quantity of water added showed that 3.5% said the quantity of water that should be added to prepare suspension is not a specific quantity, and 10.1% could not decide or they had no idea wither it is specific or not(Al Khalil et al., 2005). In another study, 25.5% of 107 mothers knew the crucial importance of viewing the lower meniscus of water at eye level to obtain the correct final volume of suspension (Iorngurum, Ogunbajo et al. 2011). In our study, similar to

other studies some caregivers don't know the correct practice regarding reconstitution of antibiotic dry powder. This requires better counseling and education from prescribers and pharmacists when suspensions are prescribed or dispensed. It would be a good practice if pharmacists perform the suspension in pharmacy using suitable cylinders and suitable water.

5.3 Administration of antibiotic dose:

Appropriate dose administration includes shaking the bottle before use, and using accurate delivery tool, and dose interval.

In this study most of the mothers 392 (98.0%) claimed to shake the drug bottle before use in order to redistribute the powder to administer right dose.

In another study from Nigeria,among 107 mothers 24.4% didn't shake the bottle immediately before measuring the dose volume which leads to incorrect dose (Iorngurum, Ogunbajo et al. 2011). In fact this wrong practice will lead to incomplete or wrong mixing of water with dry suspension. This will result in missing of the most important pharmacopeial quality test which is the uniformity of distribution of the drug and accordingly the content of uniformity of the dose(Kunague, 2011). In general our results reflected high level of awareness regarding this point.

According to this study 313 (78.2%) of mothers considered syringe as the most accurate device for dose administration, while 57 (14.3%)

considered household teaspoonful as the most accurate device for dose administration. The correct practice was followed by most of the mothers. A Ghanaian study showed that 95.0% of 97 respondents used household spoons in dosing oral liquid medications(Chan and Tang, 2006b).The American Academy of Pediatrics (AAP) Committee on Drugs in a 1975 study reported 75 % of patients used a household teaspoon or kitchen measuring spoon when dosing liquid medication. In another Israeli study, 80 % of 100 children were given medications by a household teaspoon with mean volume of 2.95ml that resulted in under dose(Hyam et al., 1989). A similar report from the UnitedState indicated a household teaspoon was the device most frequently used for measuring liquid medications in 73.0% of 130 patients. Clinicians and pharmacists need to be aware that many people continue to use inaccurate devices for measuring liquid medication, such as household spoons. They should encourage the use of more accurate devices, particularly the oral dosing syringe. Clinicians should always consider the possibility of a medication dosing error when faced with an apparent treatment failure(Madlon-Kay and Mosch, 2000).

In another study majority of adult believed that oral syringe and dosing cup would measure an accurate dose (Sobhani et al., 2008). A study by Chang in 2010 dosing cups caused the most medication errors as 99.0% of which were overdose due to assumption that cup constituted the

entireactual dose itself. In this study most of mothers 347 (86.8%) didn't assume that medicinal cup equal drug dose, which is a correct practice.

Regarding to dosing interval most of mothers 224 (56.0%) assumed that" use three times daily" means to give the drugs with major meals and this is a wrong practice. As we know three times daily for antibiotics means to administer the medication every 8 hours. A study of 359 patientstested whether the use of more explicit language to describe dose and frequency of use for prescribed drugs could improve comprehension, showed that patients were significantly more likely to understand instructions with explicit time period as in morning 89.0%, compared to instruction as twice daily 77.0%, or by hour interval 53.0%(Davis et al., 2009a). Regarding to this point, the role of pharmacists is very important and they should write the proper instructions and confirm on them during dispensing to avoid antibiotic failure or toxicity if the dosing interval are not followed properly.

According to manufacturer directions antibiotic suspensions should be discarded after 10 days of reconstitution for antibiotics as amoxicillin, cefidinir, and cefuroxime, while amoxicillin-clavulanic acids, erythromycin, cephalexin should be discarded after 7 days, and after 5 days for antibiotic azithromycin. And this practice was done by most of the mothers394 (98.5%). Regard using of left over antibiotic suspension 26 (6.5%) of mothers used left over antibiotic suspension.Study about amoxicillin suspension stability the therapeutic effects of suspension decreased after 14 days even if stored in refrigerator(Naidoo et al.,

2006).Another study showed that 15.0% of 421 parents gave left over antibiotic suspension to their children whichmeans that they keep antibiotics after reconstitution(Chan and Tang, 2006a).

Asit is well known, the medications should not be given to other individuals, this practice was followed by 374 (93.5%) of mothers.A Malaysian study showed that 24.0% of 421 parents gave shared antibiotics(Chan and Tang, 2006a), so our results reflect good awareness regarding rational use of antibiotics.

5.4 Antibiotic storage conditions:

Storage conditions of drugs are important as drugs are chemicals that may react with external environment such as temperature, humidity, and light. This leads to change in drugs concentrations properties and therapeutic effects. Most of people store medications in kitchen or bathroom cabinet, that speeds up medication breakdown process; as in both conditions drugs were exposed to humidity and warm. Instead medicinal cabinet should be placed in cool and dry place, away from direct sun light, and out of reach from children (Dugdal, 2011).

In this study a good percentage of mothers 177 (44.2%) stored dry powder antibiotic in medicinal cabinet, and 226 (56.5%) of them stored antibiotic suspension in refrigerator. In both cases around half of the mothers followed the correct practice. These results are close to results from another Palestinian study which showed that 40.6% of drugs were

stored in pharmacy cabinet, in another hand same study showed that 70.0% of the reconstituted suspensions were stored outside the refrigerator (Sweileh, et al. 2010), and another Iraqi study which showed that 42.0% of all drugs were stored appropriately (Jassim, 2010).

A mini survey determined packaging in which amoxicillin preparations are dispensed, temperature and humidity condition under which they were stored by patients by Naidoo, etal in 2006 revealed that 53.0% of 100 patients stored antibiotic suspension in refrigerator, and 47.0% stored them in common area in house, as temperature range in Durban from 31-42**°C**this could result in decrease therapeutic efficacy and increase in bacterial resistance. So storage conditions are very important and patients and caregivers in our country need more education regarding this point because many people store medications in inappropriate places. Mothers were asked about storage condition "store in dry place" the correct answer was answered by 93 (23.2%) of mothers. According to British Pharmacopeia (BP) "cool place" is between 8-15**°C,** in case that temperature in place above that rang so we can use refrigerator to avoid temperature flocculation (Winfield, 2004).This again is the responsibility of the prescribers and pharmacists who should concentrate on this point during counseling.

5.5 Limitations:

Thefirst limitation of this study is that the answers reported by the respondents cannot be validated and recall bias is possible, but this cannot be avoided in survey studies. Another limitation is the study was performed in Nablus city so it might not be representable to the practice in villages and camps. However, these results can give a baseline data that can be useful in designing and implementing suitable educational programs and performing other related studies.

5.6 Conclusions:

This study reflected a good level of awareness regarding antibiotic dry powder reconstitution, dose administration, and storage conditions for antibiotic suspensions among Palestinian mothers. However, there is a room for improvement in mothers' practice; it is the role of pharmacists to reconstitute antibiotic dry power using suitable tool and suitable water, in addition to their responsibilities to explain the manufacturer instructions to mothers and confirm on them by writing, and supply them with suitable dose administration tool, focus on dose intervals, duration of use, and storage conditions for both dry powder antibiotic and antibiotic suspensions.

5.7 Recommendations:

To achieve higher level of awareness and correct practice regarding antibiotic suspensions use,cooperation between drugs companies, pharmacists, and doctors is needed.

Drugs companies are recommended to write instructions in simple way, and may draw the directions on bottle, in addition to accompany liquid medications with suitable well calibrateddose administration devices

It is the role of pharmacists to reconstitute antibiotic dry power using suitable tool and suitable water, this role should be encouraged, in addition to explain instructions to mothers and confirm on them by writing, and to provide mothers with syringes, also it is important to concentrate on duration of use and storage conditions.

The prescribers should inform mothers the correct instructions also and confirm that antibiotic suspensions should not be shared between children, and should be used according to the correct directions.

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Appendices

Appendix (1)

المعلوماتالشخصية:

عمر الام

المستوى التعليمي للام

مكان السكن في فلسطين

مدينه □ قرية □ مخيم□

وجود تأمين صحي

نعم □ لا□

دخل الاسرة الشهري

منخفض □ متوسط □ عالي □

العمل

نعم □ لا (ربة منزل)□

عمر الطفل

المضاد الحيوي الموصوف للطفل

الداعي للاستخدام

هل تقرأي التعليمات بدقة قبل قيامك بتحضير معلق المضاد الحيوي؟

نعم □ لا □

هل تجدي التعليمات بشأن تحضير المعلق واضحة؟

نعم □ لا □

اذا كانت التعليمات غير واضحه،هل تتوجهين لطلب نصيحة الصيدلاني؟

نعم □ لا □ الدكتور □

ماهي نوعية المياه التي تستخدمينها لتحضير معلق المضاد الحيوي؟

مياه معدنية □ مياه الصنبور (باردة بعد غليها) □ مياه مقطره □

مياه الصنبور مباشرة □ الصيدلاني يقوم بتحضيره□

ما هي الاداة التي تستخدميتها لقياس كمية المياه المراده؟

الغطاء المصاحب للعلبة □ السرنجه □ الخط المرسوم ع العلبه□

ادوات اخرى.....

عدد خطوات اضافة المياه للدواء:

خطوة واحده □ خطوتين □ عدة خطوات □

هل تقومي برج العلبة قبل الاستعمال؟

نعم □ لا□

الاداة الاكثر دقة لقياس جرعة الدواء:

الغطاء المصاحب للعلبة □ الملعقه المصاحبه للعلبة □ السرنجة □

ملعقه الشاي المنزلية □

عند استعمالك للغطاء المرافق للعلبة،هل تعتقدي ان الجرعه تساوي حجم الغطاء

نعم □ لا □ لا اعرف □

اين تقومي بحفظ معلق المضاد الحيوي قبل تحضيره؟

الثلاجة □ المطبخ □ خزانة الادوية □ ظهر الثلاجة

□ غرفة المعيشة □ استعمله مباشره □

اين تقومي بحفظ المضاد الحيوي بعد تحضيره؟

الثلاجة □ المطبخ □ خزان الادوية □ ظهر الثلاجة

□ غرفة المعيشة □

ماهو تعريفك ليحفظ في مكان بارد ؟

الثلاجة □ الفريزر □ اي درجة حرارة □ خزانة

الادوية □

هل سبق لك ان استعملت المضاد الحيوي بعد اسبوعين من تحضيره؟

نعم □ لا□

هل سبق لك ان استعملت بقية المضاد الحيوي لطفل اخر؟

نعم □ لا□

إعطاء الجرعة 3 مرات باليوم تعني

كل 8 ساعات □ اي 3 اوقات خلال النهار □

مع الوجبات الرئيسية□

Appendix (2)

Personal information:

Mother age

Educational level

Elementary □ middle school □ high school □ diploma/ university or more□

Living place

City□village □ camp□

Health insurance

Yes □ no □

Monthly income

Low □ medium □high□

Work

Yes □ no □

Child age

Prescribed antibiotic

Indication

Did you read instructions carefully before preparation of antibiotic suspension?

Yes □ no □

Did you understand the instructions?

Yes □ no□

If you didn't understand instructions, you ask

Pharmacist □no □ doctor □

What was the type of water you used to prepare antibiotic suspension?

Mineral water □ boiled then cooled water □ distilled water □ tap water directly □ prepared by pharmacist□

What was the tool you use to measure volume of water?

Medicinal cup □ syringe □ line on bottle □ others

Steps to add water

One step□ two steps □ several steps□

Did you shake the bottle before use?

Yes □ no□

The most accurate tool for dose administration

Medicinal cup □ medicinal spoon □ household teaspoonful□

Does medicinal cup equal dose?

Yes □ no □ don't know□

Where did you store dry powder antibiotic?

Refrigerator □ kitchen □ medicinal cabinet □ above refrigerator □ dining room □ used directly□

Where did you store antibiotic suspension?

Refrigerator □ kitchen □ medicinal cabinet □ above refrigerator □ dining room □

What is your definition of cool place?

Refrigerator □ freeze □ any temperature □ medicinal cabinet□

Did you use antibiotic suspension after 2 weeks?

Yes □ no□

Did you use leftover antibiotic to other child?

Yes □ no□

Three times daily mean

Every 8 hours □ any tree times daily □

with major meals□

Appendix (3)

20 Jan 2013 12:13 HP Fax page 1

Palestinian National Authority
Ministry of Health - Nablus
General Directorate of Higher & Continuning Education

السلطة الوطنية الفلسطينية
وزارة الصحة- نابلس
الإدارة العامة للتعليم الصحي

Ref.: .....
Date:.....

الرقم: ٢٠١٣/٤٣/١٦٥
التاريخ: ٢٠١٣/١/٢٠

الأخ مدير عام الادارة العامة للرعاية الصحية الأولية والصحة العامة المحترم،،،

تحية واحترام،،

الموضوع: تسهيل مهمة طلاب – جامعة النجاح الوطنية

تماشياً مع سياسة وزارة الصحة المتعلقة بتعزيز التعاون مع الجامعات والمؤسسات الأكاديمية بإتاحة فرص التدريب أمام الطلبة والخريجين والباحثين في المؤسسات الوطنية وإسهاماً في تنمية قدراتهم.

يرجى تسهيل مهمة الطالبة هيا ابراهيم عينبوسي- برنامج ماجستير صيدلة سريرية- كلية الطب وعلوم الصحة/ جامعة النجاح الوطنية في اجراء بحث بعنوان " Problems Associated with reconstitution, Administration, and Storage of Antibiotic Suspensions for Pediatrics in Nablus City" وذلك من خلال السماح للطالبة بالاطلاع على الوصفات الطبية للأطفال ومقابلة امهات الأطفال المرضى في حال احتواء الوصفة على مضاد حيوي. للاستفسار عن معلومات تخص البحث وذلك في مراكز الرعاية الصحية في مدينة نابلس.

مع الاحترام،،

د. أمل أبو عوض
ق. أ. مدير عام التعليم الصحي

/ نسخة مدير دائرة الصيدلة المحترم/ جامعة النجاح الوطنية.

P.O .Box: 14 pnamoh@palnet.comE-mail: ص.ب. 14
Tel.:09-2384771 -6 Fax: 09-2384777 تلفون: 6-2384771-09 فاكس: 09-2384777

Appendix (4)

An - Najah
National University
Faculty of Medicine & Health Sciences
Department of Graduate Studies

جامعة النجاح
الوطنية
كلية الطب وعلوم الصحة
دائرة الدراسات العليا

IRB Approval letter

Study title:
"Problem Associated With Reconstitution , Administration , And Strong Of Antibiotic Suspensions For Pediatrics in Nablus City-Palestine"

Submitted by:
"Haya Anabousi"

Date Reviewed:
Nov,12,2012

Datè approved:
Dec ,27,2012

Your study titled"Role of Plasma Homocysteine levels and Other Associated Factors with Coronary Artery Disease Among Palestinian patients : A Case Control Study "Was reviewed by An-Najah National University IRB committee & approved on Dec, 27, 2012.

Samar Musmar,MD, FAAFP
IRB Committee Chairman,
An-Najah National University

IRB

نابلس – ص.ب 7 أو 707 هاتف 14/8/7/7/4/2342902(09)(970) ، فاكسميل 2342910 (09) (970)
Nablus – P.O.Box: 7 or 707 – Tel (970) (09) 2342902/4/7/8/14 – Faximile (970)(09)2342910
Email: hgs@najah.edu Web Site: www.najah.edu

جامعة النجاح الوطنية

كلية الدراسات العليا

المشاكل المتعلقة بحل واعطاء وتخزين معلقات المضادات الحيوية للأطفال في مدينة نابلس/فلسطين

إعداد

هيا إبراهيم عنبوسي

إشراف

د. رواء الرمحي

د. عبد الناصر زيد

قدمت هذه الاطروحة استكمالا لمتطلبات الحصول على درجة الماجستير في الصيدلة السريرية في جامعة النجاح الوطنية نابلس، فلسطين.

2013م

المشاكل المتعلقة بحل واعطاء وتخزين معلقات المضادات الحيوية للأطفال في مدينة نابلس/فلسطين

إعداد

هيا ابراهيم عنبوسي

إشراف

د. رواء الرمحي

د. عبد الناصر زيد

الملخص

يعاني الكثير من الاطفال من العدوى الفيروسية أو البكتيرية. في حالة العدوى البكتيريه استعمال المضادات الحيوية هو الحل الأمثل ولضمان الحصول على نتيجة علاجية فعاله يجب استعمال المضاد الحيوي بطريقة صحيحة. وتبرز اهمية هذه الدراسة في تقييم مدى صحة ممارسات الامهات الفلسطينيات بالنسبة لتحضير المضادات الحيوية، وكيفية اعطاء الجرعة، وظروف التخزين.

هذه الدراسة هي عبارة عن دراسة وصفية، تم تطبيقها في مجموعة من عيادات وزارة الصحة الفلسطينية وعيادة طبيب أطفال خاص في الفترة الواقعة بين 22-1-2013 و22-3-2013، وذلك باستخدام استبيان أعد لهذا الغرض، حيث تم تحليل البيانات بواسطة البرنامج الاحصائي SPSS.

وتوصلت الدراسة الى أن معظم العدوى التي يعاني منها الاطفال هي التهاب القصبات 110 (27.5%) والتهاب الحلق 110 (27.5%) والتهاب الاذن الوسطى 108 (27.0%)، وأن اكثر مضاد حيوي تم وصفه من قبل الاطباء هو عقار الاموكسيسلين. من بين 400 أم، قامت 200 أم بزيارة عيادات وزارة الصحة بينما قامت ال 200 أم الاخريات بزيارة عيادة أطفال خاصة، وأظهرت النتائج ان 347 (86.8%) من الامهات يقمن بقراءة التعليمات الموجودة على علبة الدواء بدقة ، بالإضافة الى ان 311 (77.8%) منهن فهموا التعليمات بشكل كامل وفي حالة عدم الفهم للمعلومات توجه 176 (44.0%) من الامهات لسؤال الصيدلاني. اما بالنسبة

لكيفية تحضير معلق المضاد الحيوي اجاب 302 (75.5%) من الامهات أن مياه الصنبور باردة بعد غليها هي المستعملة، بالإضافة الى ان 192 (84.4%) ام تستعمل السرنجة لقياس كمية المياه المرادة لتحضير المعلق، واشار 304 (76.6%) من الامهات أن عملية اضافة الماء تكون على مرحلتين. وحول كيفية تقديم جرعة المضاد الحيوي للطفل فإن 392 (98.0%) من الامهات يقمن برج الزجاجة قبل اعطاء الجرعة، واعتبر 313 (78.2%) من الامهات ان السرنجة هي الاداة الاكثر دقة لإعطاء الجرعة، بينما وجدت 39 (9.8%) من الامهات ان الكأس المرافق لعلبة الدواء يمثل الجرعة الدوائية للطفل. وعند سؤال الامهات عن كيفية اعطاء الجرعة 3 مرات يوميا اجاب معظم الامهات 224 (56.0%) انهم يقدم الدواء مع الوجبات الرئيسية. وحول مدة استعمال المعلق اجاب 6 (1.5%) انهم يستعملونه لمدة تصل اكثر من اسبوعين ، بالإضافة الى ان 26 (6.5%) من الامهات يقمن باعطاء بقية معلق المضاد الحيوي لطفل اخر.واخيرا بالنسية لظروف التخزين كانت الاجابة لدى معظم الامهات 177 (44.2%) بحفظ المعلق قبل تحضيره في خزانة الادوية ، و اجاب 226 (56.5%) بحفظ المعلق بالثلاجة. وعند سؤال الامهات عن تعريفهم ليحفظ في مكان بارد اجاب معظمهم 146 (41.0%) أن المكان هو الثلاجة.

بالرغم ان هذه النتائج تعكس معرفة الامهات الجيدة حول كيفية تحضير معلق المضاد الحيوي وكيفية تقديم الجرعة ومدة الاستخدام بالإضافة الى ظروف التخزين. هناك فرصة لتحسين الوضع وذلك يقع على عاتق الصيدلاني حيث من واجبه توضيح المعلومات للام والتأكيد عليها كتابة، بالإضافة الى تزويدها بالسرنجات بالقياس المناسب، وتذكير الام بمدة الاستعمال وبظروف التخزين.