Development of a Paediatric Intravenous Formulations Manual

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Abstract

Safe and effective administration of injectable medications is key to patient safety. A Parenteral Drug Therapy Manual (PDTM) is a document or database that includes information related to administration, reconstitution of medicinal products, compatibility with other medicines and adverse reactions. The manual is used as a guidance for the preparation and administration of medications via parenteral routes. The need for a PDTM for paediatrics at the local general acute hospital, Mater Dei Hospital (MDH), led to the development of this research project.

The objectives of the study were to 1) develop and validate drug monographs for the medications administered intravenously in paediatric wards at MDH 2) develop and administer a questionnaire to evaluate the impact of drug monographs on the knowledge, confidence and contributing factors to medication errors from the nurses' perspective in a pre- and post-test design.

The methodology was divided into three phases. The first phase entailed the identification of medications commonly used in paediatric wards. The data was collected from pharmacy databases, surveying nurses working in paediatric wards and consulting nurses in charge of the respective wards. In the second phase of the study, drug monographs were developed for the selected medications, where each monograph contained therapeutic information and information related to reconstitution, dilution, compatibility and stability, monitoring of safety and efficacy of medications and other data such as interference with lab results and sodium content. Published literature, evidence based local practice, latest updated SmPC (Summary of Product

Characteristics) and manufacturers of the medications were consulted to develop monographs. The monographs were sent to hospital pharmacists for review and approval as hospital practice guidelines. For the third phase of the study, a questionnaire entitled Assessment of Administration Practice (AAP-Q) was developed and validated by 11 experts. The AAP-Q was distributed to nurses working in paediatric wards at MDH prior to and after introducing drug monographs in the wards to evaluate the impact of the monographs on the administration practice of nurses.

Twenty active pharmaceutical ingredients were selected and a monograph was developed for all strengths and different brands of the respective medication. Fifty-five paediatric nurses out of 62 participated in the study. Thirty-five nurses acknowledged that they consulted the drug monographs when administering IV medications. Drug monographs were reported to i) assist in overcoming reported difficulties associated with the use of IV medications such as reconstitution and dilution practice (n=27) and choice of compatible fluids (n=20), ii) reduce the impact of factors leading to medication errors associated with insufficient knowledge (pre-test mean rating score (MRS) 4.49 and post-test MRS 1.74, $p<0.001$) and lack of standard guide for using injectable medications (pre-test MRS 4.05 to MRS 1.56 post-test, $p<0.001$).

The developed monographs were considered to have a positive impact on the safety of medication administration by contributing to standardisation of practice and providing an easy-to-use reference at the bed side.

Keywords

Interventions; IV medication administration; Medication administration errors; Paediatrics; Patient Safety; Standard Guidance

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List of Abbreviations

A&E	Accidents and Emergency
ADEs	Adverse Drug Events
ADR	Adverse Drug Reactions
AHFS	American Hospital Formulary Service
AHRQ	Agency for Healthcare Research and Quality
API	Active Pharmaceutical Ingredient
ARDS	Acute Respiratory Distress Syndrome
ASHP	American Society of Health-System Pharmacists
BCMA	Barcode Medicine Administration
BSA	Body Surface Area
CINV	Chemotherapy Induced Nausea and Vomiting
CPOE	Computerized Physician Order Entry
CPPU	Clinical Pharmacy Practice Unit
D10W	Dextrose in Water 10%
D5W	Dextrose in Water 5%
DRP	Drug Related Problems
EMC	Electronic Medicines Compendium
FDA	Food and Drug Administration
HID	Handbook of Injectable Drug
IDG	Injectable Drug Guide
IMG	Injectable Medicines Guide
IOM	Institute of Medicine
ISMP	Institute for Safe Medication Practice

IV	Intravenous
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
JHCO	Joint Commission on Accreditation of Healthcare Organizations
MAH	Marketing Authorization Holder
MAEs	Medication Administration Errors
MDH	Mater-Dei Hospital
MER	Medication Errors Reporting
MHRA	Medicines and Healthcare products Regulatory Agency
MIU	Medicines Information Unit
MMA	Malta Medicines Authority
MP	Medical Protocol
NHS	National Health System
NPSA	National Patient Safety Agency
NS	Normal Saline
PID	Paediatric Injectable Drugs
RMM	Risk Minimization Measures
SAMOC	Sir Anthony Mamo Oncology Centre
TPN	Total Parenteral Nutrition
UCL	University of College London
UK	United Kingdom
US FDA	United States of America Food Drug and Administration
USP	United States Pharmacopeia
WFI	Water for Injection

Chapter 1: Introduction

1.1 Background

This study will lead to the development of a Parenteral Drug Therapy Manual (PDTM) which contains information related to Intravenous (IV) drugs administered to paediatric patients at Mater Dei Hospital (MDH). The manual will be a group of drug monographs where each monograph is dedicated to only one active pharmaceutical ingredient (API). The monograph will contain information regarding reconstitution and dilution, methods of administration, stability and compatibility of medication, potential hazards of administration and monitoring requirements when administering a medication intravenously. The PDTM is a guidance for the preparation and administration of medications via parenteral routes to the paediatric patients at the acute general hospital of Malta where currently there is no PDTM for paediatrics.

The monographs will be developed in collaboration with the Clinical Pharmacy Practice Unit (CPPU) at MDH. The standard template that was used for the adult monographs of the PDTM will be used for the development of the paediatric monographs of PDTM. This template was adopted from other PDTMs such as Sheikh Khalifa Medical City (SKMC) monographs. The trade name and available strengths of each medication will be checked with the pharmacy stores at MDH. The manufacturer might be contacted for the availability of latest Summary of Product Characteristics (SmPC) and other detailed information of the product such as stability of medication following reconstitution or dilution. The prepared monographs will be reviewed by the pharmacists working at CPPU and will be validated by Quality Assurance (QA) department to be endorsed as a hospital guideline. The approved monographs will be released to the paediatric wards (Disneyland, Fairyland, Wonderland, Paediatric Day care, Rainbow and Paediatric Accidents & Emergency) and placed in the nursing station of each respective ward.

The monographs will be introduced to nurses working within these wards by conducting training on how to interpret and utilise information provided within the monographs. Testing the impact of having drug monographs on the use of IV medications at wards' level will be conducted to nurses working.

1.2 Patient Safety

One of the main concerns of health-care systems is patients' safety. Ever since the report *To Err Is Human: Building a Safer Health System* was released in 1999 by the Institute of Medicine (IOM), the subject of patient safety had grabbed the attention of several medical agencies to address the quality of healthcare (Brooke, 2007). The published number of deaths (44,000 to 98,000) caused by preventable medication errors raised the alarm to develop strategies and programs to enhance care and reduce medical errors within health systems (Di Simone et al, 2018).

World Health Organization (WHO) since 2001 has been emphasizing on patient safety and requesting organizations to implement preventive practices and measures.[1] The IOM recommended healthcare organizations to adopt non-traditional safety methodologies from other industries, such as aviation, to operate successfully high risk processes and activities with minimum failure rates (Kohn et al, 2009).

The Joint Commission on Accreditation of Healthcare Organizations (JHCO) established patient-safety standards and indicators for the accreditation process of

[1] WHO. World Health Organization regional office for Europe. Health topics. Internet [Cited 2019 Mar 28] Available from: http://www.euro.who.int/en/health-topics/Health-systems/patient-safety/patient-safety.

hospitals where several organizations had endorsed patient safety goals since then.[2] Hospitals in compliance with the patient safety standards developed written policies for medication errors and adopted the patient safety practices of Agency for Healthcare Research and Quality (AHRQ) (Altman et al, 2004).

WHO defines patients' safety as "*prevention of errors and adverse effects to patients associated with health care*" [3] whereas National Health Service (NHS) defines it as "*the avoidance of unintended or unexpected harm to people during the provision of health care*".[4] The AHRQ expands the term of patient safety to "*freedom from accidental or preventable injuries produced by medical care*" and safety practices as "*those that reduce the risk of adverse events related to exposure to medical care across a range of diagnoses or conditions*".[5] Examples of these are (i) prophylaxis of venous thromboembolism in patients at risk, (ii) patient self-management for warfarin to achieve optimal therapy and prevent adverse events (Mitchell, 2008).

Patient safety is directly linked to the quality of care. IOM recognises patients' safety as an essential component for establishing a high quality system within a health care institute (Mitchell, 2008). Nurses contribute to a major role in improving quality of care by identifying problems in safety, implementing solutions to enhance healthcare and monitoring and surveying patients for suspected patient safety incidents (Milligan and Dennis, 2005). Patient safety incidents are *"unintended or unexpected incidents which*

[2] Hoppes M, Mitchell J, Grady Venditti, E, Bunting R. Serious Safety Events: Getting to ZeroŒ [Internet]. Ashrm.org. 2012 [Cited 2019 Mar 28]. Available from: http://www.ashrm.org/pdfs/ASHRM-Whitepaper-Getting-to-Zero-Vol-1.pdf

[3] WHO. World Health Organization regional office for Europe. Health topics. Internet [Accessed 2019 Mar 28] Available from: http://www.euro.who.int/en/health-topics/Health-systems/patient-safety/patient-safety

[4] NHS. NHS Improvement. Patient safety. Internet [Cited 2019 Mar 28] Available from: https://improvement.nhs.uk/improvement-hub/patient-safety/

[5] AHRQ. Net Patient Safety Network. Patient safety. Internet [Cited 2019 Mar 28]. Available from : http://psnet.ahrq.gov/glossary.aspx#P

could have or did lead to harm for one or more patient" [6] or, *"An event or circumstance that could have resulted, or did result, in unnecessary harm to a patient*" (Cooper et al, 2018. Patient safety incidents in literature are referred to as adverse events or clinical errors (Milligan and Dennis, 2005).

1.3 Challenges with Intravenous (IV) Route

The IV route has various advantages and disadvantages. The benefits of IV medications are attributed to their immediate therapeutic effect, the potential to reach high plasma drug levels for an early target effect and it can be used in patients with difficulty in swallowing (Vijayakumar et al, 2014). The advantages of IV therapy qualified it as the preferred therapy for emergency cases and "*is considered as a critical component of current healthcare system, with over 90% of hospitalised patients receiving some form of infusion therapy"* (Corrigan A, 2010). Challenges encountered when using IV route include (i) complexity of procedure (ii) incompatibility issues and (iii) high risk of errors.

1.3.1 Complexity of IV Therapy

The complexity of the procedures and equipments used for IV therapy requires a team of healthcare professionals and advances in medical technology (McBride and Foureur, 2006a). The rapid introduction of new medications increases the opportunity of errors that endanger patient safety and affect quality of care (Anselmi et al, 2007). There is a risk of extravasation and phlebitis accompanying use of IV therapy that may not be present with the other routes such as subcutaneous and Intramuscular (IM) (Gray A,

[6] AHRQ.Agency for Healthcare Research and Quality Patient Safety network. Pharmacist's role in medication safety [Internet]. Rockville: US Department of Health and Human Services; January 2019 [Cited 2019 Mar 28]. 3p. Available from: https://psnet.ahrq.gov/primers/primer/46/The-Pharmacists-Role-in-Medication-Safety

2011). Preparation of IV medications can be complicated, time consuming and involves multiple steps and complex calculations. The preparation requires adequate knowledge of incompatible fluids and the choice of diluents/solvents while administration requires knowledge of infusion devices and ability to choose among theit different types (Mole, 2010).

1.3.2 Drug Incompatibilities

Different challenges arise with the use of IV route where the drug has to be reconstituted or diluted using a suitable diluent to prevent incompatibility issues. Incompatibility occurs when solutions are mixed in the same syringe/infusion bag or co-administered at same or different site (Murney, 2008). Incompatibility can occur between a drug and other drugs or diluents or materials of IV container or medical device (Maison et al, 2018). Complications which may arise of incompatibilities include (i) particulate contamination (ii) drug impaired stability and potency and (iii) adverse events (UCLH Pharmacy team, 2010).

Incompatibility reactions or incomplete reconstitution during drug preparation can lead to particulate contamination of IV infusions. Contamination can result from the particles of the glass of vial/ampoule or rubber stopper or even from parenteral nutrition (Jack et al, 2012). Presence of glass particles along with insoluble drug particles increase particle burden and may occlude the IV line and even some blood vessels (Yorioka et al, 2006). IV line occlusion is dangerous in critically ill patients where the introduction of many contaminated infusion fluids per day can lead to serious complications (Jack et al, 2010). Examples of such complications is damage of pulmonary endothelium either directly or by triggering an immune reaction in children with Acute Respiratory Distress

Syndrome (ARDS) or thrombophlebitis (Lehr et al, 2002). Filtration of IV infusion fluids prior to administration is recommended as a preventive measure to reduce thrombophlebitis, systemic inflammatory reactions and other sever events (ARDs, acute renal failure, circulatory failure) in critically ill paediatric patients (Lingen et al, 2004; Yorioka et al, 2006 ; Jack et al, 2012).

Drug impaired potency can result from drug-drug incompatibility where the effect of one drug is inactivated by another (Maiso et al, 2018). The action of aminoglycosides may be disrupted when co-administered with antibiotics from other classes which may be prescribed together e.g amoxicillin, cefotaxime, ceftazidime and ceftriaxone.[7]

Selection of a wrong diluent may affect solubility and stability of a reconstituted medication which would lead to drug powder precipitation and eventually administration of insoluble particles to the patient (Cousins et al, 2005). One example is the stability of imipenem-cilastatin is impaired with Lactate containing solvents (Haartman, parenteral nutrition).[8] Furthermore, drug incompatibility may not be detected at room light for example; when piperacillin–tazobactam is mixed with acyclovir, particles that are invisible to room light can form.[9] Severe chemical incompatibilities between drugs can lead to drug degradation and loss such as when mixing cefepime with theophylline (Baririan et al, 2003).

[7] Wright J, Gray A, Bruce L, Howard A. Injectable Drugs Guide - MedicinesComplete. [Internet] [cited 2019 Mar 28] London: Pharmaceutical Press. 2014. Available from https://www.medicinescomplete.com/#/content/idg/G03-mn0001?hspl=Gentamicin

[8] MHRA. SPC-PIL Imipenem/Cilastatin 250 mg/250 mg, 500 mg/500 mg MHRA. Summary of Product Characteristics. MHRA [Internet] 2017[cited 2019 Mar 28]. Available from: http://www.mhra.gov.uk/spc-pil/

[9] AHFS.Handbook on Injectable Drugs, 19th Edition [Internet]. AHFS Drug Information. 2017 [cited 2019 Mar 28]. Available from: https://about.medicinescomplete.com/publication/handbook-on-injectable-drugs/

Drug incompatibility poses a greater challenge and risk in critically ill paediatric patients and neonates (Sherwin et al, 2014). Paediatric and neonatal patients have limited number of independent IV lines, require to administer multiple dugs intravenously or to maintain an IV constant concentrations of some medications e.g. vasoactive (Stucky, 2003). These needs restrict the compatible options and pose greater difficulties with the administration of medications via IV route (Lingen et al, 2004). Co-administration of incompatible drugs or fluids can lead to fatal complications in neonatal patients, an example is ceftriaxone and calcium containing products. Ceftriaxone should never be mixed with calcium containing products or administered simultaneously or even sequentially unless infusion line is thoroughly flushed with a compatible fluid.[10,11,12,13] If co-administration occurred then calcium-ceftriaxone compounds would precipitate in the heart and lungs of neonates leading to death.[10-13] Other types of complications that would result from incompatibility are variations in pH of infusion, drug degradation or formation (Linakisi, 2016).

The complications involved in IV therapy demands experience and knowledge of the professional not only in terms of choice of therapy but as well of physiochemical compatible options (Jack et al, 2012).

[10] MHRA- SPC-PIL Ceftriaxone 500 mg, 1g, 2g Summary of product characteristics MHRA [Internet] 2014 [Cited 2019 Mar 28]. Available from http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/

[11] Buckingham R (ed). Martindale – Medicines Complete. Pharmaceutical Press [Internet] 2018. Available from: https://www.medicinescomplete.com/#/content/martindale/12547-l?hspl=CefTRIAXone%20Sodium

[12] Phelps SJ (ed). Paediatric Injectable Drugs – Medicines Complete. Pharmaceutical Press [Internet] 2017. [Cited 2019 Mar 28] Available from https://www.medicinescomplete.com/# /content/pid/CefTRIAXone_Sodium?hspl=Ceftriaxone%20Sodium.

[13] British National Formulary for Children – Medicines Complete. Pharmaceutical Press [Internet] 2018. [Cited 2019 Mar 28] Available from https://www.medicinescomplete.com/#/content/bnfc/_780622395?hspl=CefTRIAXone%20Sodium

1.3.3 Medication Errors Associated with IV Route

Medication errors are *"any preventable events that may lead to inappropriate medication use or affect patient safety*".[14] Medication errors can occur at any stage in medication therapy, for example, prescribing, labelling, packaging, dispensing, preparation, administration, education or monitoring (Aronson, 2009; Di Simone et al, 2018).

Medication administration has been defined by the Nursing Intervention Classification *(*NIC) as *"preparing, giving, and evaluating effectiveness of prescription and non-prescription medications*" (Butcher et al, 2013). Medication administration errors (MAEs) are defined as *"any deviation of preparation or administration of drug from the doctor's prescription order, the manufacturer's instructions or the hospital drug policy*" (Wirtz et al, 2003; Cousins et al, 2005; Mcbride and Foureur, 2006b; Keers et al, 2013).

Medication errors can occur with all administration routes but the incidence of errors with IV route is higher than other routes (Cousins et al, 2005; Westbrook et al, 2011; Di Muzio et al, 2017). The probability of an IV dose to be associated with MAEs is five times the probability of non-IV doses and the type of error associated with IV MAEs is more severe (Keers et al, 2015).

IV medication preparation and administration is a complex procedure with high prevalence for medication errors (Wirtz et al, 2003). Errors occur with nearly half of IV medication preparations and administrations (Taxis and Barber, 2003; Cousins et al,

[14] WHO. Medication Errors: Technical Series on Safer Primary Care [Internet]. Apps.who.int. 2016 [Cited 2019 Mar 28]. Available from: https://apps.who.int/iris/bitstream/handle/10665/252274/9789241511643-eng.pdf;jsessionid=D44CD1E12E1487B81B72006E209E33A5?sequence=1

2005). IV preparation and administration errors are classified as serious medication errors in hospitals (Westbrook et al, 2011; Hayes, 2015; Fedaku et al, 2017; Di Simone et al, 2018).

IV medications are used in different patient care areas but frequently in critical patients, who are less tolerant towards medication errors (Wilson and Sullivan 2004). The IV medications were reported to be associated with 56% of medication errors and 54% of potential adverse drug events (ADEs) (Fields and Peterman 2005). Due to the immediate bioavailability of IV route even a minor error in the dose can result in serious adverse effects such as life-threatening complications (Hicks et al, 2004; Kunle et al 2014; Fekadu et al, 2017). Preparation and administration of IV medications is one of the most risky steps in whole medication therapy process (Wilmer et al, 2010; McDowell et al, 2010).

IV MAEs were reported to occur frequently during drug reconstitution and administration (Nguyen et al, 2014). One out of every three ADEs reported were related to nurses administering medications to patients (Kale et al, 2012). A survey by Institute for Safe Medication Practices (ISMP) about administration of IV push medications gave an insight into the risky unnecessary dilution processes of several medications administered by nurses.[15] The corresponding probability an error to occur during parenteral medications administration and preparation is approximately 0.73 and reconstitution of the drug and the diluent contributed to most errors (McDowell et al, 2010).

[15]ISMP .Institute for Safe Medication Practices (ISMP). Some IV Medications Are Diluted Unnecessarily In Patient Care Areas [Internet] Horsham; 2005 [cited 2019 Mar 28]Available from: https://www.ismp.org/newsletters/acutecare/showarticle.aspx?id=82

A substantial proportion of IV MAEs occur in hospitalized paediatric patients due to the greater complexity in dosing and administration.[16] As many as 1 in 10 children who are hospitalised are affected by a medication error and up to 35% of the errors are classified as serious or life threatening (Phillips et al, 2001). A total number of 2537 MAEs were identified in 8894 doses administered to hospitalised children (Ameer et al, 2015). One of every four administered doses was almost associated with a medication preparation or administration error (Chedoe et al, 2012).

The prevalence rates of MAEs in paediatric inpatients are high but the occurred incident rates vary significantly. The variability of the incidence data is attributed to the different methodological approaches applied in detecting MAEs. Direct observation technique (prospective), reviewing incident reports of medication errors (retrospective) and reviewing medication charts were the implemented methods in literature to detect MAEs. These methods were implemented as well to assess the compliance with protocols in administration practice in a pre and post intervention design (Tromp, 2008; Jones, 2009; Hardmeier et al, 2014; Okumura et al, 2016).

Direct observation technique is where an observer (trained healthcare professional) would monitor the nurse while preparing and administering IV medications before and after introducing an intervention and document observed MAEs throughout the process (Flynn et al, 2002; Tromp, 2008; Berdot et al, 2013). The recommended method to evaluate the effect of an intervention is the observation technique which can be used together with the incident report to better characterize the scope of MAEs (Hardmeier et al, 2014).

[16] AHRQ. Agency for Healthcare Research and Quality Patient Safety network. Medication Administration Errors [Internet]. Rockville: US Department of Health and Human Services; September 2018 [cited 2019 Mar 28]. 4p. Available from: https://psnet.ahrq.gov/primers/primer/47

A study by Keers et al (2013) noticed that the occurrence rate of MAEs is between 17.4 and 33.8 per 100 opportunities of error. A study by Ghaleb et al (2010) identified a MAE occurrence rate of 19.1 per 100 opportunities of error. Miller et al (2007) focused on analysing medication error reports in paediatric wards and observed a MAE occurrence rate of 56.4 per 100 medication reports.

The risk of medication errors tend to be three times higher in paediatric patients than in adults (Ferranti et al, 2008). Paediatric patients are more prone to adverse outcomes arising from medication errors compared to adult patients (Cowley et al, 2001). A variety of factors make children more susceptible to medication errors (i) the lack of clinical trials involving paediatrics which leads to limited information about drug dosages and pharmacokinetic properties (Chua et al, 2010) (ii) the lack of appropriate medication dosages and strengths for use in children which requires frequent dilutions and (iii) inter-patient variations (Kaushal et al, 2001; Gonzales, 2010; Ameer et al, 2015). Paediatric dosing is based on body weight which requires dosage calculations, and complicates determining safe dosages for paediatric patients (Chua et al, 2010; Chedoe et al, 2012).

The most common types of MAEs associated with IV route in neonates and children were the preparation errors, administration at wrong time (Raja et al, 2009; Chedoe et al, 2012) and administration of incorrect dose (Cowley et al, 2001; Stucky 2003, Ghaleb et al, 2010).[17] The most commonly reported medication classes with MAEs in children were antibiotics (Chedoe et al, 2012; Niemann, 2015) and sedatives due to their frequent use (Cowley et al, 2001; Ghaleb et al, 2006). Antibiotics accounted for most

[17] National Reporting and Learning Service. Review of patient safety for children and young people [Internet]. National Patient Safety Agency. London; 2009 [Cited 2019 Mar 28].Available from URL: http://www.nrls.npsa.nhs.uk/resources/?entryid45=59864.

ADEs in hospitalized children (Holdsworth et al, 2003). The reasons that antibiotics are frequently associated with MAEs are due to encountered difficulties in dose calculations and preparation of IV infusions and the need to give it at correct intervals (Ameer et al, 2015). Learning the causes of the medication errors associated with IV route aid in adopting effective strategies to avert these errors during IV therapy.[18]

1.3.4 Factors Contributing to IV MAEs and Interventions to Reduce MAEs

Investigating system factors aid in understanding the causes of medication errors and the real reasons behind failures in maintaining patient safety. Multiple factors contribute to medication errors including MAEs that are associated with the IV route. Some of the contributing factors reported are:

(i) Absence of practical procedures (Taxis and Barber, 2003; Stavroudis et al, 2010; Westbrook et al, 2011; Chedoe et al, 2012).

(ii) Inadequate nurses' knowledge and training about IV medications (Benner et al, 2002 ;Lefrak, 2002; Lu MC et al, 2011; Abbasinazari et al, 2012; Lan et al, 2014).

(iii) Deviations from standard administration guidelines or lack of adherence to medications administration protocols (Manias et al, 2004; Reason, 2004; Gonzales, 2010; Ameer et al, 2015).

(iv) Nurses' experience (Taxis and Barber, 2003; Stavroudis et al, 2010; Westbrook et al, 2011).

(v) Illegible handwriting (DeHenau et al, 2016).

(vi) Drugs with similar names (Petrova et al, 2010).

[18] Shastay A, Smetzer J, Cohen M, Jenkins R. Results of Survey on Paediatric Medication Safety [Internet] .Institute for Safe Medication Practices (ISMP). Horsham; 2015 [Cited 2019 Mar 28]; 13 (7). Available from: http://www.ismp.org/newsletters/nursing/issues/NurseAdviseERR201507.pdf

(vii) Lack of double checking of the dose to be administered (Stratton et al, 2004; DeHenau et al, 2016).

(viii) Inadequate staff (You et al, 2015).

(ix) Complicated dose calculations (Dowdell, 2004)

(x) Distractions and interruptions during medication preparation and administration (Gonzales, 2010; Niemann et al, 2015; Di Muzio, 2017).

Developing an understanding of the factors that contribute to medication errors will aid in designing the most appropriate interventions and hence optimum risk minimisation could be achieved (Kaplan and Fastman, 2003).

Multiple risk minimisation measures (RMMs) were studied in literature where several different interventions were proposed to reduce preventable medication errors in particular MAEs. These interventions were set to address the reported causes and factors within a system that lead to medication errors (Niemann et al, 2015; Berdot et al, 2016). The effectiveness of these interventions in error prevention and reduction of risks associated with delivering a therapy was evaluated (Nguyen et al, 2017). The studied interventions were (i) use of barcode medicine administration (BCMA) (Hardmeier et al, 2014), (ii) computerized physician order entry (CPOE), (iii) smart infusion pumps and (iv) education and training (Ameer et al, 2015).

BCMA intervention involves the use of matching barcodes for the administered medication and the wristband worn by the patient. The barcode contains patient's identification details and has to be scanned against the barcode of the medication to verify that the medication is for the correct patient and is the correct prescribed

medication (Ameer et al, 2015; Nguyen et al, 2017). BCMA reduced the rate of MAEs to 5% of total administered doses in post-intervention (Hardmeier et al, 2014) and from a rate of 48% of total medication errors (pre-intervention) to 30% of total medication errors in paediatric patients (post-intervention) (Morriss et al, 2009).

CPOE is an electronic prescribing where a prescription for dispensing and administration is generated electronically (Samadbeik et al, 2017). MAEs were found to be lower when implementing CPOE (22.5%) compared to handwritten prescriptions (29.3%) (Fontan et al, 2003; Frith, 2013). CPOE increased the probability of detecting MAEs by nurses against handwritten prescription where 53% of MAEs were identified when using CPOE versus 40% of MAEs identified when using handwritten prescription (Sowan et al, 2010).

Smart infusion pumps are devices with in-built system designed to intercept doses of medications that are outside the safe ranges thus reducing MAEs related to incorrect doses (Trbovich et al, 2010). CPOE, BCMA and smart infusion pumps all warrant use of technology scanning for generating electronic prescription and scanning barcodes which might not be available in all settings.

Educational interventions are set to increase the awareness of healthcare professionals about medications and their use. Educational interventions were found to impact medication safety and reduce the rate of MAEs (Chedoe et al, 2012). Educational interventions were in the form of (i) simulation-based teaching (Ford et al, 2010; Stewart et al, 2010) or a (ii) combination of written material, lectures and practical teaching session (Bertsche et al, 2010; Niemann et al, 2015), (iii) posters and lectures

(Raja et al, 2009), (iv) training-related where specialised medication nurses trained nurses and supervised medication administration (Greengold et al, 2003) or a (v) pharmacist-led training programme (Nguyen et al, 2014) , (vi) interactive CD-ROM program that promote basic safety principles of medication administration (Schneider et al,2006) and (vii) guidelines and protocols to guide the safe use of medications (Ellis et al,2011; Niemann et al, 2015; Campino et al, 2016).

The effect of educational interventions on medication errors was studied in pre/post-test design or intervention group vs control group. Educational programmes in the form of posters and lectures reduced errors of wrong adminsitration time from 31% (pre-intervention) to 15% (post-intervention) (Raja et al, 2009). MAEs were decreased from 22 events (pre-intervention) to 3 events (post-intervention) in paediatric medical units (Keiffer et al, 2015). Simulation based training and education of nursing students improved the knowledge and increased the percentage of students who administered medications correctly to paediatric patients from 22% (pre-intervention) to 96% (post-intervention). Educational programs could target parents of paediatric children in addidtion to the nurses (Bertsche et al, 2010).

The types of IV MAEs affected by educational interventions were incorrect reconstitution and wrong administration where rate was reduced from 49% (pre-intervention) to 31% (post-intervention) (Chedoe et al, 2012; Nguyen et al, 2014). Educational interventions had an impact on error rate of incorrect preparation, incorrect administration technique and wrong time errors (Greengold et al, 2003; Ford et al, 2010) but no significant impact on the wrong drug/dose was observed (Berdot et al, 2016).

Double-checking or pre-printed charts which eliminate the need for calculations and reduce calculation errors can be a type of interventions (De Wildt et al, 2007). Emphasizing on a safety culture by improving awareness about the prevention of errors during preparation and administration of IV medications can be part of interventions (Valentin et al, 2013) as well. Even promoting adherence to existing practical procedures and protocols of medication administration is a form of intervention that successfully had led to reduction in errors of time of administration from 31% to 15.4% (Raja et al, 2009).

Developing institutional guidelines to guide the preparation and administration of medications were recommended as an intervention to reduce the risk of errors (Davis el al, 2009). Policies of medication administration can be introduced within a clinical setting as a uniform resource to increase knowledge and improve the safety of administration practice (Di Muzio et al, 2017).

1.4 Need for Guidance of Intravenous Administration

The practice of prescription, preparation, and administration of IV medications forms an important part of the therapeutic process. The lack of guidance for administration of IV medications has led to significant variations in practice within different sectors of healthcare organisations (Grissinger, 2017).[19] Timely access to knowledge at the point of care is critical for safety and quality in medication administration and monitoring (Hughes and Blegen, 2008). [20]

[19] Institute for Safe Medication Practices (ISMP). Some IV Medications Are Diluted Unnecessarily In Patient Care Areas. [Internet]. Horsham; 2005 [cited 2019 Mar 28] Available from: https://www.ismp.org/newsletters/acutecare/showarticle.aspx?id=82

[20] Smeulers M, Verweij L, Maaskant J, de Boer M, Krediet C, Nieveen van Dijkum E et al. Quality Indicators for Safe Medication Preparation and Administration: A Systematic Review. PLOS ONE [Internet]. 2015 [cited 29 March 2019];10(4):e0122695. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4401721/

The National Patient Safety Agency (NPSA) issued an alert in 2007 to promote the safe use of Injectable medicines. The NPSA recommends availalablity of written information about handling injectables at the point of medication preparation. NPSA highlighted risks associated with the administration of injectable medicines and suggested a multi-faceted solution approach for risk minimisation such as risk assessment of procedures, formulation for standard operating policies ,audit tools, training packages and competency assessments for staff.[21] ISMP assigned IV medications with high susceptibility to harm as high-alert medications like adrenergic agonists and antagonists, antiarrhythmic, opioids and concentrated electrolytes. [22,23]

Standardised drug information related to administration of IV medications may decrease risks associated with variations in administration practice resulting from vague information such as choice of compatible diluents (Billstein-Leber et al, 2018). References should indicate the rate of IV administration instead of using ambiguous terminology such as IV push, IV bolus, "slow" or "fast" and specify whether an adjustment of the dose or frequency of administration is required according to the patient's clinical status. [23] Standardised product information should be easily accessible for the administrator of IV medication at the point of use (Gray, 2011; Billstein-et al, 2018). The administrator should have sufficient knowledge regarding the therapeutic

[21] National Patient Safety Agency (NPSA). Promoting safer use of injectable medicines [Internet] London; 2007 [cited 2019 Mar 28] Available from: http://www.nrls.npsa.nhs.uk/resources/?EntryId45=59812

[22] Institute for Safe Medication Practices (ISMP). ISMP Safe Practice Guidelines for Adult IV Push Medications [Internet] Lakeside, Horsham; 2005 [cited 2019 Mar 28] Available from: http://www.ismp.org/Tools/guidelines/ivsummitpush/ivpushmedguidelines.pdf

[23] ISMP. List of High-Alert medications in acute care settings [Internet]. Canada: ISMP; 2018 August 23 [2019 Mar 28] Available from: https://www.ismp.org/recommendations/high-alert-medications-acute-list

properties of a medication, precautions, contraindications, side effects, interactions and dealing with ADRs.[24]

The high prevalence of MAEs and severity of the associated harm necessitated addressing the contributing factors. Commonly identified factors were lack of or poor accessibility to policies and administration protocols for the use of IV medications (Taxis and Barber, 2004; Jones et al, 2010; Ozkan et al, 2011). Other factors were violations of policies or protocols (Chua et al, 2010) and insufficient knowledge (Keers et al, 2013). Developing guidelines for appropriate and standard use of medications is recommended to avoid dilution mistakes, wrong reconstitution practices and variabilities in preparing and administering medications. [25]

1.4.1 The Need of Standardised Medication Administration Guidance for Nurses

The responsibility of proper administration of medications lies with the nursing profession (O'Shea et al, 1999). Medication administration within hospital setting represents 40% of nurses' activities (Doughtery et al, 2012; Di Muzio et al, 2017). The final step in delivering drug therapy is administering medications thus nurses are considered to be the last safeguards or checkpoints for hospitalized patients from MAEs (Dowdell, 2004; Lapkin S et al, 2016). Nurses are more likely to detect a medication error before other healthcare professionals will detect it (Kohn et al, 2009).

[24] NCC. National Coordinating Council for Medication Error Reporting and Prevention. Recommendations to enhance accuracy of administration of medications [Internet] Boston; 1999 [Cited 2019 Mar 28] Available from: http://www.nccmerp.org/council/council1999-06-29.html

[25] ISMP. Institute for Safe Medication Practices. ISMP Safe Practice Guidelines for Adult IV Push Medications [Internet] July 2015 [cited 2019 Mar 29]. Available from: https://www.ismp.org/sites/default/files/attachments/2017-11/ISMP97-Guidelines-071415-3.%20FINAL.pdf

Medication errors are common events that occur with nursing activities (Ozkan et al, 2011). Nurses can be educated about the concept of patient safety and preventive measures of MA (Despins et al, 2010).

Nurses' duties are not restricted to preparation and administration of IV medication only (Durham, 2015). Each nurse within a clinical entity is accountable for keeping abreast with current practices and to check and administer medications (Needleman and Hassmiller 2009). Nurses are also required to monitor effectiveness of treatment, report ADRs and to teach patients about their drugs (Farre A et al, 2017).

As part of the accountability of a nurse's profession a nurse has to investigate the following before administering IV therapy to avoid preventable adverse reactions such as (The nursing and midwifery council, 2008)

- Presence of patient's allergies to the medication that would be administered like penicillin allergy when administering antibiotics.
- Patient's condition if it permits administration of a medication such as use of Digoxin in patient with pulse below 60.
- Contraindicating co-existing therapy such as administration of Ceftriaxone in a neonate requiring parenteral nutrition that contains calcium.[26]

[26] NMC-Standards for medicines-management [Internet]. Nipec.hscni.net. 2010 [cited 2019 Mar 28]. Available from: http://www.nipec.hscni.net/midwivesandmedicines/NMC-Standards-for-medicines-management.pdf

The complexity associated with the administration of medications led to the developing the rights of nurses. The rights include right patient, right drug, right time, right route, and right dose (Grissinger, 2010). It is the right of the nurse to have guidance on administration of medications and the health care administrators are responsible to provide the necessary requirements for nurses to administer medications safely.[27] Nurses also have the right to have access to updated drug information when reconstitution and dilution is carried outside pharmacy area (Shastay, 2016). An updated drug reference book and a hospital formulary have to be made available to nurses who administer medications. Pharmacists being the drug experts, should be available 24 hours, and provide necessary support to nurses to improve patient safety and reduce the medication errors, but availability of pharmacists all the time is difficult.[28] The presence of a quick reference guide to be used when a pharmacist cannot be reached might perhaps compensate for the absence and inability to consult a pharmacist about administration of a medication on the spot.

Fulfilling the responsibilities and duties of a nurse in preparation, administration and monitoring of treatment requires continuous updating of pharmacological knowledge (Durham, 2015). Making healthcare safe requires redesigning the system to create a culture in which risks are identified, errors prevented and patient's safety is regarded as the responsibility of everyone. The responsibility of a pharmacist and healthcare management is to develop and adopt strategies that facilitate the reduction of preventable errors such as MAEs (Galt et al, 2019). Such strategies can be in the form

[27] NMBI.Guidance to Nurses and Midwives on Medication Management [Internet]. Nmbi.ie. 2007 [cited 2019 Mar 28]. Available from: https://www.nmbi.ie/NMBI/media/NMBI/Guidance-Medicines-Management_1.pdf

[28] Cook MC. Massachusetts Nurses Association (MNA) [Internet] 2017 [cited 2019 Mar 28]. Nurses' six rights for safe medication administration. Available from: http://www.massnurses.org/nursing-resources/nursing-practice/articles/six-rights

of a standard guidance for the safe use of IV medications where information for preparation and administration of IV medications is available and accessible for nurses to reduce preventable MAEs (Di Muzio et al, 2017).

1.5 Parenteral Drug Therapy Manual (PDTM)

A Parenteral manual is "*a document or database explaining how to handle medicinal products that are administered parenterally. Apart from therapy related information, it deals with the reconstitution of medicinal products including dissolution, dilution in infusion bags or syringe pumps, compatibility with other medicines and adverse reaction"*. [29] A manual is a collection of monographs where each monograph is dedicated to one active ingredient with all the available strengths containing all the relative information necessary to guide the safe use of IV medications; Prescription, dose calculation, preparation, reconstitution, dilution, administration and monitoring of therapeutic effects and adverse effects.

The use of manuals for drug therapies is adopted in various settings abroad in different countries. [30,31,32,33,34] Some of these manuals were developed specifically to guide the

[29] Council of Europe. Committee of Ministers. Resolution CM/Res (2016) 2 on good reconstitution practices in health care establishments for medicinal products for parenteral use adopted by the Committee of Ministers on 1 June 2016 at the 1258th meeting of the Ministers' Deputies [Internet] 2016 [cited 2019 Mar 28].Available from: https://www.edqm.eu/sites/default/files/resolution_cm_res_2016_1_quality_and_safety_assurance_requirements_for_medicinal_products_prepared_in_pharmacies.pdf

[30] The Ottawa Hospital Parenteral Drug Therapy Manual [Internet]. Ottawa: The Ottawa hospital; 2016 [cited 2019 Mar 28]. Available from: https://www.ottawahospital.on.ca/wps/portal/Base/TheHospital/ClinicalServices/DeptPgrmCS/Departments/Pharmacy/Publications

[31] Vancouver Acute Pharmaceutical sciences [Internet]. Vancouver: VGH pharmacy; 2016. [cited 2019 Mar 28]. Parenteral Drug Therapy Manual. Available from: http://www.vhpharmsci.com/PagePDTM/index.html

[32] Alberta health services [Internet]. Alberta. Knowledge resource services; 2017 January 5; [cited 2019 Mar 28]. Available from: http://krs.libguides.com/druginfoguide/parenterals

[33] Drug monographs [Internet]. London Canada: London Health Sciences Centre. January 6; cited [2019 Mar 28]. Available from: http://www.lhsc.on.ca/Health_Professionals/CCTC/monograph/

[34] Sheikh Khalifa Medical City Parenteral Drug Therapy Manual

dosing and administration of parenteral medications used in paediatrics and neonatal wards.[35] The monographs of these manuals contain information about indication, dosage, reconstitution, administration, stability, compatibility and potential hazards of administration.

The monograph will provide details from various medical resources, references, published literature, published drug monographs used in other hospital settings and evidence based practice to aid the healthcare professionals in prescribing correct dose for the licensed use of a medication, calculating necessary doses for children, preparation and administration of medications and monitoring. The paediatric drug monographs of the PDTM will be distributed to the paediatric wards at MDH to assist healthcare professionals with the use of IV medications in the paediatric patients. PDTM will provide an easy to use reliable reference and guide for healthcare professionals for the proper IV medication administration.

1.6 Pharmacist Role in IV Therapy

Hospital safety could be improved significantly by investing in clinical pharmacy services (Bond et al, 2002). The role of pharmacists is maintaining patient safety and increasing the quality of healthcare by identifying and developing solutions to drug related problems (DRP) (Vijayakumar et al, 2014). Pharmacists play a vital role in delivering safe IV therapy through participating in nurse training and education which can be obtained by pharmacological education of nursing staff and updating their

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[Internet]. Abu-Dhabi. Sheikh Khalifa Medical City C2014-2016; [Cited 2019 Mar 18]. Available from:https://www.seha.ae/SKMC/English/Pages/default.aspx

[35] Alberta health services [Internet].; 2017 January 5; [cited 2019 Mar 28]. Available from: http://krs.libguides.com/druginfoguide/parenterals

knowledge on new therapeutics and new clinical practice guidelines. [36] Pharmacist provide expert advice on the use of IV therapy whether by direct intervention during the process of preparation and administration of IV medications or by developing protocols that guide the nurses and healthcare professionals (Abbasinazari et al, 2012).

Involvement of a clinical pharmacist and clinical pharmacy services in the area of IV therapy reported to reduce medication errors (Nguyen et al, 2017). Drug information service was the most effective type of pharmacy services that lead to a decrease in medication errors which adversely affected patient outcome (Bond et al, 2002). Other services included in-service education where a pharmacist provides continuous education to other healthcare professionals (physicians, nurses and fellow pharmacists) (Ford et al, 2010; Berdot et al, 2016). Drug information service promotes better health through addressing lack of knowledge which is a common causes of adverse events (Krahenbiihl'-Melcher et al, 2007). Presence of drug information service indicates that pharmacists have a valuable input within a multidisciplinary team where they are being consulted in drug management process (Leap et al, 1995; Lesar et al, 1997).

[36] Agency for Healthcare Research and Quality Patient Safety network. Pharmacist's role in medication safety [Internet]. Rockville: US Department of Health and Human Services; August 2018 [cited 2018 Nov 14]. 3p. Available from: https://psnet.ahrq.gov/primers/primer/46/The-Pharmacists-Role-in-Medication-Safety

1.7 Rationale of the Study

There is the need to develop guidelines for IV medications administered to paediatrics. A manual for medications administered intravenously to adults was developed at MDH.

As for the Neonatal Paediatric Intensive Care Unit (NPICU) clinical pharmacist together with the nursing head developed and established guidance for the administration of high alert medications to reduce medication errors. The issued guidelines are in the form of charts designed to guide nurses with the doses, frequency and route of administration.

Developing and establishing tools such as manuals, to be used at paediatric wards will aid nurses during administration of medications. Manual will also serve as a quick reference to check any required information with regards to medications that are administered intravenously, without the need to search for the information or to contact the Medicines Information Unit. Availability of a concise guide will contribute not only to save the time spent by nurses searching for information or waiting for their queries to be answered but as well the time required by pharmacists at Medicines Information Unit to answer these queries. This might assist the pharmacists to dedicate their time to other types of queries and perhaps save the time of other healthcare professionals who are consulting Medicines Information Unit.

Despite the availability of various drug monographs online and availability of the information within different resources; developing a monograph that contains information specific for the brand and the strength of medication being used in the local setting in Malta might minimise risks associated with look-alike or sound alike

medications. This is attributed to the fact that each monograph carries the description of each available strength of a medication in terms of the vial volume, appearance of medication, manufacturer name and name of the brand if applicable. The information listed is tailored to the mentioned strength and the brand; reconstitution, dilution instructions, displacement value and even other types of common information such as therapeutic indication. These brand-specific information are directly adopted from the latest Summary of Product Characteristics (SmPC) and in some cases from the manufacturer of the brand.

1.8 Research Question

The review of underlying causes, factors and scenarios leading to MAEs with IV route in the wards' level gave rise to the research question:

Will introducing a standardised guide for the use of IV medications:

1- Address the factors contributing to MAEs in paediatric wards?

2- Improve the knowledge of nurses about the use of IV medications?

3- Can contribute to safer practice?

1.9 Aims and Objectives

The aim of this research is to develop a manual for medications administered through IV route in the paediatric wards at Mater Dei Hospital (MDH).

The objectives of the study are to:

- Develop and validate monographs for the paediatric wards at MDH.
- Develop and administer a questionnaire to evaluate the impact of drug monographs on the knowledge, confidence and contributing factors to medication errors from nurses' perspective in a pre/post-test design.

Chapter 2: Methodology

2.1 Methodology Overview

The study was conducted in three phases. The first phase involved identification of the medications for which monographs would be developed. The second phase consisted of developing monographs and identifying sources of information to be used as references. The third phase entailed the validation of the monographs and evaluation of the impact of introducing them at wards level on the administration practice.

2.2 Identification of the Medications

The most commonly used medications were identified by three processes (i) accessing pharmacy databases at Mater Dei Hospital (MDH) using Access Stats program, (ii) conducting a survey for nurses working in the paediatric wards and (iii) interviewing nurses in charge of each ward.

2.2.1 Medication Consumption Reports

Pharmacy databases (Access Dimension) provide detailed reports of the monthly consumption of each item (medications, diluents, solvents, IV fluids) by each ward at MDH. Extraction of the consumption data of the 6 paediatric wards (Disneyland, Fairyland, Wonderland, Paediatric Day Care, Rainbow, Paediatric Accidents and Emergency) during the period 2007-2016 was conducted (Figure 2.1). The reason for selecting this time period is lack of documented and accurate data for the years before the year 2007 due to transfer of the registers and change in the division of the wards during the move from St. Luke hospital to MDH.

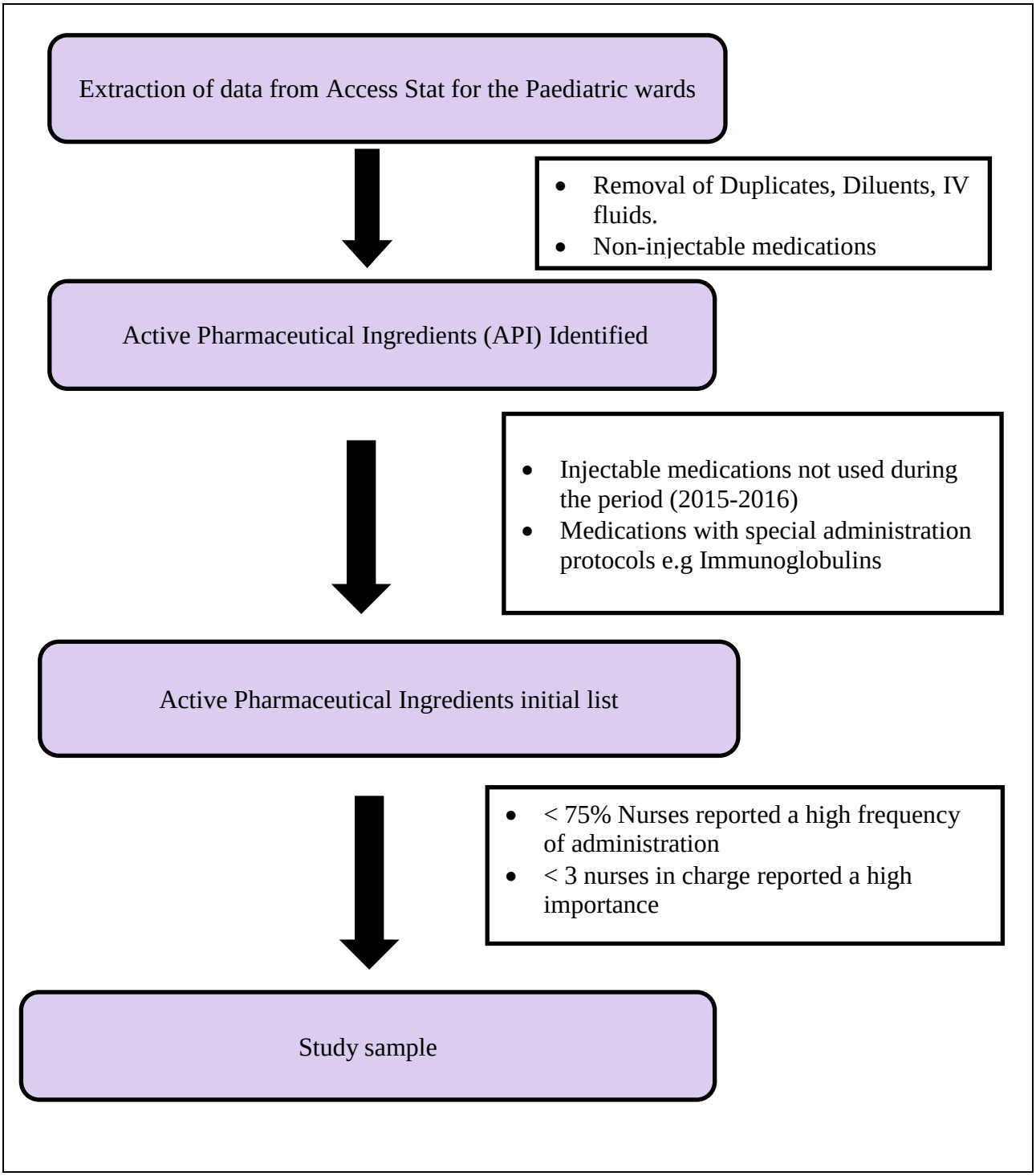

Figure 2. 1 Methodology Involved in Identification of Medication for Study Sample

Extracted data contained all the items consumed by each ward per each month of the selected period and were filtered using defined inclusion/exclusion criteria (Table 2.1) Duplicates, solvents, IV fluids and diluents were removed to retrieve consumption reports of medications. Data of medications consumed was further filtered to remove medications that are administered by non-IV route like tablets, cream, inhalers. The injectable medications were then analysed and different strengths available for each medication were merged to obtain unique active pharmaceutical ingredient (API). Microsoft® Excel programme was used for the analysis and calculation of medication consumption for each ward.

Table 2. 1 Inclusion/Exclusion Criteria for the Sample of Medications

Inclusion criteria	Exclusion criteria
Used by all paediatric wards	One or more paediatric ward reported not to use it during the period 2015-2016
Was consumed during the period 2015-2016	Has special administration protocol e.g. Immunoglobulins Chemotherapeutics
Rate of administration scored 4 or higher by at least 75% of nurses	Diluents and IV fluids e.g Normal saline (NS), dextrose in water (D5W), lactated ringer solution….etc.)

APIs that were not used by one of the paediatric wards over the past years (2015 and 2016) were excluded. The rational of selecting this period is due to lack of availability of specific medication consumption reports for the Paediatric Accidents and Emergency (A&E) ward from pharmacy databases prior to 2015.

The available data prior to 2015 was for the consumption of both adult A&E and paediatric A&E ward where the accounts for both wards were not fully separated on the pharmacy databases. As a result it was not possible to trace the quantities used solely for paediatric patients in A&E prior to 2015. Medications which had a special protocol for their administration such as immunoglobulins, methotrexate and infliximab were excluded since each administration protocol is tailored to the patient and the calculated doses depend on the patient's medical condition. Chemotherapeutics were excluded since they are pre-prepared in an aspetic unit at the pharmacy department and administered according to the standard implemented protocols. A list of medications was generated accordingly after applying the inclusion/exclusion criteria.

2.2.2 Survey of Nurses

A survey was conducted with nurses working in the paediatric wards regarding the frequency of administering the shortlisted. Nurses were requested to rate the frequency of administering on a five-point Likert scale where 1 never used and 5 always used. Medications that were reported to be administered with a high frequency (Likert scale 4 or higher) by 75% nurses or more were included in the study.

The medications identified by the staff nurses were presented to the nurses in charge of each paediatric ward to confirm the list as frequently administered medications in their wards. Nurses in charge were asked to rate the importance of having a guide for each medication on a five-point Likert scale where 1 is not important at all and 5 is very important). This assisted the researcher in prioritising the medications among the initial sample based on the identified need and importance of a guide by the nurses. Medications that scored 4 or higher on the Likert scale by more than 3 nurses in charge formed the final study sample.

The rationale for choosing only a group of medications was due to time limitations. A manual should contain all the medications used in the paediatric wards but a focus was made on the medications that are used frequently and commonly across all the paediatric wards and there is an identified priorty to develop a guidance for their administeration.

2.3 Developing the Monographs

The available products of an active ingredient including the different dosage strengths were checked at pharmacy stores at MDH. Following the identification of each product, a research for the latest Summary of Product Characteristics (SmPC) of each available brand and strength was carried out. The latest updated SmPC in English language for each available strength or brand was retrieved by searching all the platforms that withhold SmPC of medicinal products licensed in Malta: European Medicines Agency (EMA), Medicines and Healthcare Products Regulatory Agency (MHRA), Health Products Regulatory Authority (HPRA), Malta Medicines Authority (MMA) and the manufacturer's website. The Marketing Authorization Holder (MAH) was always contacted to inquire about the availability of the most recent updated SmPC officially translated to English language. The date of revision of the text of each available SmPC was checked and compared to other SmPCs of the same brand/generic to decide on the most recent version to follow.

The template used for the Paediatric Drug Therapy Manual (PDTM) for adults was used for the development of the paediatrics manual. The details of each section of a monograph were written and compiled using different sources and referenced accordingly. Each monograph contained the relevant information required by nurses for administering IV medications, which included (i) indication of treatment, (ii)

reconstitution, (iii) dilution in an infusion bag or a syringe, (iv) method of administration and (v) the parameters that are required to be monitored during and after therapy. The length of a monograph was restricted to one page long to encourage nurses to use it as a quick reference when checking information to administer injectable medications.

Types of information that were excluded from a monograph were (i) drug-drug interactions, (ii) contraindications, (iii) dealing with adverse events or overdose. This type of information was considered to be out of the scope of a monograph since the target audience is mainly nurses, the focus was made on the reconstitution/dilution of the medication and method of administration. Side effects that were listed in a monograph were (i) injection site reactions such as hypersensitivity reactions, extravasation, phlebitis and (ii) side effects that could be monitored or observed such as signs of infection and visual and behavioural disturbances. General side effects that were not related to the administration site (e.g diarrhea, nausea, vomiting) and uncommon side effect were excluded.

The development of the monographs took place in a multi-stage process (Figure 2.2) where the first drafts of the monographs were prepared and sent for review to pharmacists working at Clinical Pharmacy Practice Unit (CPPU) at MDH. Review included verifying the accuracy of information included within a monograph and evaluating the sources and references used to compile the information within the monograph. This ensures the credibility of information used at hospital level. Constructive feedback provided by the reviewer was incorporated to modify the first drafts and develop second drafts of the monographs.

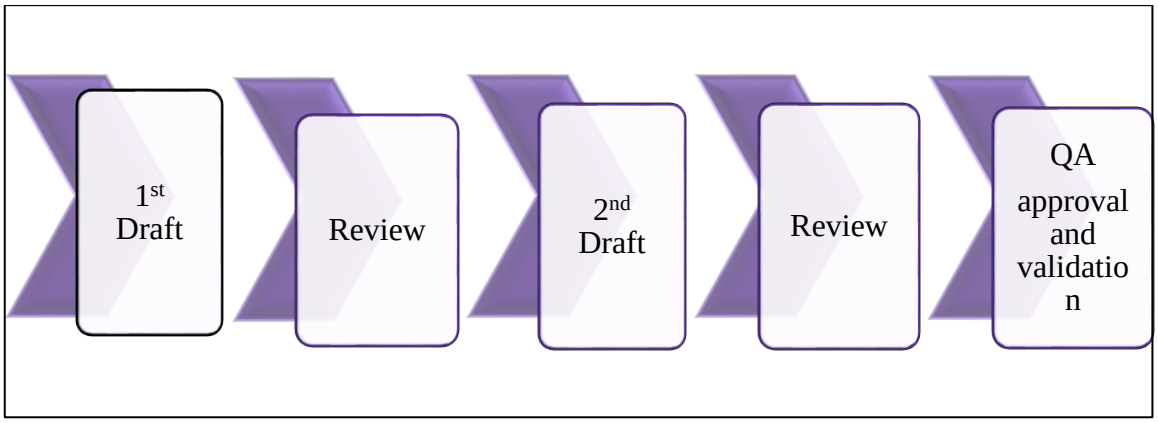

Figure 2. 2 Stages of Developing a Drug Monograph

The second drafts were further reviewed by pharmacists working at CPPU. Relevance and appropriateness of the type of information was checked. Details that were considered to be irrelevant or less significant to administration practice were remarked by the reviewer. Amendments to the monographs were done following the second feedback. Extra details were further removed to maintain the one page length and to be compliant with the scope of a monograph. The final draft of the monographs were sent to Qulaity Assurance (QA) department at the pharmacy department to be validated before its release. Corrections suggested by QA were evaluated and implemented to achieve the final version of the monographs to be released and launched at paediatric wards.

The monographs are available as hard copy placed in each paediatric ward and accessible to all healthcare professionals working in the wards. The rationale of the monographs availability in hard copy is to enable a convenient and ease of use, where use is not limited by the availability of an electronic device or internet. Nurses can carry the monographs with them when administering a medication to a patient. Each

monograph was laminated to allow sterilization without damaging the content or the paper.

2.3.1 Structure of the Monographs

The monographs are divided into the following eleven sections:

- Name of medication : Active pharmaceutical ingredient (API)
- Strength/ trade name/manufacturer: Available strengths at MDH, trade name of the available products and their respective manufacturer.
- Classification (class of medication): Antibiotic, antiemetic, corticosteroid.
- Indication for use: Licensed and unlicensed.
- Reconstitution and Dilution: Choice of diluent and volume of diluent/solvent in IV infusion and IV injection if applicable, final concentration after reconstitution/dilution.
- Method of administration: Injection or infusion or bolus, rate of administration, other possible routes of administration e.g. Intramuscular (IM) and recommendations for each route.
- Dosage: Including indication-specific information and dosage adjustments required in renal or hepatic impairment. The dosage in paediatric monographs were listed according to weight and age. The age group was divided according to the classification provided by British National Formulary for children (BNF-C) of 2016 (Table 2.2).

Table 2. 2 Classification of Age of Patients

Criteria	Age
Preterm neonate	Born at < 37 weeks gestation
Terms neonate	Born at 37 to 42 weeks gestation
Post-term neonate	Born at ≥ 42 weeks gestation
Neonate	From 0 up to 28 days of age (or first weeks life)
Infant	From 28 days up to 24 months of age
Child	From 2 years up to 12 years of age
Adolescent	From 12 years up to 18 years of age

- Compatibility and stability: Compatibility section lists fluids that can be used safely for reconstitution or dilution of the medication being described. Information related to whether medications can be safely mixed or infused into the Y-site or administered concomitantly was included. Information related to stability included details about the appearance of a medication as solution once reconstituted or diluted, duration of stability and special conditions of storage if the drug is not administered immediately to the patient.
- Potential hazards of administration: A list of frequent and serious undesirable adverse effects experienced immediately or shortly after the administration of injection and infusion either due to rapid administration or reaction to the injection site e.g extravasation).
- Miscellaneous: this section includes measures that are required to follow to ensure safe and effective use of a medication throughout therapy such as monitoring of parameters, cautionary measures, drug interactions and risk of

concomitant administration. Other information included are interference of medication with lab tests, cross-resistance or cross reactions and sodium content. Parameters that are recommended to be monitored are mainly signs and symptoms of certain adverse effects or parameters associated with the duration of therapy. Frequency and rationale of monitoring were listed if provided by literature. Frequency can be specific (daily, weekly) or undefined (periodically) where the physician would assess the need for further monitoring based on patient's case. Name of lab tests that a medication interfere with were provided.

- References (A numbered References list was developed, where each reference was indicated as a number at the end of each monograph for quick referencing).

2.3.2 References and Resources Used

A continuously updated list of resources and references that were used to develop the monographs was compiled (Appendix 1). The list is presented in the appendix of the manual. Each section of a monograph was compiled using references that are specific to its scope. Certain references were implemented to compile information presented within many sections of the monograph but for each section a different part of that reference was consulted (Table 2.3). Some of the references and resources used specialise in the preparation and parenteral administration such as (i) Injectable Drug Guide (IDG), (ii) UK National Health Services (NHS) Injectable Medicines Guide (IMG) referred to as Medusa and (iii) University of College London (UCL) Hospitals Injectable Medicines Administration Guide 3rd edition. Other references specialize in the compatibility and stability of a reconstituted/diluted product such as American Society of Health-System Pharmacists (ASHP) Handbook of injectable Drugs.

The IDG is a book designed to support the risk assessment provided by National Patient Safety Agency (NPSA) of NHS. IDG is a single point of reference for healthcare professionals in clinical use of injectable medicines. It provides a holistic approach for the safe and effective use of injectable medicines. Although the IDG is not a paediatric specific reference, information regarding drug monitoring and drug compatibility/stability was consulted as this type of information depends on the medication in use and would not differ significantly if the population changed. On the other hand, doses and routes of administration were not referred to since they should be tailored to the patient population.

The IMG (Medusa) is the NHS injectable medicines guide that it is intended to provide information on the recommended methods of preparing and administering IV medications for both public and private organizations of NHS. [37] A number of pharmacy organisations including the manufacturers are involved in developing IMG (Medusa). Medusa is divided into drug monographs where for each medication there is an adult monograph and a paediatric one. All of these monographs are checked for accuracy and for consistency with IMG Writing Guidelines by a regional Medicines Information (UK-MI) centre. The UK Neonatal and Paediatric Pharmacist Group (NPPG) review all the monographs for medicines used in children and or neonates to ensure that the information within the monographs reflects good clinical practice.[38]

[37] Skipp, M, Templeman E. A survey to determine how the Medusa Injectable Medicines Guide is used within the South West. [Internet]. Feb 2016. [cited 2019 Mar 28]. NHS Available from: http://www.swmit.nhs.uk/media/16434/medusa-survey-poster-skipp-templeman-swmit.pdf

[38]NHS Injectable Medicines Guide Group. Injectable Medicines Guide [Internet]. About Injectable Medicines Guide; July 2016 [cited 2019 Mar 28]. Available from: http://medusa.wales.nhs.uk/HomeAbout.asp

The UCL Hospital IMG provides concise and easy to interpret instructions for dilution/reconstitution and administration of injectable medicines. Information within UCL drug monographs incorporate both evidence based practice at UCL hospital and form practice guidelines including a summary of aseptic nontouch technique.

One of the references used to compile method of administration section was American Society of Health System Pharmacists (ASHP) Paediatric injectable Drug (PID) book 10^{th} edition. PID is an indispensable reference for paediatric practitioners as it provides up-to-date evidence based information to guide dosing and administration of IV medications to neonates, infants, children and adolescents. PID lists all the possible routes via which a medication can be administered to neonatal/paediatric patient and the preferred route for certain dose or indication.

The main sources for the doses of licensed indications were "Posology and method of administration" section of SmPC and British National Formulary for Children (BNF-C) online version. The doses listed in the BNF-C and SmPC were used in the cases where there was inconsistency of doses in terms of amount per Kg or age criteria between different resources. BNF-C is the main resource being implemented and is available to all healthcare professionals at MDH in both hardcopy and online version.

PID book was consulted for compiling doses within the monographs since it addresses the lack of rudimentary dosing information for paediatric use by compiling it in an evidence-based manner from primary literature, including case reports, observational

reports and comparative trials.[39] PID highlights the dosage adjustment requirement in renal or hepatic dysfunction.

References implemented for the dosage section specifically for off- license doses were paediatric and neonatal drug monographs of Neofax – Micromedex and Uptodate. Neofax is a leading source in providing neonatal and paediatric drug information in particular robust, evidence-based off-licensed doses with fully referenced content. Uptodate is another evidence based clinical resource for off-license dosing information which includes a collection of medical and patient information. It also provides access to Lexi-comp drug monographs which contain specialised paediatric dosage section. Unlicensed doses that are used at MDH and supported by evidence were searched in literature and a consultation with the prescribers was carried to include these dose.

Compatibility data was formulated using (i) section 4.2 of the product SmPC. Fluids that are mentioned in that section for preparing a solution of the medication are listed within a monograph as compatible fluids while incompatible fluids are the listed fluids in section 6.2 "Incompatibilities". ASHP Handbook of Injectable Drugs lists all the drugs and fluids that are compatible with a medication providing in detail the different circumstances of compatibility; e.g additive compatibility when mixed with another drug/s in different infusion fluids, compatibility when mixed in a syringe. ASHP HID includes reports from literature about injecting the medication into Y-sites and administration sets. UCL IMG or Medusa provides compatibility data for both fluids and medications when used as IV and when used Intramuscularly (IM). Information

[39] Goldberg L. Indispensable reference for paediatric injectable drugs [Internet]. Pharmaceutical Journal. 2019 [cited 2019 Mar 28]. Available from: https://www.pharmaceutical-journal.com/opinion/books-and-arts/indispensable-reference-for-paediatric-injectable-drugs/20205569.fullarticle

regarding drug compatibility with Total Parenteral Fluids (TPN) was obtained from Appendix D of PID.

The main reference for information about product stability was the product SmPC. SmPC included information about time after which a reconstituted vial or a diluted infusion could be given and the specific conditions under which it should be stored or kept. Other references were reviewed to determine the stability of a reconstituted product when added to one or admixture of drugs e.g. ASHP HID and Trissel LA HID.

Table 2. 3 References and Sources Used to Develop each Monograph Section

Monograph section	Reference
Classification	1- AHFS. 2- Martindale. 3- Drug information Handbook.
Indication	1- Therapeutic Indications listed in the SmPC. 2- Martindale. 3- BNF-C. 4- AHFS (American Health Formulary System).
Reconstitution and dilution	1. Section 6.6 of product SmPC (Special precautions for disposal and other handling-Preparation of solution). 2. "Instructions for reconstitution" and "instructions for dilution and suitable diluent" parts of Medusa. 3. Method of administration section in IDG. 4. UCL Hospitals Injectable Medicines Administration Guide (IMG) 3rd edition. 5. MDH hospital Guideline for Paediatric Intravenous Drug Reconstitution developed by clinical pharmacist from CPPU and Paediatric Practice nurse.

Table 2.3 (*cont'd*) References and Sources Used to Develop Sections of Monograph

Monograph Sections	References
Method of administration	1. Section no 4.2 of the product SmPC for the licensed methods. 2. Paediatric IV monographs of NHS IMG. 3. Local guidelines for Paediatric IV Drug Reconstitution. 4. UCL Hospital IMG 3rd edition. 5. IDG. 6. PID.
Dosage	1. "Posology and administration in paediatric population" section of SmPC. 2. BNF-C. 3. Neofax drug monographs of Micromedx. 4. PID.
Compatibility	1. ASHP HID 19th edition. 2. IDG. 3. UCL Hospitals IMG 3rd edition. 4. IMG- (Medusa). 5. Section 6.3 (Shelf life) of the product SmPC. 6. "Stability after preparation" sections in IDG.

Table 2.3 (*cont'd*) References and Sources Used to Develop Sections of Monograph

Monograph Sections	References
Stability	1- "Pharmacy notes" in Medusa IMG. 2- "Shelf life" section 6.3 of the product SmPC. 3- ASHP HID. 4- Trissel LA HID.
Potential hazards of administration	1- "Infusion related cautions" section in PID. 2- "Adverse effects which may be caused by injectable administration" section in Medusa IMG. 3- "Injection/infusion-related of common and undesirable side effects of the additional information in the IDG. 4- Section 4.8 undesirable effects of SmPC. 5- Warnings and Contraindications section of PID. 6- "Warnings/precautions and adverse drug reactions" section of Lexicomp, 7- Side effects section of BNF-C. 8- "Adverse effects which may be caused by injectable administration" section in Medusa IMG. 9- Adverse effects section of Neofax. 10- "Common and serious undesirable effects" section of IDG.

Table 2.3 (*cont'd*) References and Sources Used to Develop Sections of Monograph

Monograph section	Reference
Potential hazards of administration (continued)	11- Precautions of Martindale. 12- "Potential hazards of administration" section of the PDTM monographs of Sheikh Khalifa Medical City.
Miscellaneous	1- "Monitoring parameters" section of SKMC monographs. 2- "Monitoring" section of IDG. 3- "Monitoring parameters" section in Lexicomp. 4- "Adverse effects, Treatment of adverse effects and Precautions" sections of Martindale 5- "Monitoring requirements" section of BNF-C. 6- Monitoring section of Neofax. 7- "Additives" section of PID, 8- "Sodium content" part of IDG. 9- "Effect on laboratory tests" section of BNF-C. 10- Section 4.5 of SmPC "Interactions with other medicinal products and other forms of interactions". 11- "Miscellaneous" section of SKMC.

2.4 Introduction of Monographs to Nurses

A 10 minutes power point presentation was developed to introduce the drug monographs to nurses working in paediatric wards before the release of the monographs (Appendix 2). Training about monographs and different sections within a monograph was carried out first to nurses in charge and in a later stage to staff nurses. The purpose of training was to ensure that all nurses were aware of the availability of drug monographs in the wards to guide the preparation and administration of parenteral medications for paediatric patients. The accessibility of the monographs and how to use them was explained in the training. The template, structure and type of information listed in the monograph was explained.

A referral to another healthcare professional was always advised as the monograph focuses mainly on administration practice in terms of preparation and method of administration while other issues such as dealing with adverse drug reactions (ADRs), overdose or contraindications were considered to be out of the scope of a monograph. Nurses were advised to contact the CPPU for further clarification in case of encountering a variation between the prescribed dose and the listed dose or a variation in the volume of the diluent to be used or method of administration

2.5 Evaluation of the Monographs

The prepared monographs were validated by pharmacists working at QA department and by “Assessment of administration practice AAPQ” questionnaire.

2.5.1 Quality Validation

QA validation involved verifying that the information within a monograph is accurate and the resources and references used are credible. QA pharmacists ensured that instructions given are clear and would not be misinterpreted in a way leading to a medication error. This was conducted by analysing the orders and converting them into various possible forms of actual scenarios. Following a risk assessment, phrases or sentences that had a potential of being misleading were suggested to be removed or to be amended to avoid causing confusion when using a monograph.

2.5.2 Assessment of IV Medication Administration Practice Questionnaire (AAP-Q)

The aim of the questionnaire (Appendix 3, Appendix 4) is to assess knowledge, self-certainty and confidence regarding IV medication knowledge and administration practice, perception of factors that contribute to medication errors and obstacles encountered when administering IV medications in paediatric patients.

2.5.2.1 Design of the APP-Q (Pre-test and Post-test)

The questionnaire was adapted from Hsaio et al (2009) and Lu et al (2011). Similar studies that investigated the knowledge level of nurses in different topics including medication administration practice (Raja et al, 2009; Gonzales, 2012; Bülbül, 2014; Niemann et al, 2015), dose calculation and mathematical skills (Simonsen et al, 2011; Lan et al, 2013) and contributing factors to medication errors (Keers et al, 2013; Ameer et al, 2105) were consulted.

The questionnaire used a combination of four close-ended and multiple-choice questions in which respondents could choose more than one answer from a list of

options. A 5-point Likert scale ranged from 1 to 5, where 5 is the highest score and 1 is the lowest score used.

Close ended questions were chosen over open-ended questions for their ease, less time is needed to answer and they yield a higher response rate (Reja et al, 2003). The advantage of close-ended questions is there is less risk in obtaining missing data and fewer difficulties encountered in the statistical analysis when compared to open-ended questions. Furthermore, the respondent should possess sufficient knowledge on the subject of the question to be able to respond effectively in the open-ended questions (Bircham-Connolly et al, 2005) while the answers for close-ended questions are already present. The limitation of using close ended question is it has more potential for bias in answering since the available responses are limited (Reja et al, 2003). Validation of the questionnaire was conducted using DELPHI validation tool (Appendix 4).

The questionnaire were administered prior to introducing drug monographs at wards' level and after the release of the monographs in a pre-test/post-test design. Answers of questions testing knowledge and self-reported certainty were compared prior to and after introducing the monographs. The results of comparison demonstrated the impact of monographs on the knowledge of nurses and the administration practice of IV medications. Feedback about the released monographs and their potential impact on the factors and obstacles that contribute to unsafe medication administration were obtained in the post-test stage.

2.5.2.2 Structure of the AAP-Q

The designed questionnaire is divided into four different sections. Section A collected information about related experience and educational background, Section B is self-evaluation regarding the need of training in medication administration. Section C is an assessment of knowledge and the sources of information consulted at wards' level in the administration practice. It also evaluates self-confidence in different aspects of administration practice (indication of medication, stability and compatibility and method of administration) of selected medications. Obstacles encountered when administering medications to paediatric patients and the impact of monographs on these obstacles was identified by the questions of this section. Section D addresses perceptions and opinions of nurses about factors that contribute to medication errors and scenarios affecting safety of medication administration.

Section A: Demographic Data

Demographic information included work related experience; years of practice, education level, training background and whether the training received in the past is related to paediatric area, the current position occupied and ward practicing at.

Section B: Self-evaluation

This section dealt with self-evaluation where respondents were asked to classify their proficiency and knowledge of IV medication preparation and administration. Nurses were asked to identify their training requirements in preparation and administration of IV medications and to choose among different types of training the areas they feel there is a lack of experience and deem necessary to expand their knowledge in these areas. The section consisted of multiple choice questions where respondents were asked to rate their proficiency and knowledge level and to indicate the type of training they require.

Section C: Assessment of administration practice

This section is dedicated to assess the sources of information consulted at wards' level when preparing and administering IV medications and the choice of preferred reference to have in the wards. It consisted of 5 questions; 4 multiple choice questions and 1 Likert scale. Respondents were asked to select the type of references they use when administering IV medications and the types they prefer to have as well as the difficulties that are encountered in the administration practice such as dose calculations, dealing with ADRs and choice of compatible fluids.

A question was dedicated to identify scenarios related to errors in preparation and administration of IV medications which can be easily encountered in the administration practice. These scenarios were reported to occur in the wards. Experts of the validation panel participated in formulating these scenarios by providing structured feedback and by including and eliminating part of the listed scenarios. Nurses in charge of the paediatric wards, clinical pharmacists and a paediatrician consultant helped to identify these common scenarios. These scenarios were based on the factors that lead to medication administration errors where a nurse would choose to proceed with the order/prescription given or would check with a colleague or refer to a healthcare professional (Pharmacist or a doctor or a nurse) or an available reference.

Studies that assessed nurses' knowledge using scenarios were consulted (Stewart et al, 2010; Jacobson et al. 2010; Gonzales, 2012). The idea of incorporating these scenarios was to assess the knowledge of nurses in identifying an incorrect prescription or order and to assess the behaviour and their choice of reference consulted when they are placed in these situations. These scenarios include (i) use of commonly prescribed

abbreviations that are error-prone according to Institute for safe Medication Practices (ISMP), (ii) administration orders where a medication is incompatible with a fluid and concomitant administration would lead to an ADR such as concomitant administration of ceftriaxone injection with calcium containing fluids, , (iii) an incorrect administration technique where a medication can only be administered as IV infusion at a minimum rate to avoid ADRs for example potassium chloride as IV push. Other scenarios were about monitoring requirements in medications that need to be monitored for example (serum gentamicin) or monitoring of signs and symptoms that are indicative of adverse effects which warrants dose adjustment or discontinuation of a medication or gradual tapering e.g. Corticosteroids adverse events and gradual tapering of a hydrocortisone.

The medications selected for the scenarios were based on commonly used medications for which monographs were developed to test the impact of introducing these monographs on the knowledge of nurses about these medications in terms of their administration technique, special precautions, important parameters to monitor and potential hazards of administration.

The last question in this section was related to the confidence level of medication administration and knowledge, respondents were asked to rate their level of confidence using a five-point Likert scale where 1 is not confident at all and 5 is highly confident in terms of administering these medications. The medications selected for this questions were medications for which monographs were developed. Baseline level of confidence prior to having drug monographs was identified and then compared to the level of confidence collected in the post test stage.

Section D: Safe medication administration

Two questions were included in this part as a Likert scale. The first question contained factors that contribute to medication errors in the administration practice in different stages of giving a medication such as similar drug packages, similar drug names, unclear labelling of a product or lack of product information in the leaflet, unfamiliarity with the medication, illegible writing (DeHenau et al, 2016) and being a new staff or a recent graduate. Respondents were asked to rate the level of contribution of each factor on a Likert scale 1 to 5; 1 not contributing at all and 5 highly contributing. These factors were derived from literature research where they were identified as common factors that lead to medication errors and interventions were developed and designed to address one or more of these previous factors (Mayo and Duncan, 2004; Petrova et al, 2010; Brady et al, 2010). Other factors contributing to medication errors included; quality of the prescription (Kazaoka et al, 2007), deviations from procedures (Taxis and Barber, 2003; Westbrook et al, 2011; Keers et al, 2013), workload staffing (Tang et al, 2007; Keers et al, 2013), lack of medication knowledge, insufficient experience (Hughes and Blegen, 2008; Keers et al, 2013) and mathematical skills of nurses (Polifroni et al, 2003; Simonsen et al, 2011).

If the scores of contributing factors in the pre-test stage remained the same or increased in the post-test stage then the monographs were considered as having no positive impact on these factors. Factors that scored less in the post-test stage than in the pre-test stage were regarded as the factors that drug monographs have the potential in reducing them.

The second question contained scenarios from practice that have an effect on safe medication administration. Respondents were asked to rate their level of agreement on a Likert scale 1 to 5 (1 strongly disagree, 5 strongly agree) with the impact of each

scenario on safe administration practice and whether addressing these issues would contribute to safer practice.

Answers that were collected in the post-test stage were compared to the pre-test stage. If the respondents would still rate their level of agreement with factors and scenarios the same degree as in the pre-test stage this would be considered that the monographs had no influence in addressing these factors and handling these scenarios and reducing their effect on the safety of administering the medications.

The final section in the post-test questionnaire was dedicated to collect direct feedback from the nurses regarding the monographs and their use. Respondents were asked to rate their level of agreement on a Likert scale with each statement where 1 is strongly disagree and 5 is strongly agree. An open ended question was included to allow the nurses to give their suggestions to improve the monographs' structure.

2.5.2.3 Validation of AAP-Q

Questionnaires were validated using Delphi method carried out in a two round sessions (Delphi I and Delphi II). Delphi is a multiple iteration survey technique that enables systematic refinement of several experts' opinions in an attempt to consensus-building, it is conducted as a series of individual interviews with each one of the chosen subjects (Bowels, 1999; De Meyrick, 2003; Hsu and Sandford, 2007; McMillan, 2016). The idea of having an interaction with each subject individually is to avoid the bias of a group, enable each participant to provide his/her opinion without the influence of others and to maintain confidentiality of the identity of participants (Hsu and Sandford, 2007).

Delphi method was selected as there is a lack of similar survey tools in previous literature or questionnaires investigating similar topics to the research topic (Hasson et al, 2000). DELPHI provides the benefit of using subjective judgments on a collective basis to generate ideas and survey tools where there is no history of adequate communications of this issue between different experts (Hasson et al, 2000; Yousuf, 2007). While other surveys seek to identify "what is," the Delphi technique attempts to address "what could/should be" (Hsu and Sandford, 2007). The Delphi technique has been used in several nursing articles as a research tool (Wilkes, 2015; Paans et al, 2017).

The advantages of this method it provides direct interaction between researcher and the experts to collect different opinions/perspectives by repeated questioning about a topic in an anonymous manner (Bowels, 1999 ; De Meyrick, 2003 ;Yousuf, 2007) , it allows a diversity of experts to communicate their opinions and knowledge to each other in an anonymous manner, to learc about their evaluation of the topic in view of others and to change their opinions if desired after being exposed to the findings of the panel's group (De Meyrick, 2003). Thus it enables developing both qualitative and quantitative data (Bowels, 1999) through controlled feedback where the results of each round is fed to all the panellists in the following rounds while maintaining anonymity of the participants (Paans et al , 2017).

The recommended number of panellists in a Delphi method is still debatable where it varies form one study to another however the more the reference groups (pharmacists, doctors, nurses) involved the more number of participants in total needs to be recruited (Delbecq et al, 1975; Hsu and Sandford, 2007). Ten to fifteen participants are enough if

they have a homogenous background provided that they include 4 to 9 knowledgeable participants of both professional staff and decision makers who can act upon the results generated which would make Delphi an effective tool (Delbecq et al, 1975). The smaller the size of the sample and the more homogenous is better than larger sample and heterogeneous groups (Wilkes, 2015).

Minimal requirement for Delphi is 30 days but it can take up to 45 days and even longer (McMillan, 2016). Although the number of rounds for a classical DELPHI technique is three to five varying according to the degree of agreement and amount if information being sought (Delbecq et al, 1975), more recent evidence recommends two or three rounds only (Hasson F, 2000; Hsu and Sandford, 2007; Wilkes, 2015) and in most studies two rounds were used (McMillan, 2016).

Eleven healthcare professionals with different specialities were contacted personally by the researcher and invited to participate in the expert panel after explaining the aims of the study. The group consisted of : one consultant paediatrician, four nurses (two nurses in charge of the paediatric wards and two nurses working in Paediatric Practice Unit), six pharmacists; (two working at CPPU at MDH and two working at QA at MDH, one specialises in drug safety and a foreign pharmacist practicing outside Malta and who specialises in public health).

The eleven panellists were selected based on their relevant experience with the topic. All eleven panellists agreed to participate in the validation and individual interviews were conducted with each one personally. The first round of Delphi validation (Delphi I) took place in June, 2107 where all of the eleven panellists filled in the

validation tool and provided their feedback directly. The second round of Delphi took place in August, 2017. The period between the 2 rounds of validation didn't exceed 45 days limit. Panellists were asked about the relevance, level of agreement with the options of the answer, clarity, structure and layout of each question. Likert scale was implemented to assess the level of agreement with each criterion where 1 is the least agreement and 5 is the highest. Participants were given the opportunity to comment or add or recommend further changes to questions.

Questions that scored 3 out of 5 or less in relevance in Delphi round I were excluded in Delphi round II. Amendments to questions were made if the majority of the panellists recommended to (six or more of the panellists in round I and five or more in round II). The same panellists who participated in round I participated in round II except one panellist who refused to continue. Delphi II was conducted as the same method as Delphi I, however the questionnaires provided in Delphi II were the modified version that resulted from the feedback and amendments of Delphi round I.

Face validity was conducted for the questionnaire to identify areas that might be expected to be unclear or respondents would hesitate to answer (Bolarinwa, 2015). Despite the fact that face validity is considered the weakest type of validity as it is subjective assessment it provides an insight into how respondents would interpret and answer questions (Krabbe 2017). Experts or lay persons can be consulted to review the used tool for the grammar, clarity, structure appropriateness and logical flow (DeVon et al, 2007).

Face validity should be carried by people who will participate in answering the tools. This is due to the reason that experts are not part of the target chosen to answer the tool therefore they will be less effective at assessing this type of validity from the targeted audience's perspective (Bolarinwa, 2015;Krabbe 2017). Seven nurses practicing in the paediatric wards were approached by the researcher for the face validity. The same procedure adopted in Delphi was used in face validity since there are no specific guidelines or statistical test to carry out face validity (DeVon et al, 2007). A four point Likert scale was developed for face validity tool. The panellists were asked to rate each of the following: clarity of the questions, readability and feasibility, consistency of style and layout. The average for each question responses was calculated for each aspect (clarity, ability to answer, style &layout) separately. Then the total average of these three aspects' averages was calculated, it was decided if the total average value was over 3.50 (cut-off point) then the question was considered face valid.

2.5.2.4 AAP-Q Dissemination

Questionnaires (Appendix 3, Appendix 4) were disseminated in a prospective cohort at the paediatric wards in MDH. Being the only hospital in Malta for acute services and with wards specialised for paediatric patients the study was conducted there with a focus on nursing practitioners. All nurses working in paediatric wards at MDH (Fairyland, Wonderland, Disneyland, Paediatric Accidents & Emergency, Paediatric Day care and Rainbow) were included. The main focus of the study was the nurses due to the reason that nurses at the paediatric wards are the main administrators of medications.

2.5.2.5 Statistical Analysis

Statistical Package for Software Sciences (SPSS) version 24 was used for statistical analysis. Microsoft® office and Excel software were used for the graphical representation of the results. The Likert scale was selected as it is an easy to use rating scale for running questions and for data analysis. Directionality as a feature of the Likert scale enables the respondents to determine the intensity of the answer with a graded range without the need to give a Yes/No answer. Thus a respondent would have the freedom to choose a neutral answer in case he/she neither agree/disagree with the provided options.

The percentage of nurses who gave the high rating score '4' or '5' was used to evaluate the perception of the factors that contribute to medication errors at wards' level. The contribution of each factor when monographs were introduced and consulted was analysed. The number of nurses who chose the highest degree of agreement '4' or '5' was used to assess the potential role of drug monographs in maintaining a safe administration practice in view of the scenarios that might lead to medication administration errors.

The Friedman test was used to compare the mean rating scores between numbers of related factors and scenarios where the null hypothesis states that there is a marginal difference between mean rating scores of the contributing factors and scenarios. The alternative hypothesis states that the mean rating scores vary significantly between the contributing factors.

The Wilcoxon signed rank test was used to compare mean rating scores provided to a contributing factor or scenario prior to and after implementing drug monographs. Mean rating scores range from 1 to 5 where 1 corresponds to not contributing at all, not confident, strongly disagree and 5 corresponds to highly contributing, highly confident and strongly agree. The null hypothesis specifies that the mean rating score before and after introducing the intervention are similar or comparable and is accepted if p-value exceeds 0.05. The alternative hypothesis specifies that the pre-test and post-test mean rating scores vary significantly and is acceptable if p-value is less than 0.05. The paired sample t-Test was used to compare between level of confidence in the pre-test and post-test stages. In all the previously mentioned tests, the null hypothesis would be accepted if the p-value is less than 0.05 criterion.

2.6 Approvals Obtained

Approvals for conducting the study at MDH was sought from the pharmacy department at MDH, chairman of paediatric committee, director of the nursing, hospital management and data protection (Appendix 5). Since personal information is required to conduct the study, ethics approval was sought prior to the initiation of the study. Ethics approval was granted from the University Research Ethics Committee (UREC) (Appendix 5).

2.7 Publications

The results of the study were dissmentated in the form of abstract in local and international forums for the poster presentation. The abstracts were (Appendix 6):

1- “Developing a standard guidance for IV medications at wards’ level” submitted for 78th International Pharmaceutical Federation (FIP) World Congress of

Pharmacy and Pharmaceutical Sciences held in Glasgow, UK from 2nd to 6th September 2018.

2- "Development of Paediatric Intravenous Formulation Manual" submitted for the 10th Malta Medical School conference held in Malta from 29th November to the 1st of December 2018.

3- "Nurses perception of intravenous medication administration errors in paediatrics" submitted for the 79th International Pharmaceutical Federation (FIP) World Congress of Pharmacy and Pharmaceutical Sciences held in Abu Dhabi, UAE from 22nd to 26th September 2019.

Chapter 3: Results

3.1 Identification of the Medication

Identification of the medication was conducted in three steps: (i) Analysis of medication consumption reports from Access Dimension software for the years 2007-2016, (ii) Survey of frequency of medication administration and (iii) Interview with nurses in charge of each paediatric ward.

3.1.1 Results of the Medication Consumption by Wards

Records retrieved from the Access stat program were showing quantities of each item consumed by each ward (Fairyland, Wonderland, Disneyland, Paediatric Day Care, Rainbow, Paediatric Accidents and Emergency (A&E) over the years 2007 to 2017 (Table 3.1).

Table 3. 1 Number of Injectable Medications Used in Paediatric Ward

Ward	Number of injectable medications
Disneyland	153
Wonderland	132
Fairyland	127
Rainbow	120
Paediatric A&E	92
Paediatric Day care	32

Injectable medications with same active pharmaceutical ingredient (API) such as (amoxicillin 250 mg injection and amoxicillin 500 mg injection) were merged and considered as one API. A total of (N=175) different APIs used in the paediatric population via parenteral route was identified. Total quantities and percentages of use for each medication were calculated for each ward and in total of all the wards for the years 2007-2016. The results for each medication are displayed in Appendix 7.

APIs that were not used in one of the paediatric wards during the years 2015 and 2016 were removed which generated a preliminary list of 39 medications (Figure 3.1). Among the 39 medications, five medications were identified to have specific protocols guiding their administration for each patient. Heparin was found to be used for flushing of IV lines to prevent incompatibility and coagulation within. Thirty-three APIs formed the initial list of medication (n=33).

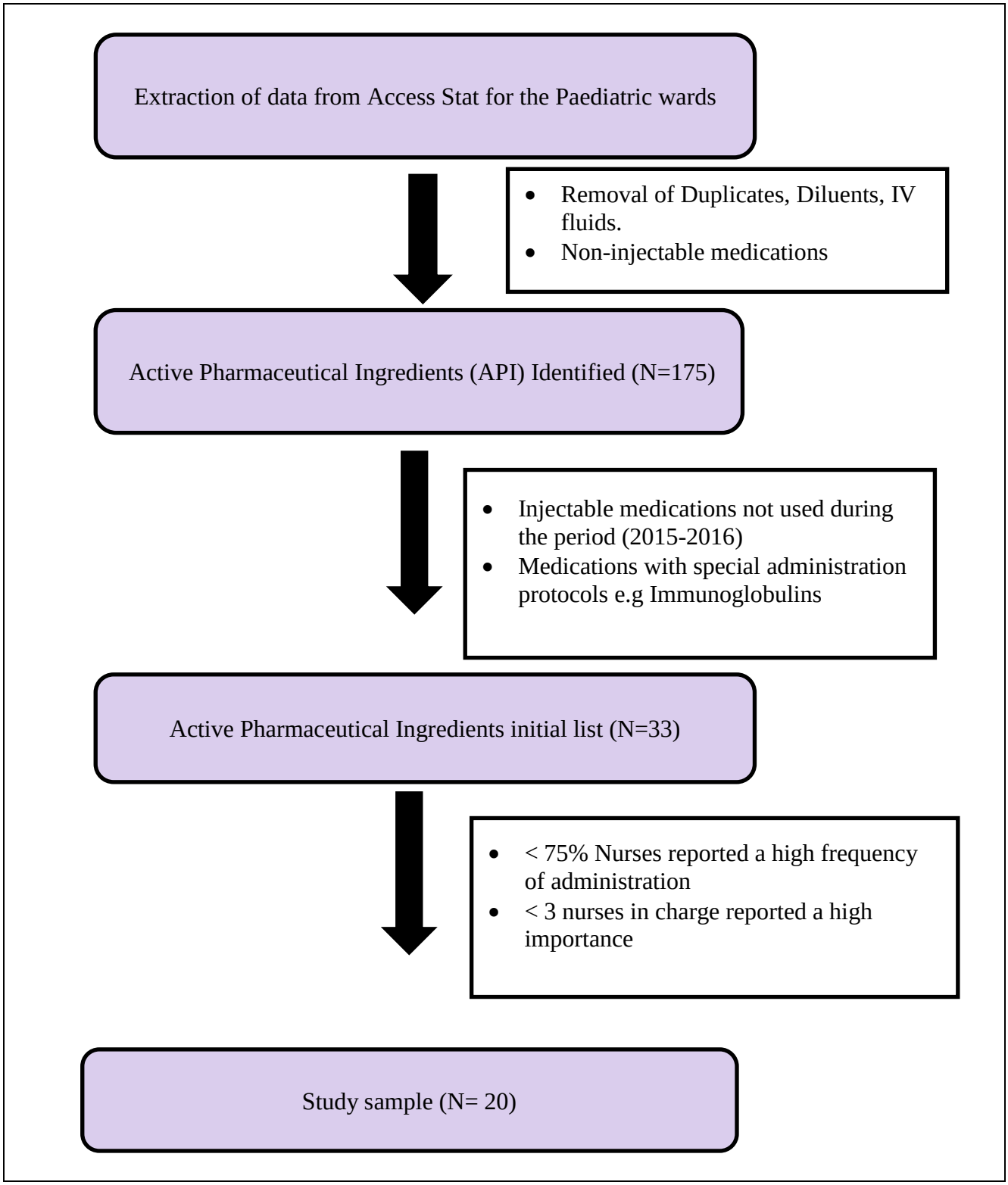

Figure 3. 1 Methodology Involved In Identification of Medication for Study Sample

3.1.2 Results of Survey of Nurses

A survey regarding frequency of administration for the 33 APIs previously identified was distributed to the nurses working at paediatric wards. Twenty-seven medications were identified as being frequently (frequent 4 or very frequent 5) administered by more than 75% of nurses selected (Table 3.2).

Table 3. 2 Medication Administration Frequency

Active Pharmaceutical ingredient	Number of nurses reported to administering them frequently >4	% of nurses reporting administering them frequently
1- Co-amoxiclav	51	89%
2- Cefotaxime	48	84%
3- Metronidazole	47	82%
4- Paracetamol	47	82%
5- Meropenem	46	81%
6- Piperacillin/Tazobactam	46	81%
7- Ceftazidime	45	79%
8- Ceftriaxone	45	79%
9- Cefuroxime	45	79%
10- Dexamethasone	45	79%
11- Ondansetron	45	79%
12- Teicoplanin	45	79%
13- Ciprofloxacin	44	77%
14- Clarithromycin	44	77%
15- Clindamycin	44	77%
16- Enoxaparin	44	77%

Table 3.2 (*cont'd*) Medication administration frequency

Active Pharmaceutical ingredient	Number of nurses reported to administering them frequently >4	% of nurses reporting administering them frequently
17- Hydrocortisone	44	77%
18- Aciclovir	44	77%
19- Amoxicillin	43	75%
20- Amphotricin B (liposomal)	43	75%
21- Benzylpenicillin	43	75%
22- Chlorpheniramine	43	75%
23- Flucloxacillin	43	75%
24- Gentamicin	43	75%
25- Midazolam injection	43	75%
26- Potassium Chloride	43	75%
27- Ranitidine	43	75%
28- Morphine Sulphate	31	54%
29- Furosemide	30	53%
30- Methylprednisolone	29	51%
31- Bumetanide	27	47%
32- Vancomycin	26	46%
33- Lidocaine	16	28%

Nurses (n=6) in charge of the relevant paediatric wards and a Paediatric Practice nurse confirmed the selected sample (n=27). They were asked to rate the level of importance of having a guide developed for each API. Twenty APIs were rated with a score of 4 or higher by more than 3 of the nurses in charge and therefore these APIs (n=20) were selected as the study sample (Table 3.3). The consumption amount of the selected sample per ward for the years (2007-2016) are presented in Appendix 8.

Table 3. 3 Importance of Developing a Guide for the Medications of the Initial List

Medication	Number of nurses in charge selected importance level >4
1- Paracetamol	6
2- Ceftriaxone	6
3- Teicoplanin	6
4- Clarithromycin	6
5- Amphotricin B (liposomal)	6
6- Benzylpenicillin	6
7- Potassium Chloride	6
8- Ceftazidime	5
9- Cefuroxime	5
10- Hydrocortisone	5
11- Amoxicillin	5
12- Co-amoxiclav	4
13- Cefotaxime	4
14- Metronidazole	4
15- Piperacillin/Tazobactam	4
16- Ondansetron	4
17- Aciclovir	4
18- Flucloxacillin	4
19- Gentamicin	4
20- Ranitidine	4

Table 3. 3 (*cont'd*) Importance of developing a guide for the medications of the initial list

Medication	Number of nurses in charge selected importance level >4
21- Enoxaparin	3
22- Meropenem	2
23- Dexamethasone	2
24- Ciprofloxacin	2
25- Clindamycin	1
26- Chlorpheniramine	1
27- Midazolam	1

3.2 Developed Monographs:

The available medications at Mater Dei Hospital (MDH) that contained the study sample APIs were checked at the pharmacy stores of MDH. A total of 45 medications with different strengths and trade names/generics were identified for the selected 20 APIs. Twenty monographs were developed where each monograph contained all the relevant information for the identified medications of one API (Table 3.4). The name of APIs in the monographs were listed according to Institute for Safe Medication Practices (ISMP) tallman lettering to help drawing attention to the differences in look-alike drug names in an attempt to reduce medication errors (DeHenau et al, 2016). Tallman lettering is "c*apitalizing parts of a medication name to distinguish it among look-alike or sound-alike medications"*. [40]

[40] ISMP. Institue of Safe Medication Practices. Look-Alike Drug Names with Recommended Tall Man Letters. [Internet] Horsham; 20 Nov 2016 [Cited 2019 Mar 29] Available from: https://www.ismp.org/recommendations/tall-man-letters-list.

Table 3. 4 List of Medications Selected for Developing Monographs

Active pharmaceutical ingredient	Strength	Available generic/brand
Aciclovir	250 mg	1. Mylan 2. Wockhardt 3. Claris Lifesciences
Liposomal Amphotericin B	50 mg	4. AmBisome® (Gilead)
Amoxicillin	250 mg	5. Bowmed Ibisquis 6. Wockhardt
	500 mg	7. Wockhardt
Benzylpenicillin (Penicillin G)	600 mg	8. Genus Pharmaceuticals 9. Cooper Pharmaceuticals
Cefotaxime	1 g	10. Wockhardt
Ceftazidime	1 g	11. Wockhardt, 12. Villerton 13. Fresenius Kabi
Ceftriaxone	500 mg	14. Sagent Pharmaceuticals
	1 g	15. Sirtap® Sose Pharm 16. Wockhard
Cefuroxime	2 g	17. Travilan®, Anfarm Hella 18. Villerton
	250 mg	19. Villerton 20. Bowmed Ibisquis
	750 mg	21. Axetine® (Medochemie)
Clarithromycin	500 mg	22. Bowmed Ibisquis 23. Maxilin ®(Anfarm Hellas S.A)

Table 3.4 (*Cont'd)* List of Medications Selected for Developing Monographs

Active pharmaceutical ingredient	Strength	Available generic/brand
Co-amoxiclav	500 mg/100 mg	24. Wockhardt 25. Bowmed Ibisquis
Flucloxacillin	250 mg	26. Wockhardt 27. Bowmed Ibisquis
	1 g	28. Wockhardt 29. Bowmed Ibisquis
Gentamicin	40 mg / 1 mL	30. Sopharma
	80 mg / 2 mL	31. Gentamed ® (Medochemie)
Ondansetron	4 mg / 2 mL	32. Accord Healthcare 33. Hamlen
	8 mg / 4 mL	34. Accord Healthcare
Piperacillin/ Tazobactam	2 g/0.25 g	35. Accord Healthcare 36. Wockhardt
	4 g/0.50 g	37. Wockhardt 38. Stragen
Potassium Chloride	20%	39. Marindale Pharmaceuticals
Ranitidine	25 mg /1 mL	40. Ptinolin®(Help S.A) 41. Pep-Rani® (Medinfar)
Teicoplanin	200 mg	42. Targocid® (Sanofi, Demo S.A)

3.2.1 Variations between First Draft and Second Draft

The first draft (Appendix 9) of the monographs were prepared and sent to Clinical Pharmacy Practice Unit (CPPU) for evaluation. Pharmacists reviewed the information within and evaluated the reference/resources of the information. The first draft was sent back to the researcher with the feedback. A second draft was prepared in view of the

provided feedback and forwarded to CPPU. The variations between the first draft and second draft are summarized in Table 3.5.

The first drafts of the monographs were detailed and exceeded the one page limit (Appendix 9). The indications listed included all licensed and unlicensed indications mentioned in literature for example the drafts of aciclovir, amoxicillin and liposomal amphotericin B monographs (Appendix 9). The dosage section was more detailed providing the dose range for each age of each indication and it was presented in a table form for example the draft of ceftriaxone monograph and aciclovir monograph (Appendix 9). Doses for pre-term neonates or low birth weight infants were listed along with the dose adjustments in renal and hepatic failure for example benzylpenicillin draft, ceftriaxone draft (Appendix 9). Unlicensed doses were listed without indicating that they are not licensed.

Doses in the second draft were not presented in table form and were grouped according to the indication. General dose ranges were used instead of detailed dose ranges with the recommendation to increase the dose in severe infections. Unlicensed indications or unlicensed doses included in the second draft were the the indications confirmed by literature research, guidelines and established evidence based practice for example indications listed in the second draft of clarithromycin, acyclovir and gentamicin monographs. Unlicensed data were highlighted in the second draft in bold to alarm the user of the unlicensed use. Dose adjustments in the second draft were not explained in detail but instead a general note of the need of dose adjustment in case of renal or hepatic failure was provided.

Details regarding other routes of administration were listed in the first draft such as intrapleural and intra-articular routes e.g the first draft of flucloxacillin monograph (Appendix 9). The second draft included information regarding IV route and limited information about the IM route.

Displacement values and final volumes were listed in the first draft for each strength of a medication for example displacement value for amoxicillin 250 mg vial is 0.2 mL and the final volume when reconstituting with 5 mL Water for injection (WFI) is 5.2 mL. The reconstitution/dilution instructions within the second draft were modified to consider displacement values in the final preparations without mentioning it directly. Standardisation of the concentrations of final preparations was the focus of second draft instead of mentioning final volumes or only displacement value as in the first draft.

Incompatibility of a medication with other medications whether at Y-site or in an infusion solution or in a syringe were included in first draft for example benzylpenicillin draft: benzylpenicillin is incompatible with amphotericin B, aminophylline, cimetidine, cytarabine, flucloxacillin, hydroxyzine, methylprednisolone, promethazine and solutions containing metal ions.[41] The second draft contained only drug-fluid compatibility data. The conditions and duration of time for a reconstituted or diluted medication to remain stable for administration were explained in the first draft but this type of information was omitted in the second draft for example liposomal amphotericin B first draft "*should be used immediately, however reconstituted vials are single use only but may be stored at 2 – 8°C for 24 hours or less at the responsibility of the user;*

[41] Medicines Complete.Benzylpenicillin [Internet]. Injectable Drugs Guide. 2019 [cited 2019 Mar 29]. Available from: https://www.medicinescomplete.com/#/content/idg/b03-mn0001?hspl=Benzylpenicillin%20sodium

prepared infusions may be stored at 2 – 8°C & infused (at room temperature) within 24 hours".[42]

The side effects mentioned in the first draft were general and common side effects which are classified as severe and non-severe side ADRs for example the side effects of aciclovir in the first draft monograph were listed as other undesirable effects include headache, nausea, vomiting, rash, pruritus, urticaria and reversible increase in liver enzymes.[43] The second draft contained mainly injection site reactions and sever ADRs that could be monitored for. Dealing with an ADR was explained within the potential hazards of administration section in the first draft of the monographs e.g ceftriaxone first draft "*In case of severe hypersensitivity reactions, treatment should be discontinued immediately and adequate emergency measures must be initiated (treatment with epinephrine, oxygen, IV steroids, antihistamines, pressor amines and airway management)*".[44]

Miscellaneous information in the first draft included drug-drug interactions, contraindications and treating an overdose. This type of information were excluded in the final version of monographs and it was kept to the nurse to consult a clinician and the pharmacy department for addressing cases of overdose, contraindicative treatments and severe ADRs.

[42] HPRA. AmBisome Liposomal Amphotericin B 50mg Powder for Concentrate for Dispersion for Infusion [Internet]. SmPC.Hpra.ie. 2019 [cited 2019 Mar 29]. Available from: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2322-001-001_22112018145008.pdf
[43] MHRA.Aciclovir 250mg powder for solution for infusion (aciclovir) [Internet].SmPC. Mhra.gov.uk. 2019 [cited 2019 Mar 29]. Available from: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con2033840.pdf
[44] MHRA- SPC-PIL Ceftriaxone 500 mg, 1g, 2g Summary of product characteristics MHRA [Internet] 2014[cited 2019 Mar 28]. Available from http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/

Table 3. 5 Differences between First and Second Draft of Drug Monographs

Parameter	First Draft	Second Draft
Indication	• Licensed and unlicensed. • Specific indication (listing all types of infection an antibiotic is indicated for)	• Mainly licensed • General indication (specifying susceptible bacteria for antibiotics) • Protocol number provided for antibiotics
Reconstitution/Dilution	• Information provided for using part of vial • Displacement value • Final volume	• Final concentration for a preparation
Method of Administration	• All parenteral routes provided	• Max Concentration to be injected/infused provided
Dose	• Detailed for each indication • Table form • Dose adjustment details provided in renal and hepatic impairment	• Usual dose range • paragraph form • Dose adjustment is only mentioned as a general requirement in cases of renal and hepatic impairment
Compatibility/Stability	• Drug-Drug compatibility • Conditions of Stability after preparing a medication	• Drug-fluid compatibility only • Recommendation to use prepared medications immediately
Potential hazards	• General and common side effects	• Serious ADRs and side effects that can be monitored
Miscellaneous	• Drug-Drug interaction • Dealing with overdose • Dealing with ADRs	• Monitoring signs and symptoms that lead to ADRs • Interference with Lab test • Sodium content

3.2.2 Indication and Dosage

Indications were listed in a summarized form where rather than mentioning all types of infections an antibiotic is effective against such as wound infections, soft tissue infections, respiratory tract infections and middle ear. These indications were abridged to "penicillin-sensitive microorganisms or infections due to susceptible non-beta lactamase producing organisms" (benzyl penicillin monograph). Another example is of cefotaxime antibiotic where the indications listed in various references and SmPC for this antibiotic are "*Treatment of serious infections including osteomyelitis, septicaemia, bacterial endocarditis, meningitis, peritonitis and other serious bacterial infections,, Pre-operative prophylaxis in patients undergoing surgical procedures which may be classified as contaminated or potentially so".*[45] Cefotaxime indications were summarized to the term "Treatment of infections due to susceptible Gram-positive and Gram-negative bacteria and surgical prophylaxis" (Appendix 9, 10) (Table 3.5).

The indications of antibiotics, which use are protocol regulated at MDH, were listed in align with the indications mentioned in the protocol. The protocol abbreviation MP (Medical Protocol) and number was provided in the respective monograph to refer to the indications it can be used for. An example is in the teicoplanin monograph where the protocol number (MP 280) was provided and similarly piperacillin/tazobactam monograph where the MP number (162) was included.

Unlicensed indications that were based on evidence based literature and established practice were included in the monograph such as use of piperacillin/tazobactam in children under 12 years old for various indications. Piperacillin/ tazobactam is licensed

[45] MHRA.Cefotaxime 1g powder for solution for injection or infusion [Internet]. SmPC.Mhra.gov.uk. 2019 [cited 2019 Mar 29]. Available from: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con2025203.pdf

for use in children 2 to 12 years only for complicated intra-abdominal infections & neutropenic children with fever indications [46,47] but other indications were listed in the monograph for the age range neonates to 12 years old (piperacillin/tazobactam monograph-Appendix 10). These unlicensed indications are hospital-acquired pneumonia, septicaemia and complicated infections involving urinary-tract, skin and soft tissues for the age range neonates to 12 years old. The unlicensed indications were included in the monograph since they were mentioned in all references (Table 2.3) and the United States of America Food Drug and Administration (US FDA) licenses the use of piperacillin/tazobactam in children 2 months and older.[48]

Clarithromycin IV injection is unlicensed for use in paediatric patients younger than 12 years old but the indications and the doses for its use in children were provided within the respective monograph. There is growing evidence of the benefits of the off-license use of Clarithromycin in the paediatric population within different guideline and references such as: (i) The Management of Community-Acquired Pneumonia in Infants and Children Older than 3 Months of Age: Clinical Practice Guidelines by the Paediatric Infectious Diseases Society and the Infectious Diseases Society of America (IDSA), (ii) Guidelines for the prevention and treatment of opportunistic infections in HIV exposed and HIV infected children, (iii) British National Formulary for Children (BNF-C), (iv) Martindale and (v) product literature. The lack of experience in using and administering Clarithromycin IV injection versus its frequent prescribing had given rise

[46] HPRA. Health Products Regulatory Authority. Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Infusion - Summary of Product Characteristics (SmPC) - (HPRA) [Internet] 2018 [cited 2019 Mar 28]. Available from: http://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results

[47] HPRA. Piperacillin/Tazobactam 2 g/0.25 g Powder for Solution for Infusion - Summary of Product Characteristics (SmPC) - (HPRA) [Internet] 2018 [cited 2019 Mar 29]. Available from: http://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results

[48] US FDA. Piperacillin/Tazobactam for injection Zosyn® Product label- US FDA [Internet]. FDA.gov. 2012 [cited 2019 Mar 28]. Available from:https://www.accessdata.fda.gov/drugsatfda_docs/label/2012

for the need to develop a monograph including information about its unlicensed use in paediatrics younger than 12 years old (1 month-11 years).

Other unlicensed indications that were included within a monograph were (i) use of ondansetron IV in radiotherapy-induced nausea and vomiting, (ii) use of Ambisome® in the treatment of visceral leishmaniasis in immunocompetent and immunocompromised patients and (iii) use of ranitidine as IV in prophylaxis of stress.

Doses that were listed in the monographs were licensed and unlicensed. Unlicensed doses were for both licensed and unlicensed indications. Unlicensed doses for a licensed indication were included in a monograph if it was confirmed by literature review, evidence based practice and listed in accredited references specific for paediatric patients such as Neofax, Paediatric Injectable Drug book (PID), BNF-C or guidelines.

Gentamicin solution for injection can be administered in neonatal and paediatric populations in different methods and doses; extended interval and conventional dosing (multiple daily dosing). The extended interval dosing allows administration of a dose every 36 hours while the multiple daily dosing is administration of a dose every 8 hours. The SmPC of the available products (Gentamed® and the generic Sopharma) do not license the use of gentamicin in an extended interval dosing (every 36 hours); the Sopharma brand licenses the multiple daily use (every 8 hours) while Gentamed® brand licenses the use every 24 hours (once daily dose regimen). The use of gentamicin in an extended interval dosing is supported by literature (Darmstadt et al, 2008; El-Chaar et al, 2016; Moon K, 2017), the protocols utilized at the paediatric wards (MDH Department of Paediatrics-Neonatal IV gentamicin protocol (PID002, version 3), 2015;

Hospital Antibiotic team policy, 2015, policy number: ICU/01Guide/2015v01.0) and the established resources; Neofax, PID, BNF-C and IMG Medusa paediatric and neonatal monographs. Since the established paediatric references recommends the extended interval dosing (every 36 hours) particularly in neonates the doses listed in gentamicin monographs for neonates were unlicensed or licensed by one SmPC such as *the "Dose of 5 mg/Kg to be administered every 36 hours in neonates (0 up to 7 days)"* which is unlicensed and *"once daily dosing (every 24 hours) in neonates (7-28 days)"* is licensed in one SmPC (Gentamed ®).

Doses of ondansetron in paediatric patients over 6 months for the indication of chemotherapy induced nausea and vomiting (CINV) are given based on Body surface area (BSA). The doses listed in the SmPC of the available products (Hamlen, Accord) is 5 mg/m^2 IV before the start of chemotherapy and can be repeated again every 12 hours after chemotherapy. Other references such as BNF-C and Neofax allows repeating ondansetron after 4 hours and 8 hours of chemotherapy. The evidence based practice at Rainbow ward at SAMOC (Sir Anthony Mamo Oncology Centre) hospital and the guideline (Great Ormond street hospital; Paediatric Haematology & Oncology supportive care protocol) recommends administering the second dose of ondansetron after 8-12 hours of receiving chemotherapy. The frequency of dose repetition listed in ondansetron monograph was compiled to be every 8 to 12 hours after receiving the chemotherapy. This compilation was performed since specialised references, evidence based practice and paediatric guideline recommends administering another dose after 8 and 12 hours following administration of chemotherapy. The final version of the ondansetron monograph listed the dose repetition as every 8 to 12 hours instead of every 12 hours as in the SmPC (Hamlen, Accord).

Unlicensed use of a medication in neonates and paediatrics can be brand specific. Amoxicillin as an active ingredient is licensed to be used in neonates and infants, however the Wockhardt brand of amoxicillin should not be administered in patients younger than 1 year old. The Marketing authorization holder (MAH) of amoxicillin Wockhardt does not recommend its use in neonates and paediatrics due to the reports of extravasation and injection site reactions caused by the additives and excipients. Ranitidine as an active ingredient is licensed for use in infants and paediatric patients aged 6 months to 11 years old. Pep-rani® 50mg/2mL solution for injection- a brand of ranitidine used at MDH- is not recommended to be used in paediatric population as per the product SmPC where it was listed that "*Pep-rani® should be used with caution in children, since its safety and efficacy have not been completely proven yet"*.

Dosing section included not only therapeutic doses but as well test doses if applicable such as liposomal amphotericin B should where a test dose should be administered first to detect idiosyncratic anaphylactic reactions. A test dose of 1 mg/kg (maximum 1 mg per dose) is administered over 10 minutes as slow injection and then the patient should be monitored for 30 minutes afterwards. The infusion has to be discontinued if a severe anaphylactic reaction occurs and no further doses should be administered.

3.2.3 Reconstitution, Dilution and Method of Administration

Choice of reconstituting fluids and diluents is listed in every monograph for each medication in the "Reconstitution and Dilution" section. The common practice is to use WFI as the reconstitution fluid while normal saline (NS), 5% dextrose in water (D5W) or 10% dextrose in water (D10W) are the diluents unless they are not suitable for use. Use of D5W is preferred over NS as a diluent in patients with sodium restriction such as

heart or renal failure, particularly with the medication benzylpenicillin sodium since the sodium content per vial is significant and would add to the diluent sodium content. Some medications are incompatible with NS such as Liposomal amphotericin B, thus D5W is the choice of diluent while other medications are incompatible with D5W such as co-amoxiclav. Although some medications are considered to be compatible with a diluent, the stability of the drug might be affected. Amoxicillin and aciclovir in dextrose containing solutions or ceftazidime in bicarbonate containing solutions exhibit a lower stability as a result it is not recommended as the choice of diluent.

The reconstitution and dilution of some medications require special steps to follow such as ceftazidime and teicoplanin. First, the diluent needs to be injected into the ceftazidime vial and carbon dioxide would be released while ceftazidime dissolves. Once the carbon dioxide is released pressure is generated within the vial. The vial has to be inverted and the syringe to be inserted through the vial stopper with plunger fully depressed. The needle has to remain within the solution while the dose is being withdrawn. The pressure within the vial resulting from the carbon dioxide aids in withdrawing the dose. Finally following the dose withdrawal, bubbles of carbon dioxide have to be expelled from the syringe before injection. Teicoplanin is prepared by slowly injecting the entire amount of the supplied solvent into the powder vial. The vial needs to be rolled gently between hands to dissolve the powder completely and the solution has to be left standing for 15 minutes if it becomes foamy.

3.2.3.1 Displacement Value

The reconstitution and dilution sections were expanded to include information for the administration of part of a vial when the administrator will use a small amount of the vial such as in cefotaxime monograph and ceftazidime monograph.

Moreover, the displacement value was not mentioned directly as in the first draft where the calculations need to be done by the administrator or nurse. The instructions were modified to include the calculated displacement value and to make sure that standard concentration is obtained to reduce dilution mistakes that may lead to under or over dosing of the medication.

The displacement value is the increase in the fluid volume that occurs when a solid is dissolved in a fluid. The displacement value is important to consider when reconstituting/diluting medications that are in the form of dry powder. For example: A 250 mg vial of amoxicillin has a displacement value of 0.2 mL and is reconstituted with 5 mL WFI. If the prescribed dose is 250 mg, then the administrator should administer the full amount of 5.2 mL to the patient. If the prescribed dose is less than 250 mg such as 100 mg the volume to be administered has to be calculated using the final concentration that is 48 mg/mL taking into account the volume of fluid and displacement value. An alternative method is to add 4.8 mL WFI to the 250 mg amoxicillin vial which would yield a final volume of 5 mL and a final concentration of 50 mg/mL. Thus the volume to be administered would be easier to calculate and to withdraw from the vial.

Displacement values were considered using five different methods:

1- **Using the term "Up to" in diluting/reconstituting instructions of the medication to obtain a standard volume and concentration**: This term was used for the monographs ceftriaxone, co-amoxiclav, cefuroxime, and gentamicin. This would allow reconstitution to a standard final volume for example in co-amoxiclav monograph the instructions of reconstitution were as follow "*reconstitute co-amoxiclav 600 mg (500 mg/100 mg) in 10 mL WFI and then dilute the solution up to 15 mL (final volume)*". Following these instructions, the resultant concentration will be 40 mg/mL (33.33 mg/ 6.67 mg). Another example is ceftriaxone where reconstituting 500 mg vial with up to 20 mL WFI obtains a concentration of 25 mg/mL; reconstituting 1 g vial and 2 g vial with up to 40 mL WFI to arrive to the concentrations 25 mg/mL. Reconstituting cefuroxime 250 mg vials with 2 mL WFI and the 750 mg vial with 6 mL WFI and diluting each with 5 mL and 15 mL respectively to obtain the final concentration of 50 mg/mL. Listing the final concentration allows for a standard calculation of the dose required to be administered rather than having a variation in concentrations which would affect volume calculations and eventually the amount of dose to be administered.

2- **Specifying the volume required to reconstitute/dilute the medication to achieve the desired concentration**: for example reconstitution of Flucloxacillin a volume of 4.8 mL of WFI is required to be added to a 250 mg vial and 19.4 mL WFI need to be added to a 1 g Flucloxacillin vial to obtain a final concentration of 50 mg/mL. Twelve mL of WFI is required for the reconstitution of liposomal Amphotericin B vial and 37.5 mL of D5W or

D10W is required to dilute the reconsitutited vial to obtain a final volume of a 50 mL taking into consideration the displacement value for the medication is 0.5 mL. A final concentration of 1 mg/mL (50 mg medication / 50 mL) would be obtained by following the listed instructions.

3- **Specifying the amount of diluent/reconstituted fluid to be added when using part of a vial:** for example when using part of a vial of the benzylpenicillin 600 mg; 1.6 mL of WFI has to be added to the vial for the IM use and 3.6 mL WFI need to be added for the IV use. Adding these specific amounts of diluents would lead to standard concentrations of 300 mg/mL and 150 mg/mL respectively which makes it easier to calculate the volume of the required dose. If a whole benzylpenicillin vial is to be used then the amount of WFI to be added would be 2 mL for IM injection and 4 mL for the IV injection respectively and the final concentrations would be 250 mg/mL and 136.36 mg/mL respectively. In the example of ceftazidime the 1 g vial has different displacement values depending on the brand used (0.9 mL for Wockhardt and Fresenius Kabi and 0.5 mL for the Villerton brand). When using part of a vial of Wockhardt or Fresenius Kabi 9.1 mL NS is required for reconstitution while for Villerton brand 9.5 mL NS is required for reconstitution. Adding the previous volumes yields a standard concentration of 100 mg/mL for all of the different brands. When using a whole vial of any of ceftazidime brand 10 mL of NS is required.

4- **Listing the resultant final concentration when adding a standard amount of fluids:** for example when adding 5 mL WFI to 250 mg amoxicillin vial and

10 mL WFI to a 500 mg amoxicillin vial a concentration of 48 mg/mL is obtained.

5- **Providing the final volumes to be infused if the medication is administered only by IV infusion:** for example clarithromycin is only to be administered as IV infusion therefore the reconstituted clarithromycin vial should be added to a 250 mL NS or D5W bag to obtain a 2 mg/mL solution for IV infusion. Similarly the reconstituted piperacillin/tazobactam 2 g/0.25 g and 4 g/0.5 g vials have to be diluted to at least 50 mL NS or D5W to be infused and the reconstituted hydrocortisone vial needs to be diluted to 100 mL NS or D5W.

6- **Listing the final concentration to be infused for medications which need to be in a specific concentration range before infusing:** for example potassium chloride needs to be diluted to a concentration in the range of 20-40 mmol/L for administration as peripheral infusion and concentrations higher than 40 mmol/L can be given only through central infusion. The required concentration of ondansetron to be infused is between 0.32 and 0.63 mg/mL. To obtain this concentration each 1 mL of ondansetron should be diluted up to 5 mL.

3.2.3.2 Maximum Concentrations and Rate of Administration

Reconstituted or diluted medications administered through IV peripheral line should not exceed the maximum allowed concentration or dose. Exceeding the maximum concentration of the administered medication can lead to side effects at injection site such as administering solution of potassium chloride with osmolality higher than 40 mmol/L or infusing aciclovir at concentrations higher than 5 mg/mL would lead to

extravasation or phlebitis. Exceeding the maximum concentration would affect the stability of the admixture of the medications and fluids at Y-site infusion for example concentrations higher than 5 mg/mL of aciclovir are less stable in admixtures at Y-site infusion. Similarly reconstituted ceftazidime is compatible with other medications and fluids at concentrations of 40 mg/mL or lower, higher concentrations form less stable admixtures at Y-site infusion.

The concentration of certain medications in the infusion fluid needs to be within specific range before administration for example concentration of ondansetron in the infusion fluid has to be in the range of 0.32-0.64 mg/mL and concentration of Ambisome® in the final solution for infusion should be between 0.2 mg/mL and 2 mg/mL. Osmolality of potassium chloride solutions needs to be in the range of 20-40 mmol/L for peripheral administration, solutions with osmolality higher than 40 mmol/L has to be administered via central line to avoid extravasation and phlebitis.

Not all medications have a maximum concentration for administration for example teicoplanin can be diluted by adding the reconstituted solution to a suitable volume for infusion. The administrator can select the volume of a compatible that is suitable to the patient's needs and clinical condition.

Method (IV bolus or IV infusion) and rate of administration depends on the required dose and concentration of the administered medication. For each medication there is a maximum concentration or dose that can be administered safely through a route. For example:

- Amoxicillin can be given via IV injection into vein or drip tubing (administered over 3-4 minutes through a large vein) only if the dose is less than or equal to 30 mg/kg. Doses higher than 30 mg/kg warrant infusion over at least 30 minutes preferably through a central venous access or large peripheral vein.
- Ambisome® is administered over 1 hour if the dose is less than or equal to 5 mg/kg and has to be given over 2 hours if the dose exceeds 5 mg/kg.
- Doses of ceftriaxone which are less than 50 mg/kg can be given through IV injection but higher doses need to be given through IV infusion.
- Clarithromycin has to be infused over 60 minutes at a maximum concentration of 2 mg/mL but in fluid restricted patients it can be administered at concentrations up to 5 mg in 1 mL. Use of concentrations higher than 5 mg/mL is off-license and restricted to central venous access devices.
- The maximum concentration of benzylpenicillin to be infused via peripheral vein is 60 mg/mL. Doses more than 50 mg/kg are to be infused over 15-30 minutes while doses less than 50 mg /kg can be given through slow IV injection provided that the rate of administration doesn't exceed 300 mg/min.
- Reconstituted solutions of cefotaxime with concentrations higher than 200 mg/mL has to be administered over at least 3 to 5 minutes to avoid arrhythmia.

The rate of administration for some medications depend on other parameters such as age or PH for example:

- Administration as IV bolus is unlicensed for co-amoxiclav and ceftriaxone in infants younger than 3 months and neonates respectively. The minimum infusion time required for co-amoxiclav is 60 minutes in infants younger than 3 months compared to 30 minutes in older patients.
- The preferred method of administration of gentamicin and ondansetron is IV infusion through central venous access device since these medications have low pH that causes venous irritation and tissue damage. If a central route is not available then gentamicin and ondansetron is to be preferably administered via large peripheral vein diluted to a concentration of 2 mg/mL.

Some medications are to be administered only through IV infusion and cannot be administered through IV injection such as piperacillin/tazobactam, potassium chloride, metronidazole and paracetamol. Maximum infusion rate of potassium chloride is 20 mmol/hour. The maximum rate for peripheral infusion is 0.2 mmol/kg/hour and for central route is 0.5 mmol/kg/hour

3.2.3.3 Infusion Fluids

The amounts of infusion fluids to use along with the final volume of the infusion fluid and final concentration of the medication in the infusion fluid were specified in most of the monographs. The volumes were listed as in these examples:

- The final infusion volume and concentration were listed in the monograph of aciclovir where the phrase "*Further dilute up to 50 mL using NS – final concentration: 5 mg/mL"* was used.
- The volume of infusion fluid to be added to reconstituted Ambisome® and final concentration were listed in the monograph as per the phrase "*Instil the reconstituted solution through a 5 micron filter into a syringe containing 37.5 mL of D5W or D10W. Final concentration of solution is 1 mg/mL*".
- The instructions for the final volume of amoxicillin were listed for different strengths in the respective monograph as *"IV infusion: dilute up to 10 mL for the 250 mg vial and up to 20 mL for the 500 mg vial with a compatible infusion fluid. Final concentration after dilution: 25 mg/mL",* where different vial strengths require different volumes of infusion fluid.
- The instructions for reconstitution and dilution of benzylpenicillin sodium listed in the monograph as "*600 mg dissolved in 4 mL WFI or NS, Dilute up to 10 ml to administer*" would provide the maximum concentration which is 60 mg/mL and then the administrator can choose to either administer the 10 mL or else use a larger volume of infusion as per the phrase *"The solution can be added to 50 mL NS or D5W bag for IV infusion*" depending on the volume and quantity of the required dose and taking into consideration maximum administration rates.

The volume of the infusion fluid depends on the admininistered dose for example if the dose required of co-amoxiclav is less than 500 mg/100 mg then the reconstituted solution must be added to 50 mL of infusion fluid while higher doses need to be added to 100 mL infusion fluid. Clarithromycin after reconstitution needs to be diluted to 250 mL NS or D5W. If the dose needed is less than 500 mg (part of vial) then each 1 mL of

the reconstituted clarithromycin solution to be mixed with 25 mL of NS or D5W. The final concentration should be 2 mg/mL.

Different strengths of a medication can be diluted with the same volume of infusion fluids such as both strengths of flucloxacillin 250 mg and 750 mg can be diluted with the a standard volume of diluent such as 100 mL. A 50 mL of NS can be used to dilute piperacillin/tazobactam 2 g/0.25 g and 4 g/ 0.5 g for administration via IV infusion.

Medications such as gentamicin 80 mg/2 mL and reconstituted hydrocortisone 100 mg do not require dilution for administration. A small volume of diluent can be added to the solution to aid in slow administration. Ready diluted medications are either added to an infusion fluid if their volume is small e.g gentamicin and ranitidine where the vial volume is 2 mL or they can be infused directly if their volume is large e.g paracetamol and metronidazole.

Details for other routes of administration were provided such as flucloxacillin, ondansetron (Appendix 10). IM injection is an alternative when the IV route is not available for some medications but the maximum dose and volume that can be administered through IM route is much smaller for example maximum dose of benzylpenicillin to be administered through IM route is 100,000 unit. Ceftriaxone where doses over 2 g can't be given intramuscularly and doses greater than 1 g had to be divided between more than one site. Cefotaxime, ceftazidime and cefuroxime require to be administered through deep IM injection which could be painful for children and should only be used when IV route is unavailable. Hydrocortisone when injected should not be in the deltoid muscle because of the high incidence of tissue atrophy.

3.2.4 Drug Compatibility and Stability

The compatibility of drugs with fluids available at MDH; NS, NS 0.45% (Sodium chloride 0.45%), D5W, D10W, Haartman or lactated ringer (compound sodium Lactate), D5NS (Glucose 5% and sodium chloride 0.9%), D5 ½ NS (Glucose 5% and half sodium chloride 0.9%) and bicarbonate were provided for every medication. The diluent or flushing fluid of choice was given in every monograph.

Incompatibilities that were included in a monograph were general drug-drug incompatibility such as incompatibility with a drug class such as aminoglycoside which is incompatible with the following medications. Incompatibilities can occur at any stage of medication preparation and administration: (i) when mixing medications in the same syringe or IV fluid container for example aminoglycoside with amoxicillin or cefotaxime or cefuroxime or co-amoxiclav, (ii) when administering medications at the same site for example ceftazidime and flucloxacillin.

Other examples of drug-drug incompatibility listed within a monograph are ondansetron with penicillin or cepahlosporin, teicoplanin with ciprofloxacin or ceftazidime, gentamicin with penicillin or cephalosporin.

Some medications are in incompatible with other medications and should not be co-infused or mixed or combined with other medications for example (i) teicoplanin should not be co-administered with other medications, (ii) aciclovir must not be mixed with other IV medications in the same tubing or same infusion set, (iii) Ambisome® cannot be mixed with other medications (iv) benzylpenicillin should not be mixed or co-administered with other medications and (v) flucloxacillin must not be combined

with other drugs. Incompatibility can be brand specific where amoxicillin as an active ingredient is incompatible with aminoglycosides and bicarbonate containing fluids however only the Wockhardt brand of amoxicillin was reported to be incompatible with ciprofloxacin.

Incompatibility for some medications can be with specific types of compounds for example (i) benzylpenicillin is inactivated by acids, alkalis, oxidising agents and glucose solutions containing bircarbonates (ii) flucloxacillin, ceftazidime and amoxicillin should not be mixed with blood products, proteinaceous fluids (e.g protein hydrolysates) or IV lipid emulsions (iii) Ambisome® is incompatible with electrolytes, (iv) cefotaxime is incompatible with alkaline solutions e.g. sodium bicarbonate (v) ceftriaxone is incompatible with calcium-containing infusion fluids such as compound sodium lactate, Ringer's solution and IV nutrition; because of the risk of precipitation of ceftriaxone-calcium salts ceftriaxone can only be used with calcium containing preparations if they are administered one after the other through different infusion lines and at different sites or adequate flushing of the infusion lines is done thoroughly provided that the patient over 28 days old.

Concentration-specific compatibilities for medications and diluents were not listed in the monograph. This type of information was excluded to avoid misinterpreting by nurses that a medication is generally incompatible with the listed fluids or medications in the monograph, while the incompatibility in this case occurs at specific concentrations that are higher than the maximum concentration listed within the respective drug monographs. Nurses were informed to check with the pharmacist or

medicines information unit if further information regarding medication incompatibilities are required such as incompatibilities with materials of administrative sets.

The provided stability data in the monographs was focused on the appearance of a solution following reconstitution or dilution. Potential colour changes or precipitate formation were mentioned and the impact on the safety and potency of administered medications was explained if it was provided from the manufacturer or literature. Emphasis to discard any remaining medication in a vial/bottle was listed in each monograph. This is to discourage the administrator from using a single use vial multiple times or storing reconstituted/diluted medication for another administration. The change in colour and its effect on stability was confirmed for the brands/generics if the information was available in SmPC or if the information was obtained directly from Marketing Authorization Holder (MAH) or manufacturer.

The colour of a reconstituted solution of ceftazidime ranges from light yellow to amber depending on the concentration, diluents and storage conditions used. An aciclovir solution for infusion may become cloudy or may crystallizes prior to or during the infusion in such case the solution is considered to be no longer stable and should be discarded. The reconstituted solutions of amoxicillin, cefotaxime, ceftazidime, cefuroxime, clarithromycin, co-amoxiclav and ranitidine all undergo a change in colour or intensity of colour which affect the stability of the solution and warrants discarding preparation.

Variations in the colour or intensity of colour do not always affect stability or potency of reconstituted/diluted medications where medications are still safe for administration

for example cefuroxime as an API has the property to change in colour with no effect on stability or potency (Table 3.6). Some medications when stored a change in colour might occur without affecting potency for example ranitidine solution is a clear, colourless to light yellow solution when stored correctly, slight darkening of the solution does not affect potency.

Other details of stability data included were storage conditions and protection from light. The medications should be stored in their original container at room temperature below 25 degrees. Aciclovir, liposomal amphotericin B, ceftazidime, cefuroxime, hydrocortisone, metronidazole and ondansetron need to be stored in their containers and protected from light to maintain their stability.

Data was not provided for the duration of stability of a medication after preparation. The SmPC and other references such as IDG lists the time for which a reconstituted/diluted medication would remain stable when stored at room temperature or in the fridge. This type of information was removed from the first draft of the monographs so the infusions would not be prepared a long time prior to their use in a clinical area since from a microbiological point of view the diluted solution should be used immediately. If the reconstituted/diluted medication was not used immediately then in-use storage times and conditions are the responsibility of the administrator.

Table 3. 6 Expected Changes in the Solution of Reconstituted/Diluted Medications

Active Pharmaceutical Ingredient (API)	Expected changes	Comments
Co-amoxiclav Amoxicillin (Bowmed brand)	Transient pink colour may appear during reconstitution	Reconstituted solution should be colourless or pale straw in colour. Not be administered if the reconstituted solution is pink
Flucloxacillin Clarithromycin Hydrocortisone	Development of particles	Reconstituted solutions should be clear, colourless and particles free. Not to be administered if particles developed
Cefotaxime Ranitidine	Variation in intensity of colour	Stability and potency would not be affected. Can be safely administered.
Cefuroxime (Axetine®)	Colour of solution turns darker upon standing	Reconstituted solution for IV administration is yellowish while suspension for IM administration is almost white, safety or effectiveness is not affected. Can be safely administered.
Cefuroxime Villerton (generic)	Colour of solution turns darker upon standing	Reconstituted solution of brand can vary from light yellow to amber. Safety and effectiveness is not affected Can be safely administered.

3.2.5 Potential Hazards of Administration

Potential hazards of administration listed in the monographs are the side effects related to injection site reactions, anaphylactic reactions and adverse effects. These were categorised as follows

- **Injection site reactions** are pain and inflammation at injection site, extravasation (aciclovir), phlebitis and thrombophlebitis (co-amoxiclav, ceftriaxone, clarithromycin, metronidazole, piperacillin/tazobactam and teicoplanin), extravasation (ondansetron) and hypersensitivity reactions (teicoplanin).
- **Anaphylactic reactions:** acute infusion reactions such as fever, chills and rigors (liposomal amphotericin B, teicoplanin), angioedema (ranitidine), urticaria (amoxicillin), rashes (benzylpenicillin sodium), bronchospasm (ceftazidime, liposomal amphotericin B) or allergic dermatitis (ceftriaxone).
- **Side effects that can be monitored by signs and symptoms**: neurological reactions such as tremor, ataxia and convulsions (e.g. aciclovir, amoxicillin, benzylpenicillin sodium, ceftazidime) and ototoxicity e.g. gentamicin, teicoplanin.
- **Side effects that can be monitored by lab tests**: hepatic events (Cholestatic jaundice; co-amoxiclav, cefuroxime, clarithromycin), nephrotoxicity (gentamicin), prolongation of prothrombin time (ceftazidime, cefuroxime, piperacillin/tazobactam), leukopenia and thrombocytopenia (benzylpenicillin sodium, ceftazidime, cefotaxime) and electrolyte disturbances (benzylpenicillin sodium, liposomal amphotericin B, piperacillin/tazobactam).
- **Serious and life-threatening adverse events**: amoxicillin-induced flare of DRESS (Drug Rash with Eosinophilia and Systemic Symptoms).

Jarisch-Hersheimer reaction by benzylpenicillin sodium with symptoms of fever, chills, myalgia, headache, tachycardia, hyperventilation, mild hypotension, Torsade de pointe and Stevens-Johnson syndrome (clarithromycin, piperacillin/tazobactam), pheochromocytoma crisis (hydrocortisone sodium succinate).

- **Cross hypersensitivity reactions**: such as cross reactions with penicillin and cephalosporin (amoxicillin, cefotaxime, ceftazidime, co-amoxiclav, cefuroxime, ceftriaxone). Cross reactions with vancomycin may occur, including fatal anaphylactic shock (teicoplanin).
- **Side effects that can be minimized**: renal dysfunction and crystalluria which can be minimized by slow infusion rates and adequate patient hydration (aciclovir, amoxicillin), leukopenia, thrombocytopenia that can be minimized (ambisome®, benzylpenicillin sodium, teicoplanin).
- **Long-term therapy complications**: emergence of resistant viral strains (aciclovir), superinfection (co-amoxiclav, amoxicillin), impaired wound healing or growth retardation and muscle weakness (hydrocortisone sodium succinate).
- **Side effects associated with high doses**: Congestive heart failure (due to high sodium intake) and fatal electrolyte abnormalities which occurs after large doses of benzylpenicillin sodium, acute myopathy (hydrocortisone sodium succinate), convulsive seizures with metronidazole, neurotoxicity with large doses of piperacillin/tazobactam and impaired renal function.
- **Side effects associated with rapid administration**: arrhythmia following rapid administration of cefotaxime via central venous access device and hypersensitivity reactions “red man syndrome” caused by rapid administration of teicoplanin.

3.2.6 Miscellaneous

Miscellaneous sections included the measures required to ensure safe and effective use of a medication throughout therapy. Information in this section included (i) clinical monitoring, (ii) cautionary measures and recommendations, (iii) interference with lab tests and (iv) sodium content. Other types of information are (v) cross-resistance between antibiotics (such as clarithromycin and lincomycin and clindamycin, valaciclovir and aciclovir) (vi) significant removal of a medication by haemodialysis such as amoxicillin, (vii) cross sensitivity of antibiotics for example ceftazidime with other beta-lactams antibiotics, (viii) drug-drug interactions where the impact of combining one medication with other medication/s on an ADR or a condition was mentioned and (ix) risks of concomitant administration of a medication with other medications for example "*concomitant use of clarithromycin with oral hypoglycaemic agents and/or insulin can result in significant hypoglycaemia"*.[49] Increased risk of haemorrhage and elevations of prothrombin time when used with Warfarin (clarithromycin, metronidazole).

3.2.6.1 Monitoring Parameters

Parameters such as signs and symptoms of an ADR and lab tests that are indicative of toxicity were recommended to monitor. Frequency of monitoring was listed if provided

[49] EMC.Clarithromycin 500mg powder for solution for infusion vials - Summary of Product Characteristics (SmPC) - (eMC) [Internet]. Medicines.org.uk. 2019 [cited 1 September 2019]. Available from: https://www.medicines.org.uk/emc/medicine/34557/SPC

in literature and SmPC. Examples of parameters were listed in the monographs for monitoring are in Table 3.7.

Table 3. 7 Parameters to be Monitored during Therapy with Medications

Parameter	Recommendations	Example
Renal function and liver function	• Monitored to evaluate hepatic effect and nephrotoxicity of a medication	• Ambisome® • Benzylpenicillin • Gentamicin
Urinalysis and electrolytes such as magnesium, potassium		• Ambisome® • Hydrocortisone sodium succinate
Prothrombin time	• For medications that cause prolongation of prothrombin time	• Co-amoxiclav • Ceftazidime • Clarithromycin Piperacillin/tazobactam
Full blood count (FBC)	• For medication that causes leukopenia and thrombocytopenia	• Ambisome® • Benzylpenicillin sodium • Cefotaxime • Ceftazidime
Serum level of medications	• For medications with narrow therapeutic window • When a medication is used in neonates for a long-time	• Gentamicin • Metronidazole • Potassium chloride
Serum levels of glucose	• To monitor frequently in acute illness during Hydrocortisone therapy • To monitor at start of Potassium chloride infusion	• Hydrocortisone sodium succinate • Potassium chloride
ADRs	• When a high dose will be used	• Teicoplanin 12 mg/kg twice daily
Auditory and vestibular function	• For ototoxic drugs	• Gentamicin • Teicoplanin

Table 3.7 (*cont'd*) Parameters to be monitored during therapy with medications

Parameter	Recommendations	Example
Visual disturbances such as blurred vision		• Ondansetron
Psychiatric reactions (depression and mood disorders or convulsions)	• for mood affecting medications	• Hydrocortisone sodium succinate
Signs of infection	• For immunosuppressive therapy and antibiotics	• Hydrocortisone sodium succinate
Signs of superinfection (diarrhea)	• Prolonged or recurrent with antibiotics	• Co-amoxiclav
Signs of neuropathy (numbness of an extremity, paraesthesia, convulsive crisis)		• Metronidazole

3.2.6.2 Recommendations and Cautionary Measures

Recommendations that were listed within monographs were targeted to optimize therapy and to minimize side effects. Recommendations to maximize benefit of a medication such as: (i) use of shorter dosing intervals or larger doses for example gentamicin in patients with cystic fibrosis, major thermal burns or dermal loss, ascites or in patients with febrile granulocytopenia , increasing doses of hydrocortisone sodium succinate in patients subject to stress (e.g trauma, surgery, severe infection).

Recommendations to minimize ADRs such as:

(i) Ensuring good hydration status and correction of dehydrations during therapy of nephrotoxic medications such as gentamicin.

(ii) Avoiding live vaccinations in patients receiving immunosuppressive doses of hydrocortisone sodium succinate.

(iii) Tapering off the dose of hydrocortisone sodium succinate gradually and slowly following a long-term therapy.

(iv) Avoiding products that contain alcohol and/or propylene glycol during and for 3 days after therapy with metronidazole.

(v) Increasing infusion time to prevent or resolve dizziness occurring with rapid IV administration of ondansetron.

(vi) Correction of hypokalaemia and hypomagnesemia prior to ondansetron administration.

(vii) Avoiding glucose infusion at the beginning of potassium replacement therapy

(viii) Administration of small doses of potassium chloride to avoid hyperkalaemia

(ix) Availability of cardiopulmonary resuscitation during IV administration of liposomal amphotericin B due to possibility of anaphylactic reactions.

(x) Slowing or stopping infusion of teicoplanin to reduce hypersensitivity reactions "red man syndrome"

Cuationary measures that were listed within the monographs were mainly warnings regarding use of a medication with other classes for example use of clarithromycin with statins or use of a medication in certain clinical conditions such as the following examples:

- Use of clarithromycin in patients with hepatic failure.
- Use of gentamicin or clarithromycin in electrolyte abnormalities.
- Use of gentamicin in patients with neuromuscular disorders or hypoglycaemia.
- Use of metronidazole in hepatic impairment.
- Use of piperacillin/tazobactam in patients with low potassium reserves.

Special warnings and contraindication were listed as part of Miscellaneous section of the monographs. Examples of special warnings and contraindications are:

- Discontinuation of treatment if an ADR occurred such as in the case of development of skin rash during treatment of amoxicillin warrants discontinuation of treatment with amoxicillin.
- Ambisome® is not interchangeable with any other lipid-based or conventional amphotericin formulations. The dosing of Ambisome® is different from other formulations.
- Use of flucloxacillin is contraindicated in patients with history of beta-lactam hypersensitivity.
- Use of ceftriaxone is contraindicated in preterm neonates or in neonates with hyperbilirubinaemia, jaundice or other conditions in which bilirubin binding is impaired.
- Concomitant use of ondansetron with apomorphine and/or in patients with congenital long QT syndrome.

3.2.6.3 Lab Interference

Interference with lab results or false elevations of a serum concentration of a medication may occur if collected through a certain type of catheters for example serum levels of gentamicin in a blood sample collected through central venous Silastic catheters may be falsely elevated.

Urinary glucose tests that are carried out with reducing agents (Fehling's, Clinitest, Benedict's tests) and Coomb's test yield false positive results when conducted during

the therapy with the following medications; benzylpenicillin sodium, ceftazidime ,cefotaxime, ceftriaxone, cefuroxime, co-amoxiclav, piperacillin/tazobactam. Urinary glucose tests need to be carried enzymatically when using these medications.

Metronidazole may decrease level of enzymatic assay of hepatic enzymes, serum triglycerides and serum glucose. Rantidine result in a false positive urine protein test therefore testing with sulfosalicylic acid instead is recommended.

3.2.6.4 Sodium Content

Some medications have higher sodium content than others. Sodium content should be considered in sodium restricted patients for example heart failure and/or renal failure. Sodium may form part of the drug such as benzylpenicillin sodium, thus each vial contains 1.68 mmol sodium and hydrocortisone sodium succinate. Sodium could be part of the diluents where diluted medications for example metronidazole are formulated in NS (Sodium content: 13.13 mmol/100 mL for Fresenius Kabi metronidazole and 14 mmol/100 mL for B. Braun metronidazole). Other non-pharmaceutical ingredients that have to be considered are potassium and glucose. A 600 mg vial of co-amoxiclav contains 0.5 mmol potassium and 1.2 g vial of co-amoxiclav contains 1 mmol potassium. A vial of Ambisome® contains 900 mg sucrose which should be taken into consideration when used in a diabetic patient (Table 3.8).

Table 3. 8 Sodium Content of Medications per Strength

Medication	Sodium content (mmol)
Piperacillin/Tazobactam 4.5 g vial	9.40
Piperacillin/Tazobactam 2.25 g vial	4.72
Ceftriaxone 1 g vial	3.60
Co-amoxiclav 1.2 g vial	2.70
32 mg Ondansetron (Accord)	2.50
32 mg Ondansetron (Hamlen)	2.30
Flucloxacillin 1 g vial	2.26
Ceftazidime 1 g vial	2.26
Cefotaxime 1 g vial	2.09
Cefuroxime 750 mg vial	1.80
Co-amoxiclav 600 mg vial	1.40
Amoxicillin 500 mg vial	1.30

3.2.7 Monographs Appendices

Two monographs had appendices attached to them explaining in detail about their use: potassium chloride and gentamicin monographs (Appendix 10). The appendix of potassium chloride contained detailed information regarding the dilution of the potassium chloride concentrate 20% that is available at MDH. Institute for Safe Medication Practices (ISMP), the U.S. Pharmacopeia (USP) and the Joint Commission with other organizations highlighted the risks associated with the use of potassium chloride concentrate in the clinical area based on the medication error reports that lead

to serious ADRs and fatal reported cases resulting from inadvertent administration (Grissinger, 2011). Patient safety recommendations were set to restrict the use of potassium Chloride concentrate to pharmacy only and to use the premixed or diluted potassium Chloride in the wards (JCAHO, 2003; Tubman, 2005). [50]

Potassium chloride concentrate is not premixed in the pharmacy in the local setting and the administrator has to dilute it in the clinical area. The appendix was designed to assist the administrator throughout the process of dilution and dose calculations of the concentrate. The appendix contains steps of a formula on how to dilute the concentrate and how to calculate the dose in mmol, volume of diluent required and rate of infusion. A supplementary material was provided for the calculations with examples on each dose (mmol/kg) and for different weights of the patient. Amount of daily potassium and amount of daily fluid to be calculated were demonstrated for each prescribed dose and for different weights of the patient. Calculations of the: numbers and volume of NS bags needed for infusion, volume of potassium concentrate to be withdrawn and added to each bag and the rates of infusion (intermittent, continuous) were explained for different doses and weights. A warning was included to check that the concentration of potassium Chloride in each 500 mL NS should not exceed the maximum allowed concentration 40 mmol/L and the infusion rate should not be above 0.2 mmol/kg/hour (20 mmol/hour) (Appendix 10).

The appendix of gentamicin monograph contained information regarding serum gentamicin level monitoring and dose intervals adjustments. Gentamicin is an

[50] NHS. National Health Services Potassium Chloride concentrate and other strong Potassium solutions for IV administration policy [Internet] 12 June 2018 [[cited 2019 Mar 28] Available from: https://www.porthosp.nhs.uk/guidelines/Potassium%20Chloride%20Concentrate%

aminoglycoside for which routine monitoring is required to individualise dosage and dosing intervals based on patient's conditions. The peak levels are measured to monitor efficacy and trough levels are measured to monitor dose accumulations to avoid toxicity. The adjustment of the dosage and dosing intervals based on the trough and peak concentrations are explained in the appendix of gentamicin monograph (Appendix 10).

3.3 Results of Quality Assurance Validation

Risk Assessment of the information included within the monograph was conducted where phrases that could be misinterpreted in a way leading to MEs were removed or modified as the following:

1- The doses of co-amoxiclav to be written in full similar to the method it is written for the strength in all sections of the monograph. Doses must be written in detail such as 25 mg/5 mg instead of the combined form 30 mg. This is done to avoid misinterpretation when calculating the dose since the strength is written as 500 mg amoxicillin/100 mg clavulanic acid and 1000 mg amoxicillin/ 200 mg Clavulanic acid. A dose of Co-amoxiclav is expressed in literature and SmPC as 25 mg Amoxicillin/ 5 mg Clavulanic acid per kg. Listing doses of co-amoxiclav as 30 mg/kg might lead to interpretation that the dose of 30 mg refers to amoxicillin dose only and not to both amoxicillin and clavulanic acid. Thus the nurse would administer the volume that contains 30 mg amoxicillin per each kg of bodyweight rather than the volume that contains 25 mg of amoxcillin per each kg of body weight which might lead to administration of higher doses. Writing strength and dose of co-amoxiclav 600 mg as 500 mg/100 mg.

2- Writing strength and dose of piperacillin/tazobactam 2.25g as 2g piperacillin/0.25 g tazobactam and strength and dose of piperacillin/tazobactam 4.5 g as 4 g piperacillin/0.5 g tazobactam.

3- Separating between a number and a unit by a space e.g 1 mg 1 mL to avoid misreading of the values and units.

4- Correcting Ambisome® reconstitution and dilution calculations where the diluent to be added is 37.5 mL and not 38 mL as it was explained in the first draft of the monograph. The phrase listed in the first draft in Reconstitution and Dilutions sections was "*Reconstitute each 50 mg vial with 12 mL sterile WFI*; *resultant concentration is 4 mg/mL. Instil the 12 mL reconstituted solution into a syringe containing 38 mL of D5W or D10W. Final concentration of solution is 1 mg/mL*". Listing the volume of WFI to dilute Ambisome® as 12 mL and diluent 38 mL does not take into consideration the displacement value thus the final concentration of solution would be lower than 1 mg/mL.

5- Add the term "unlicensed" for each unlicensed indication /dose listed within a monograph.

6- If an indication/dose is licensed only in one SmPC then the name of the generic/brand should be listed next to it to indicate that this indication or dose is only applicable to the respective brand.

7- Liposomal amphotericin B monograph should be specified it is only for Ambisome® and can't be used for any other liposomal amphotericin brand/generic so Ambisome® word was added next to the "name of medication" box and not in the strength/medication/manufacturer.

8- The sources for unlicensed doses and unlicensed indications were checked and verified if they are accredited sources. A min number of three sources was requested to accept an unlicensed dose/indications.

9- Removal of the paracetamol monograph from the IV manual (Appendix 9). The risk of approving a monograph that would allow using paracetamol in its available pack size (100 mL) at MDH in paediatrics and neonates was assessed. The 100 mL pack size of paracetamol solution for injection is unlicensed to be used in neonates and children weighing less than 33 kg.[51, 52] Using a 100 mL vial in paediatrics has a high risk of inadvertent administration of the whole vial which leads to serious ADRs and fatalities and safety circulars and risk minimisation measures (RMMs) warning against use of 100 mL pack size and recommended use of 50 mL or even 10 mL pack sizes. [53, 54]

The monograph was not approved for release, despite the warning and explanation included in the monograph and the indication that it is not licensed for children weighing less than 33 kg and that 50 mL pack size should be used instead (Appendix 9). A request to obtain the 50 mL pack size was sent to Directorate of Pharmaceutical Affairs (DPA) and Central Procurement Supplies Unit (CPSU).

[51] HPRA. Health Products Regulatory Authority. Fresenius Kabi Paracetamol 10 mg/ml solution for infusion- Summary of Product Characteristics (SmPC)-HPRA [Internet] 2018 [cited 2019 Mar 29]. Available from: https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results

[52] HPRA. Health Products Regulatory Authority. Paracetamol Actavis 10 mg/ml solution for infusion- Summary of Product Characteristics (SmPC)-HPRA [Internet] 2018 [cited 2019 Mar 29]. Available from: https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results

[53] NHS. National Health Services. In-use product safety assessment report for IV Paracetamol in neonates, infants and children [Internet]. NHS. 2018 [cited 2019 Mar 28]. Available from: https://www.sps.nhs.uk/wp-content/uploads/2018/07/Paracetamol-IV-risk-asessment_Final.pdf

[54] MHRA. Medicines and Healthcare Products Regulatory Agency. Drug Safety Update. Intravenous paracetamol (Perfalgan ▼): risk of accidental overdose [Internet]. MHRA. 2010 [cited 2019 Mar 28] Available from : https://www.gov.uk/drug-safety-update/intravenousparacetamol-perfalgan-risk-of-accidental-overdose

3.4 Results of Validation of Assessment of Administration Practice Questionnaire (AAP-Q)

The questionnaire was developed to assess knowledge, self-certainty and confidence regarding IV medication knowledge and administration practice, perception of factors that contribute to medication errors and obstacles encountered when administering IV medications in paediatric patients.

3.4.1 AAP-Q Validation Delphi Round I

Eleven individuals from different areas of expertise were invited to participate in questionnaire validation and all of them accepted. The group consisted of five males and six females and among them were five pharmacists, five paediatric nurses and one paediatrician. The panellists provided positive comments and feedback on the questionnaire and stated that it fulfils the aim of the research. Changes suggested by the panel were modifications of the original questionnaire; rewording, adding or removing questions and restructuring questions which were done after gathering feedback from both rounds.

3.4.1.1 Amendments to Part A: Demographics and Background Data

The selected age brackets reflecting the participants' age were amended from the original questionnaire following Delphi round I. The age ranges were changed to five years range to be consistent with each other. The second question about gender was opted to be irrelevant by most of the panellists (n=8) therefore it was removed. The options of the third question regarding "Education level" were increased to include "others" since nurses might have attended different courses than the "Diploma", "Bachelor of Sciences" or "Master's Degree".

The position question was amended to include “Paediatric Practice Nurse” position as another position since some nurses working in paediatric wards and participating in this study were joining this unit. The question regarding “Years of experience” was changed from >5-10 years to 6-10 years to be more consistent with age brackets in question 1. It was argued as well that years of experience above 20 years old should be divided into more ranges since some nurses spend 40 years working and even more thus there should be more ranges added (20-30), (30-40) and above 40.

The question regarding training was reworded and divided into 2 sections (a and b). The question changed from *“Q7 Have you ever received training about IV drug administration in paediatric patients in the last five years?”* to “Q7a *Have you ever attended training about IV drug administration in the last five years*?” This change was agreed on by seven panellists since the word “*training received*” in the original question could be misinterpreted as referring solely to training delivered at work or the undergraduate obligatory training given to students whereas there are some training courses that a nurse could follow for example online courses or training in other institutes/countries. The question “ Q7b Was it paediatric specific?” was added as a separate section to allow participants first to list all forms of general or specialised trainings they attended in section a and then to specify which of these trainings were paediatric oriented.

3.4.1.2 Amendments to Part B: Self-Evaluation

The question assessing self-evaluation of knowledge level of IV medication was modified to include proficiency level as well since both knowledge and proficiency forms the aspects of administration practice.

A five point Likert scale was introduced to question "need for further training" instead of the option "Yes/No" to allow participants to give a wider range for their answers by rating the need for training rather than answering a close-ended question. A parameter of the question type of training was modified from "Knowledge of IV medication" to "Pharmacology education" since it was agreed by seven panellists (n=7) that pharmacology is a more general term and deals with knowledge of all aspects of a medication. Furthermore in literature continuous pharmacology education was one of the identified essential interventions for nurses in administration practice.

3.4.1.3 Amendments to Part C: Assessment of Administration Practice

The answer "Hospital Administration Protocol" listed in the two questions regarding sources used/preferred to have in the wards was recommended to be removed. This was suggested so the drug monographs would not be considered a different resource from a hospital protocol. The medications which have an established hospital administration protocol would not have drug monographs developed for therefore these two resources should not be listed as separate answers in the same question. The listed options of the answer "online medical resources" were agreed on by most of panellists (n=8) to be removed since nurses do not have access to the mentioned resources within the answer. The panellists recommended to leave the question empty and ask the respondent to specify the online resource they use by listing it next to the question.

The following parameters were removed from the question regarding scenarios encountered in administration practice: (i) *A prescribed dose of Ceftriaxone for a child weighing 15 Kg is 20mg/Kg and the volume ordered to be administered is 5 mL. Given that 1g vial of ceftriaxone is reconstituted with 10 mL diluent.* (ii) *15 mg/Kg is the dose*

of Paracetamol in a child weighing (10-50 Kg) and volume of administration ordered is 4mL/Kg. All the panellists agreed that listing a prescribed dose in terms of volume per weight can be misleading for the nurses in particular the recent graduates. An emphasis is made on not to accept any prescription with the dose expressed in volume since this would lead to incorrect dosing. The volume could be interpreted as concentrate or the reconstituted powder or even the diluted which would contribute to under or over dosing and serious adverse events.

3.4.1.4 Amendments to Part D: Safe Medication Administration

The statements "new staff" and "recent graduates" of question regarding contributing factor were amended to include the word "being". The phrases on their own could have been misinterpreted as a new staff or a recent graduate is a contributing factor to medication errors

The parameter "*Unfamiliarity with the side effects*" was removed as the other parameter "*Unfamiliarity with medication*" was considered sufficient instead since unfamiliarity with a medication addresses unfamiliarity with the indication, side effects and other characteristics of a medication. Other parameters that were removed was "*new patient*" as the phrase "*Unfamiliarity with the patient condition*" was considered sufficient.

Two parameters were removed from scenarios affecting safe practice question such as "*Have to accept oral order*" and "*Unclear dose calculation*". It was agreed that the calculation part was addressed in the previous question regarding contributing factors in the parameter "*complicated calculation*".

3.4.1.5 Amendments to Part E: Feedback about monographs

The parameter "*Inconsistent opinion between nurses*" and "*Inconsistent opinion between a nurse and a doctor*" in the scenarios question were joined to one parameter "*Inconsistent opinion between healthcare professionals"* since the scope of this parameter is regarding inconsistency in opinions among healthcare professionals despite their position.

3.4.1.6 Relevance of Questions after Delphi Round I

Participants were asked to rate their opinion on their relevance of questions on a five point Likert scale ranging from 1 "Not relevant" to 5 "Highly relevant" (Figure 3.2).

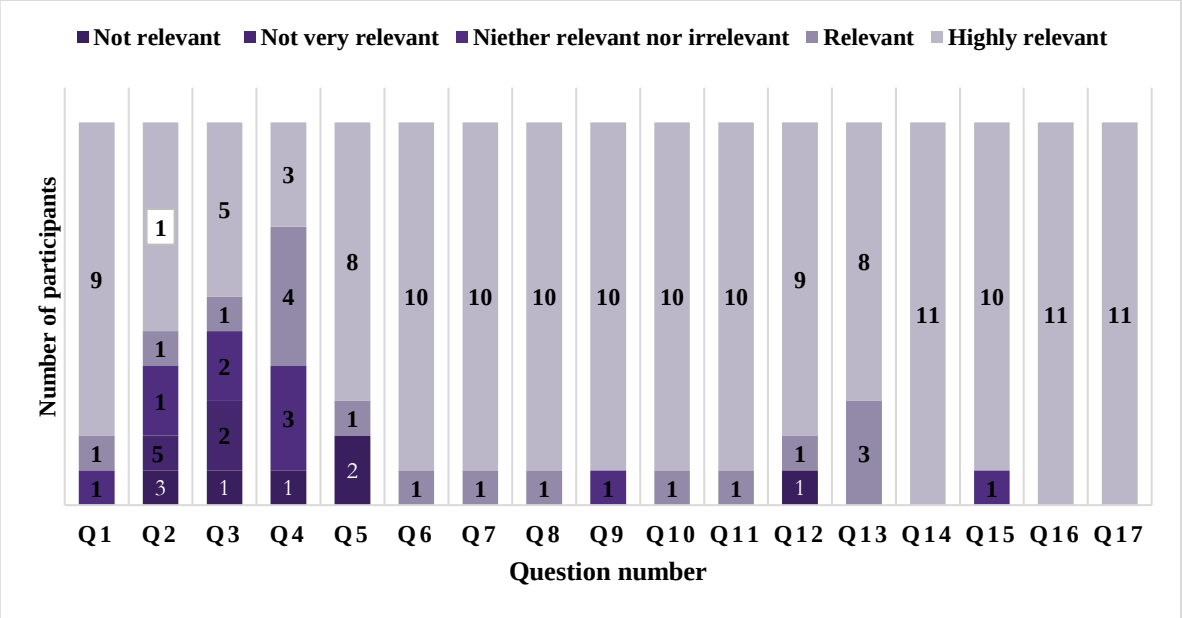

Figure 3. 2 Participants Response on Question Relevance of AAP-Q Delphi Round I (N=11)

3.4.2 AAP-Q Validation Delphi Round II

Ten individuals from Round I, five males and five females, participated in Round II. The group was composed of four nurses, five pharmacists and one paediatrician. Nine

questions were rated as “Relevant” or “Highly relevant” by all panellists (n=11) while the remaining questions were rated by more than 6 panellists as “Relevant” or “Highly relevant”.

3.4.2.1 Amendments to Part A: Demographics and Background Data

The suggested change for the range related to the question about the years of experience ranges was accepted following Delphi round II as the majority of panellists (n=7) argued that experience would not be affected by the increase in years after 20 years.

3.4.2.2 Amendments to Part B: Self-Evaluation

The question regarding training was amended to involve the term “Preparation and Administration” instead of administration only. This was highlighted by nearly all panellists (n=9) to refer to administration practice in general and not only to the process of giving the medication via IV route. The administration practice involves checking the prescription, preparing and giving the medication and monitoring the effects of medication (Butcher et al, 2013). One statement was added to the “Type of training” question which was “Calculating rate of infusion” since it was argued that calculating rate of infusion is as essential as dose calculations where both statements are mathematical skills required for administration practice.

3.4.2.3 Amendments to Part C: Assessment of Administration Practice

The answers of the two questions assessing the sources of information used and preferred to use were modified to be more detailed. The panellists (n=6) agreed on the suggestion emerging from round I that the option of health care professional should be more specified where a participant can choose from a list (doctor, pharmacist , nurse).

Similarly it was agreed that the answer of BNF-C should more specified as online BNF-C and Hardcopy BNF-C since the available editions of both versions differ.

The parameter "*The dose for Ondansetron calculated based on body surface area (BSA) instead of weight"* was removed from the question of scenarios encountered in administration practice. The panellists highlighted that this phrase is unclear since Ondansetron dose can be calculated based on BSA or based on weight according to the indication and the age of the patient.

3.4.2.4 Amendments to Part D: Safe Medication Administration

The parameter "*complicated prescription*" was removed in question regarding factors contributing to MEs since there were other parameters addressing different aspects of a complicated prescription; "*prescription full of abbreviation*" and "*unclear expressions in a prescription*".

"Complicated administration" was modified to "*complicated method of administration*" to specify that the parameter is related to the method of administration and not to the administration practice. Parameter "*Unclear labelling*" was modified to "*Unclear labelling of medication*".

3.4.2.5 Amendments to Part E: Feedback about monographs

No further amendments were made to this section in round II. All items in this question received unanimous consent.

3.4.2.6 Relevance of Questions after Delphi round II

Figure 3.3 shows that 11 questions out of 17 were rated being "Relevant" or "Highly relevant" by all of the panellists (n=10). The other questions were rated by 5 or more panellists as being "Highly relevant". Questions 1-6 were related to demographics data, questions 7-10 concerned self-evaluation, questions 11-14 assessed administration practice, questions 15-16 were regarding safety of administration practice.

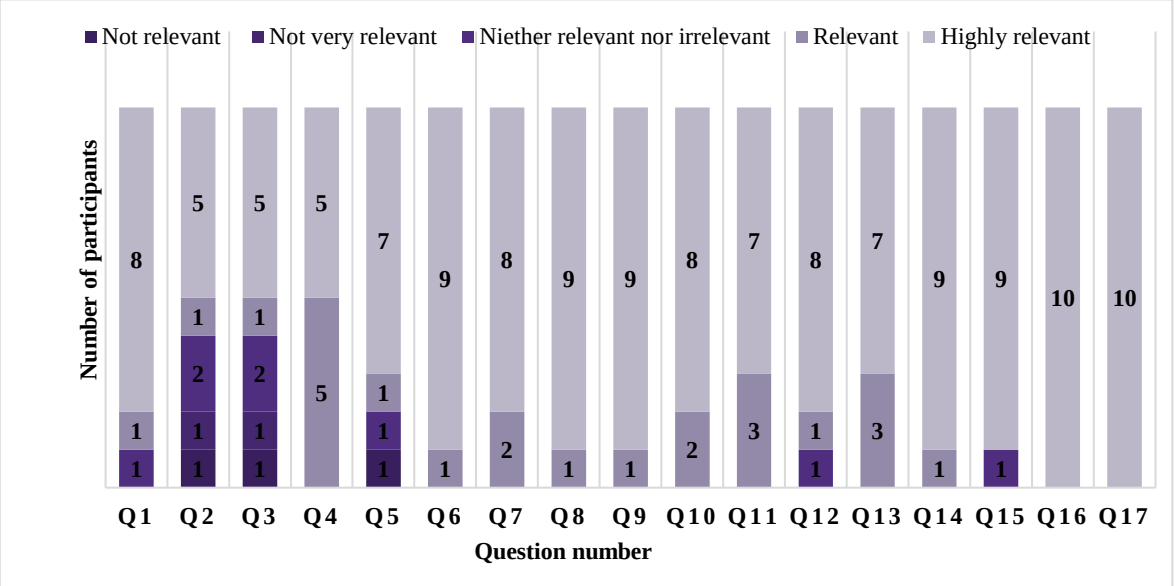

Figure 3. 3 Participants Response on Question Relevance of AAP-Q Delphi Round II (N=10)

3.4.3 Face Validity Results

The questions were rated on four point Likert scale their three aspects; clarity, ability to answer, structure and layout. Seven nurses practicing in the paediatric wards were approached by the researcher for the face validity and filled in the tool.

All of the questions scored 4 and the calculated average for each question for the three aspects was 4 (Appendix 11). Since the total average responses for each question was

higher than 3.50 (cut-off point) all of the questions were considered face valid and maintained in the questionnaire. Twelve questions out of 17 questions had an average of 4 and the rest had an average higher than 3.50.

3.5 Analysis of Assessment of Administration Practice Questionnaire

This section explains the descriptive statistics by the analysis of responses following dissemination of the questionnaire. Fifty-five nurses out of sixty-two working in the paediatric wards at MDH participated in the pre-test and fifty-three nurses participated in the post-test.

3.5.1 Demographics and Background Training and Experience

Twenty of the nurses hold a diploma in nursing, 22 graduated with a bachelor of sciences, 8 had master degree and only one selected "other" type of education who attended a "*general course in nursing*". The majority of the participating nurses (n= 39) were staff nurses, 10 nurses were senior staff while 4 of them held a position of deputy charge nurse and only 2 reported to specialise as paediatric practice nurses (figure 3.4).

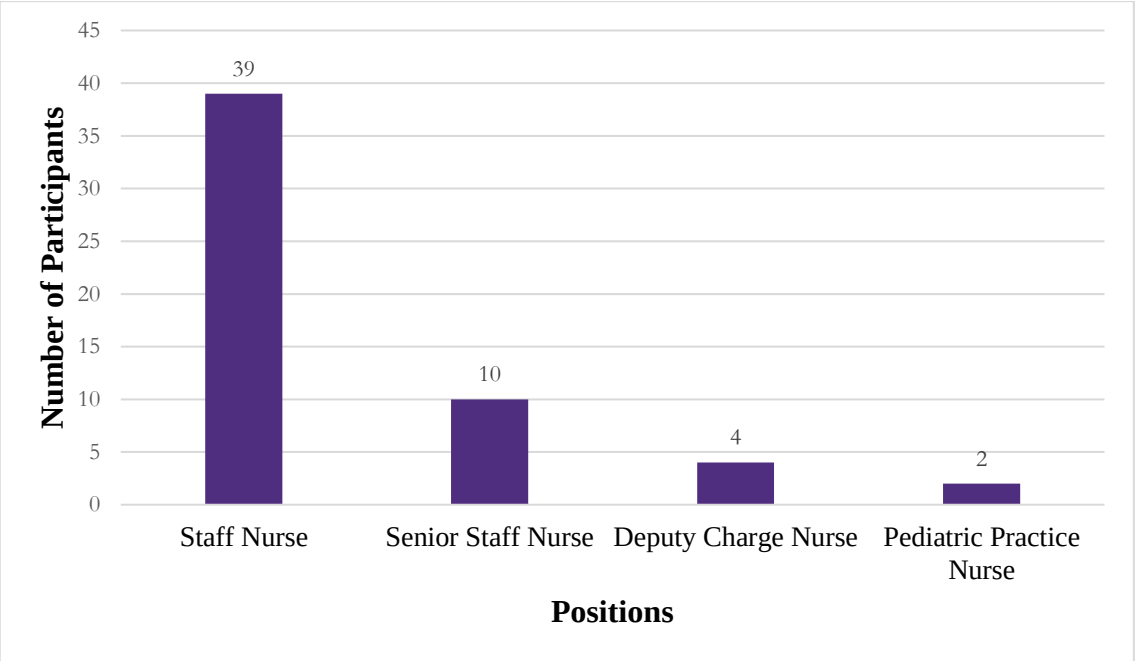

Figure 3. 4 Positions of the Participants (N=55)

Nearly half of the nurses (n =22) had a working experience of over 20 years as a nurse followed by six nurses with experience of 16 to 20 years, followed by 12 nurses with experience of 11 to 15 years, 5 nurses had an experience of 6 to 10 years, 8 nurses reported their experience years in the range of 2 to 5 years and only 2 nurses had an experience of less than 2 years (Figure 3.5).

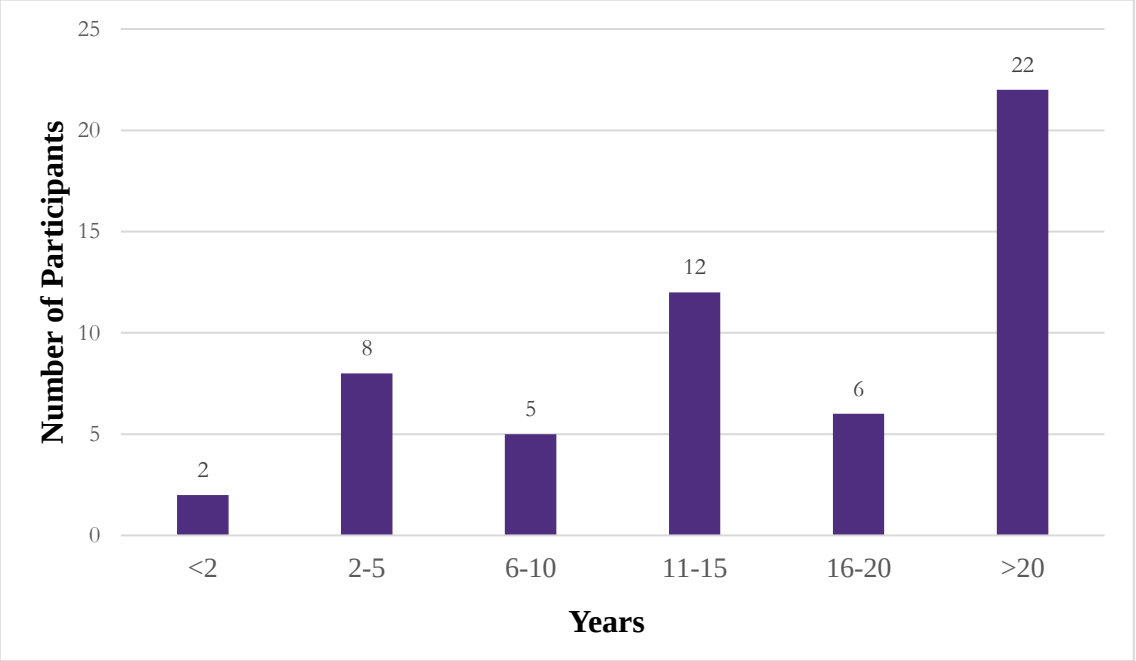

Figure 3. 5 Years of Experience in Nursing Profession (N= 55)

The three paediatric wards Rainbow, Wonderland and Disneyland had 11 practicing nurses each. Ten nurses reported to work at Fairyland ward while 8 nurses were working at Paediatric (A&E) and 4 reported to work at Paediatric Day Care (Figure 3.6).

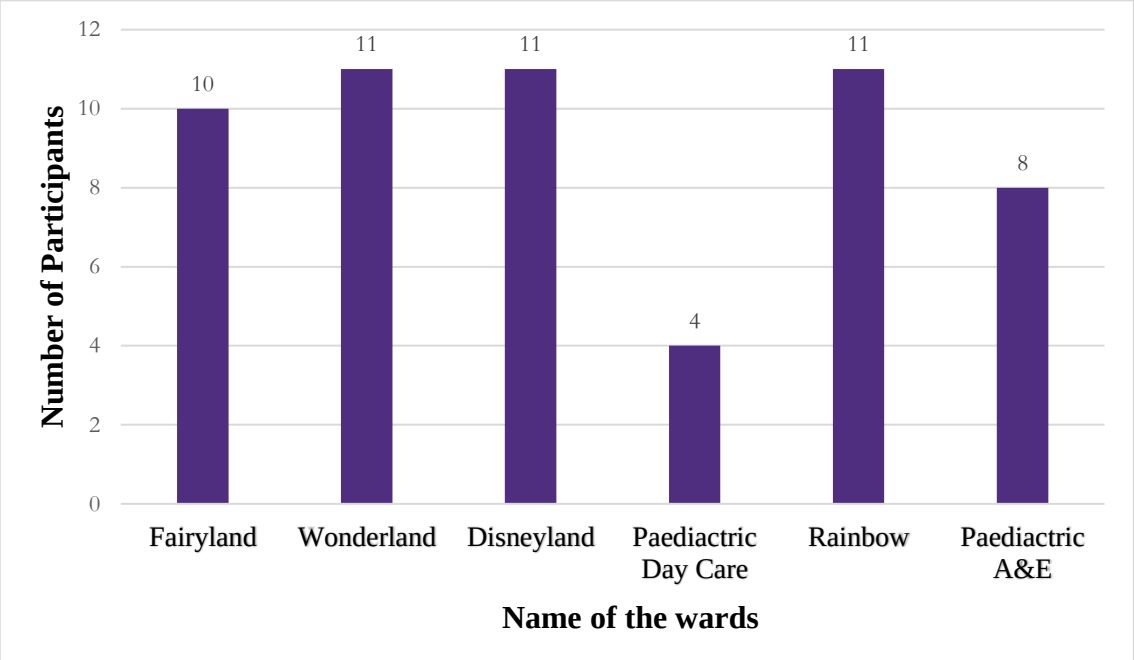

Figure 3. 6 Wards in which Participants Practiced (N=55)

Thirty-five nurses reported to have attended a training about IV medication preparation and administration during the years 2013-2017. Nurses were asked to identify the type of training they followed (Table 3.9). Ten out of the 35 nurses attended more than one training during the years 2013-2017.

Table 3. 9 Background Training (N= 55)

Type of training / Year	2017	2016	2015	2014	2013	Total
Undergraduate training	1	3	0	1	2	7
Postgraduate training	2	0	0	1	1	4
Continuing professional development	4	3	7	2	5	21
From work	7	0	2	2	2	13
Total	14	6	9	6	10	

3.5.2 Self Evaluation of Administration Practice

Nurses were asked to classify their proficiency and knowledge and identify their training requirements in preparation and administration of IV medications of IV medications.

The majority of the nurses (n= 33) rated their level of knowledge of preparation and administration of IV medication as “Good”, followed by 13 nurses who rated their knowledge as “average”. Seven nurses assessed their level of knowledge as “Excellent” while only two nurses reported their knowledge as “fair”. No one assessed their knowledge and proficiency level as “poor” (Figure 3.7).

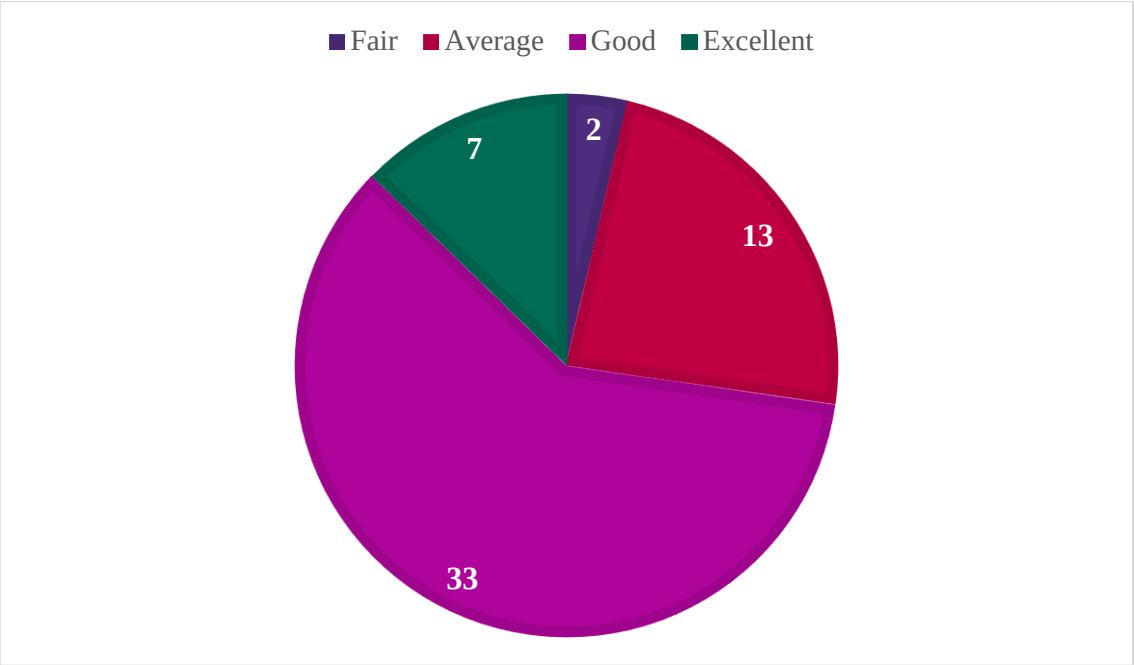

Figure 3. 7 Level Of Knowledge and Proficiency of IV Medications (N=55)

Thirty nurses considered that they often need updating their knowledge in IV medication preparation and administration while 10 nurses reported that they always need to update their knowledge. Three nurses reported that they sometimes consider the need to update their knowledge while 5 nurses reported rarely. Seven nurses acknowledged that they never considered the need to update their knowledge (Figure 3.8).

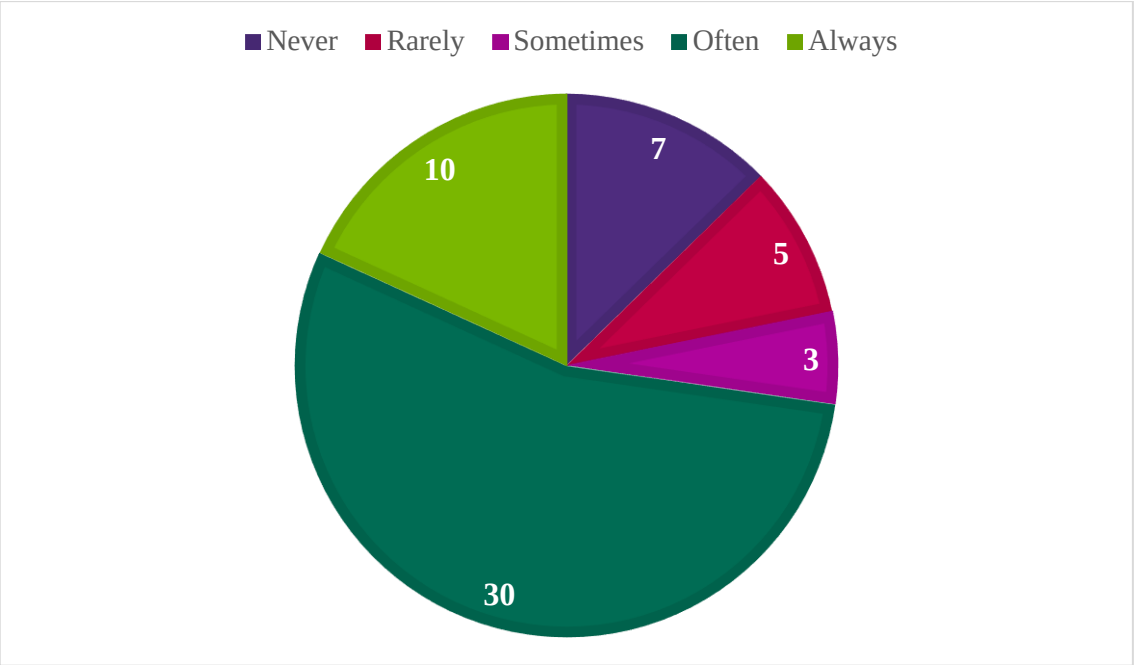

Figure 3. 8 Need for Updating Knowledge (N=55)

Nurses were asked to identify the type of training related to IV medication preparation and administration they would like to have (Figure 3.9). The majority of nurses (n=36) selected pharmacology training regarding IV medications which is related to knowledge about the therapeutic indication, properties of IV medication, drug class and side effects. Thirty-four nurses selected mixing of IV preparations which is related to compatibility and stability of the medications when mixed in an infusion bag/syringe or co-infused together. Twenty-one nurses chose a training in IV preparations which regards reconstitution and dilution practice of IV medications including choice of reconstituting fluid or diluent. Thirteen nurses picked the option of training in IV administration techniques and only 9 selected a training in dose calculations and mathematical skills.

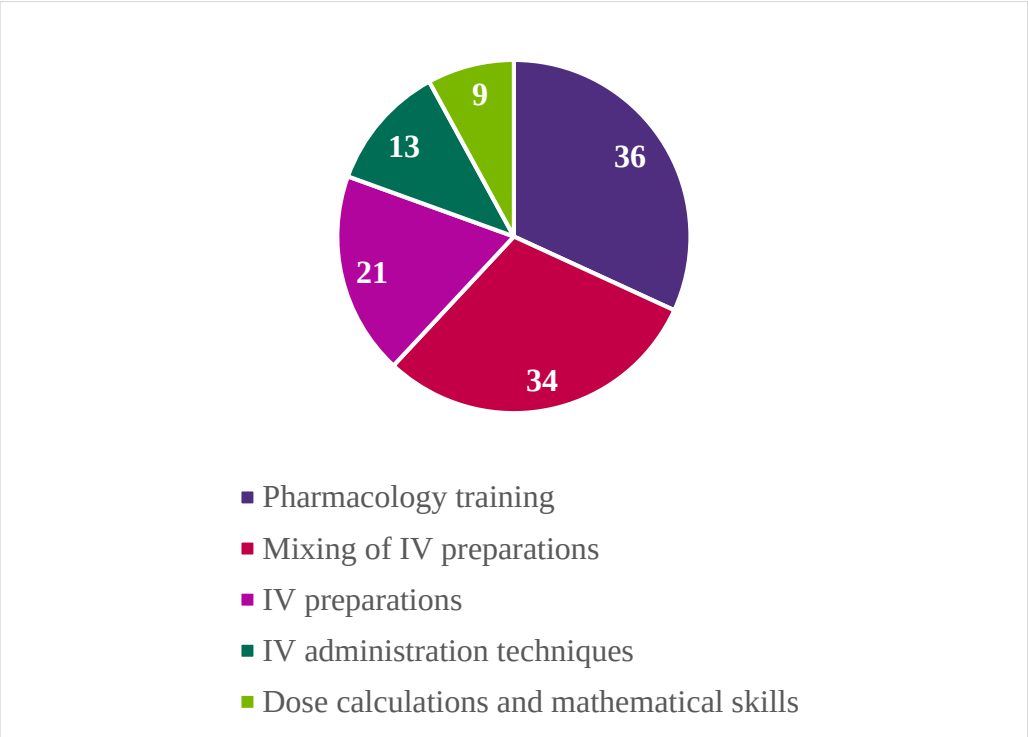

Figure 3. 9 Type of Training Required by Nurses at Paediatric Wards (N=55)

3.5.3 Assessment of Administration Practice

Nurses were asked to identify the sources of information they refer to when preparing and administering an IV medication prior to and after introducing drug monographs in the wards (Table 3.10). Fifty-four nurses answered the question in the pre-test and 52 nurses answered in the post-test. Forty-two nurses referred to the package insert/label when administering an IV medication in the pre-test compared to 20 nurses who referred to the package insert/label in the post-test. The number of nurses who referred to a healthcare practitioner (doctor, pharmacist, nurse), BNF-C (online, hardcopy) and online medical resources in the pre-test and post-test was almost similar when excluding the two nurses who did not participate in the post-test. The number of nurses who reported to use the drug monographs post introducing them in the wards was 35 out of 52 nurses who answered the question.

Table 3. 10 Sources of Information Referred To When Using IV Medications (Pre-Test and Post-Test)

Source of information used in the wards	Pre-test (N= 54)		Post-test (N= 52)	
	Frequency	Percentage	Frequency	Percentage
Package inserts/label	42	66.7%	20	37%
A health practitioner (Nurse, Pharmacist, Doctor)	36	77.8%	34	65.3%
BNF children (Online, Hardcopy)	24	44.4%	22	42.3%
Online medical resources	9	16.7%	7	13.4%
Summary of product characteristics	4	7.4%	3	5.8%
Drug monographs	N/A	N/A	35	67.3%

Nurses were asked in the pre-test and post-test to determine the sources of information they prefer to have in the wards to guide their use of IV medications (Table 3.11). The number of nurses who selected "*Medication administration charts*" in the pre-test (n=30) was similar to their number in the post-test (n=28). Medication administration charts are large charts that specify volumes of reconstituting fluids and diluent, solution concentrations, rate and method of administration of a medication. Twenty one nurses preferred to have medical references/resources (e.g. BNF-C, PID, IDG, HID, Neofax monographs, UCL) as hardcopy version compared to only 6 nurses who preferred having these references as online version. Drug monographs were favoured by only 10

nurses in the pre-testing phase while in the post-testing stage the number increased to 41 nurses.

Table 3. 11 Sources of Information Preferred to Have at Wards' Level When Using IV Medications (Pre and Post-Test)

Source of information preferred to have in the wards	**Pre-test (N= 49)**		**Post-test (N= 52)**	
	Frequency	Percentage	Frequency	Percentage
Medication administration charts	30	61.2%	28	53.8%
Hardcopy medical resources (BNF, IDG, PID etc)	21	42.9%	14	26.9%
Online medical resources (BNF, IDG, PID etc)	6	12.2%	14	26.9%
Drug monographs of the IV manual	10	20.4%	41	78.8%

Nurses were requested to report the type/s of difficulty they encountered prior to and after placing drug monographs in the wards (Table 3.12). The most frequent type of difficulty encountered by nurses (n= 27) was "*Reconstitution and dilution practice*". This type of difficulty is related to steps entailed in the preparation of a medication for IV administration, specifying the volume of fluid/diluent to be added to the medication and determining the final concentrations for administration.

Twenty nurses in the pre-test stated that they encounter difficulty with choosing compatible fluids and determining incompatibilities compared to 7 nurses in the post-test. The number of nurses selecting "*Dealing with adverse reactions*" difficulty did not vary significantly from pre-testing (n=22) to post-testing (n=18). Knowledge of IV

medications difficulty decreased significantly from pre-testing (n=18) to post-testing (n= 7). Dose calculations was the least chosen difficulty by nurses both in the pre-test (n=12) and post-test (n=6) phases.

Table 3. 12 Difficulties Encountered in Administration Practice (Pre and Post)

Encountered difficulty	**Pre-test (N= 52)**		**Post-test (N=46)**	
	Frequency	Percentage	Frequency	Percentage
Reconstitution and dilution practice	27	52%	7	15%
Choice of compatible fluids	20	38%	7	15%
Dealing with adverse reactions	22	42%	18	39%
Infusion rate calculations	21	40%	14	30%
Knowledge of IV medications	18	35%	7	15%
IV administration techniques	13	25%	11	24%
Dose calculations	12	23%	6	13%

Scenarios from administration practice were provided about the medications which had monographs developed for. These scenarios were based on factors leading to medication errors and nurses were asked to determine their action for each scenario whether to proceed with the prescription/order/scenario or refer to a healthcare professional or check a reference or the drug monographs (Table 3.13).

Nurses (n=23) acknowledged that they would consult a doctor when receiving a prescription with an abbreviated term "*strength of dose is expressed as U*" compared to 5 nurses consulting a doctor and 23 nurses checking the drug monographs in post-test. Twenty nurses in the pre-test identified that they would proceed with an order of diluting Ambisome® in 0.9% NS for administration as IV infusion compared to only 6

nurses in the post-test while 26 nurses acknowledged that they would consult the drug monographs in the post-test.

Thirty-eight nurses in the pre-test stated that they would consult a pharmacist when they are requested to co-infuse ceftriaxone with calcium containing infusion fluids compared to 14 nurses in the post-test and 27 nurses stated that they would check the drug monographs in this scenario. Thirty-seven nurses in the pre-test stated that they would consult a pharmacist if a cloudy solution developed following reconstitution of aciclovir powder for injection compare to 35 nurses who would consult the drug monographs in the post-test. Sixteen nurses in the pre-test stated that they would proceed with the orders of "*Infusing potassium chloride at rate 0.5 mmol/kg/hour*" and "*administering gentamicin injection without serum level monitoring*" compared to one nurse in the post-test. Nurses (n=23) claimed that they would consult the respective drug monographs in these scenarios.

Ten nurses stated that they would proceed with the order of "*abrupt discontinuation of Hydrocortisone treatment without gradual tapering*" or refer to a doctor (n=26) in the pre-test compared to one nurse who would proceed with the same order and 11 nurses who would refer to a doctor in the post-test. Nurses (n=33) would consult a pharmacist when they are ordered to dilute co-amoxiclav injection in D5W but they would refer to a drug monograph (n=31) in the post-test. Thirteen nurses admitted that they would proceed with the co-administration order of teicoplanin with other antibiotics without checking in the pre-test but they would check the provided drug monographs (n=24) in the post-test. Eighteen nurses in the pre-test claimed they would proceed or refer to a pharmacist (n=26) with the order of mixing penicillins or cephalosporins with

aminoglycosides in the same infusion bag/set compared to 3 nurses who would proceed with this order and 10 nurses who would refer to a pharmacist in the post-test. Twenty-six nurses reported to consult the drug monographs in the post-test. The maximum number of nurses who stated that they would refer to online medical resources in the pre-test and post-test stages was 6 nurses.

Table 3. 13 Scenarios Encountered In Administration Practice

No	Statement	Participants	Proceed without consultation	Consult a Colleague	Consult a Doctor	Consult a Pharmacist	Check Online resource	Check Drug monograph
1	Receiving a prescription where the strength of doses is expressed as *U*.	**Pre (n=55)**	16	8	23	7	1	N/A
		Post(n=53)	11	4	5	4	0	23
2	An order to dilute Ambisome® in 0.9% normal saline for administration as IV infusion.	**Pre (n=55)**	20	8	9	15	3	N/A
		Post(n=53)	6	3	3	9	6	26
3	An order to co- infuse Ceftriaxone with calcium containing infusion fluids (e.g nutrition fluids).	**Pre (n=55)**	5	2	10	38	0	N/A
		Post(n=53)	0	3	9	14	0	27
4	Development of a cloudy solution after reconstitution of Aciclovir injection.	**Pre (n=55)**	8	0	9	37	0	N/A
		Post(n=53)	2	0	5	13	0	35
5	A paediatric patient who is receiving IV Gentamicin and no order for serum level monitoring was initiated.	**Pre (n=55)**	16	0	34	2	1	N/A
		Post(n=53)	1	3	27	2	0	23
6	An order for Potassium chloride 20% w/v to be infused at a rate 0.5 mmol/kg/hour peripherally.	**Pre (n=55)**	16	6	19	14	1	N/A
		Post(n=53)	2	3	14	6	5	23
7	An order to administer Co-amoxiclav as IM injection.	**Pre (n=55)**	12	2	21	19	1	N/A
		Post(n=53)	0	2	13	10	3	25

Table 3. 13 (*cont'd)* Scenarios Encountered in Administration Practice

No	Statement	Participants	Proceed without consultation	Consult a colleague	Consult a Doctor	Consult a Pharmacist	Check Online resource	Check Drug monograph
8	An order for abrupt discontinuation of Hydrocortisone Sodium Succinate after long term therapy.	**Pre (n=55)**	10	4	26	12	3	N/A
		Post(n=53)	1	2	11	9	6	24
9	An order to administer Co-amoxiclav as IV infusion diluted in 5% dextrose in water.	**Pre (n=55)**	10	1	10	33	1	N/A
		Post(n=53)	2	0	8	12	0	31
10	An order to administer Teicoplanin simultaneously with other antibiotics.	**Pre (n=55)**	13	5	11	24	2	N/A
		Post(n=53)	3	2	7	14	3	24
11	An Administration order of reconstituted Clarithromycin undiluted.	**Pre (n=55)**	15	7	10	22	3	N/A
		Post(n=53)	10	4	7	15	6	28
12	Development of a pink colour solution when reconstituting Co-amoxiclav and Amoxicillin.	**Pre (n=55)**	4	6	10	21	2	N/A
		Post(n=53)	1	4	2	14	6	26
13	An order to add a Cephalosporin or Penicillin antibiotic to an infusion set/bag containing Aminoglycoside.	**Pre (n=55)**	18	3	5	26	3	N/A
		Post(n=53)	3	5	3	10	6	26
14	Development of particles in a reconstituted solution of Flucloxacillin and a reconstituted solution of Clarithromycin.	**Pre (n=55)**	12	8	5	27	3	N/A
		Post(n=53)	1	4	3	13	5	27

Nurses were asked to rate their level of confidence regarding the use of IV medications prior to and after using the drug monographs for the selected medications (Table 3.14). There was a statistically significant difference ($p<0.005$) in the level of confidence in the administration of 8 medications: piperacillin/tazobactam ($p<0.001$), Ambisome® ($p<0.001$), benzylpenicillin ($p< 0.001$), cefotaxime ($p< 0.001$), ceftazidime ($p< 0.001$), clarithromycin ($p< 0.001$), ceftriaxone ($p< 0.002$) and gentamicin ($p= 0.015$).

Table 3. 14 Confidence Level of the Administered Medications Pre-Test and Post-Test

Medication	**Pre-test (N= 54)**		**Post-test (N= 53)**		**P-value**
	Frequency	**Mean**	**Frequency**	**Mean**	**<0.05**
Aciclovir	54	3.35	53	4.02	**0.007**
Ambisome®	54	2.7	52	4.35	**<0.001**
Amoxicillin	54	4.33	50	4.5	0.186
Benzylpenicillin	51	3.61	52	4.42	**<0.001**
Cefotaxime	54	4.24	53	4.79	**<0.001**
Ceftazidime	52	4.73	54	4.17	**<0.001**
Ceftriaxone	53	4.34	53	4.77	**0.002**
Cefuroxime	53	4.19	53	4.45	0.102
Clarithromycin	54	3.52	53	4.42	**<0.001**
Co-amoxiclav	54	4.63	52	4.71	0.355
Flucloxacillin	54	4.26	52	4.63	**0.028**
Gentamicin	53	4.32	52	4.58	**0.015**
Hydrocortisone	54	4.65	52	4.79	0.193
Metronidazole	54	4.28	52	4.4	0.173
Ondansetron	54	4.57	52	4.85	0.115
Paracetamol	54	4.89	53	4.57	N/A
Piperacillin/Tazobactam	53	3.91	52	4.73	**<0.001**
Potassium Chloride	53	4.09	52	4.25	0.770
Ranitidine	53	4.72	52	4.25	0.005
Teicoplanin	54	4.24	52	4.15	0.772

3.5.4 Safe Medication Administration

This section investigated factors contributing to medication errors, scenarios that affect safety of medication administration and the impact of drug monographs on these factors and scenarios.

Nurses (n=55) were asked to rate the contribution of selected factors to MAEs prior to and after having drug monographs in the wards (Table 3.15). Drug monographs had a statistically significant impact ($p<0.001$) on the factors: insufficient training, unclear package insert/label of the medication, no warnings included in the instructions, being a recent graduate and complicated calculations. Other factors that were significantly affected were similar drug packages ($p= 0.003$) and being a new staff ($p= 0.11$).

Factors that were considered to contribute strongly to medication errors in the wards (Figure 3.10) were illegible writing with the highest mean rating score (MRS=4.53) compared to other factors, followed by insufficient training (MRS=4.49), unclear labelling of medications (MRS=4.33) and unclear expressions in a prescription (MRS=4.29). Similar drug packages and no warning included in the instructions were considered to have equal contribution to medication errors (MRS=4.13). Complicated calculations and similar drug name were considered to have nearly the same degree of contribution (MRS= 3.95) and (MRS=3.93) respectively. The least contributing factor was personal neglect (MRS=3.49) followed by unfamiliarity with the patient's condition (MRS= 3.51).

Table 3.15 Contributing Factors to Medication Administration Errors (Pre and Post)

Factors	Pre-test (N=55)		Post-test (N=52)		P-value < 0.05
	Frequency	Mean	Frequency	Mean	
Personal neglect	55	3.49	52	2.9	**0.011**
Being a new staff	55	3.67	52	1.75	**0.011**
Being a recent Graduate	55	3.8	53	1.94	**0.001**
Heavy workload	55	3.84	53	3.83	0.992
Unfamiliarity with patient's condition	55	3.51	52	3.6	0.491
Unfamiliarity with the medication	55	3.71	53	1.83	**0.001**
Similar drug names	55	3.93	52	2.13	**0.001**
Similar drug packages	55	4.13	53	3.53	**0.003**
Unclear label/package insert of the medication	55	4.33	53	1.87	**0.001**
Illegible writing	55	4.53	53	4.34	0.185
Unclear expressions in a prescription	55	4.29	52	4.38	0.646
Complicated calculations	55	3.95	53	2.47	**0.001**
Complicated method of administration	55	3.62	53	3.79	0.185
No warning included in the instructions	55	4.13	54	1.83	**0.001**
Insufficient training	55	4.49	54	2.17	**0.001**

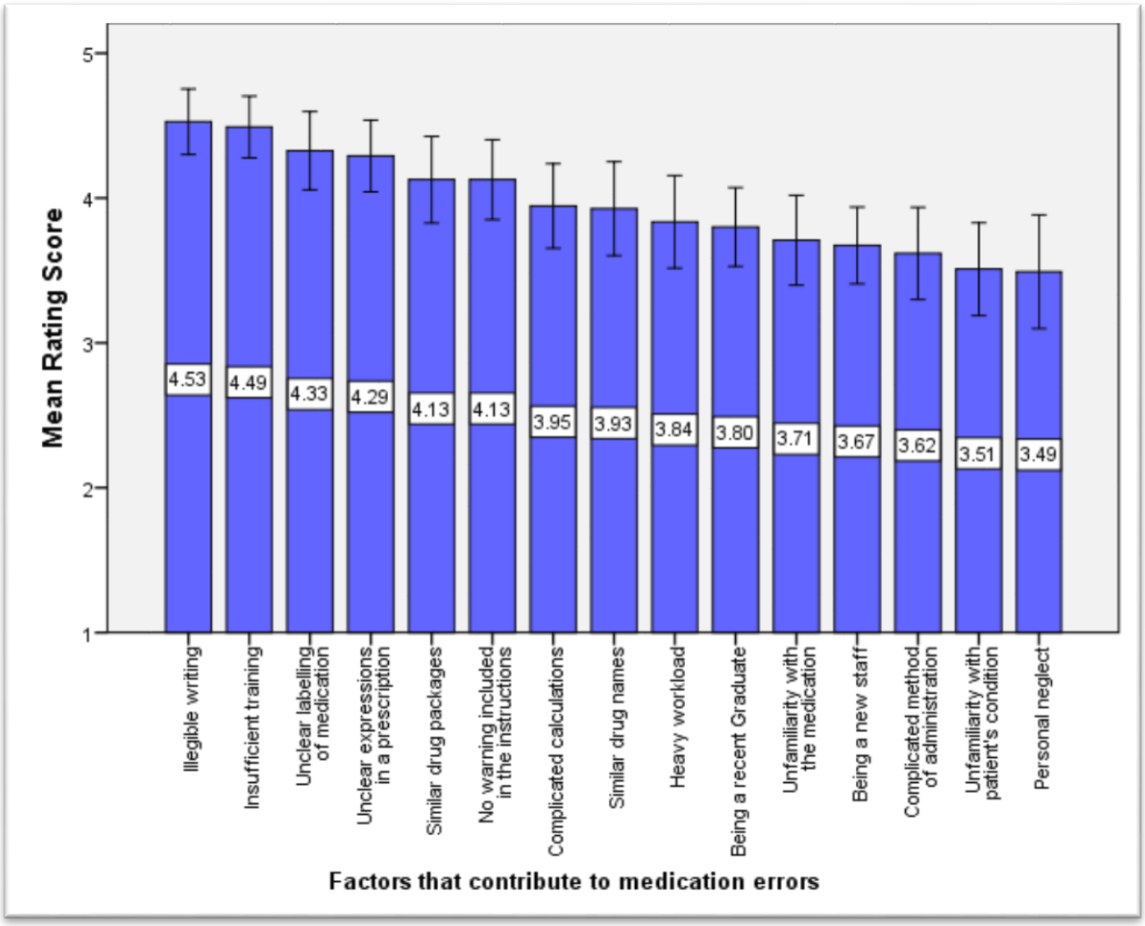

Figure 3. 10 Factors That Contribute to Medication Errors in the Administration Practice (N= 55)

Nurses (n=55) were required to rate the impact of certain scenarios on the safety of medication administration before and after introducing drug monographs to the wards (Table 3.16). Drug monographs were found to have a statistically significant impact on all of the listed scenarios ($p < 0.001$). "*Insufficient knowledge*" was the most influenced scenario by drug monographs (pre-test MRS=4.49 and post-test MRS=1.74), followed by "*Lack of availability of standard guide for administration*" (pre-test MRS=4.05 to post-test MRS=1.56), next was "*Inconsistencies between different resources and references*" (pre-test MRS=4.16 and post-test=1.88) and "*No accessibility to a*

pharmacist or a medical practitioner during shift" (pre-test MRS=4.24 and post-test MRS=2.40).

The scenarios that had the strongest impact on the safety of medication administration were insufficient knowledge where the (MRS=4.49), followed by "*prescription full of abbreviation*" and "*No accessibility to a pharmacist or a medical practitioner during shift*" with equal impact on the safety of medication administration (MRS=4.24), followed by "*Inconsistencies between different resources and references*" (MRS=4.16) and "*Lack of availability of standard guide for administration*" (MRS=4.05).

Table 3. 16 Scenarios Affecting Safe Medication Administration (Pre and Post)

Scenarios	**Pre-test N= 55**		**Post-test N = 53**		**p-value <0.05**
	Frequency	**Mean**	**Frequency**	**Mean**	
Insufficient knowledge	55	4.49	53	1.74	<0.001
Prescription full of abbreviations	55	4.24	53	1.98	<0.001
Lack of availability of standard guide for administration	55	4.05	53	1.56	<0.001
Lack of time to check a reference for administration	53	4.00	50	2.70	<0.001
Inconsistencies between different resources and references	55	4.16	49	1.88	<0.001
Inconsistent opinions between nurses	54	3.91	51	2.61	<0.001
Inconsistent opinion between doctor and nurse	55	4.00	51	3.14	<0.001
No accessibility to a pharmacist or a medical practitioner during shift	55	4.24	53	2.40	<0.001

Nurses were asked regarding to give feedback about the drug monographs after having them in the wards (Table 3.17). Nurses agreed that the information included within a monograph is concise (MRS = 4.38± 0.867) and that monographs assist in overcoming difficulties encountered in IV medication administration (MRS=4.37± 0.929).

Nurses agreed that the monographs facilitate medication administration (MRS=4.19± 0.864) and that they would refer to monographs if they are in doubt regarding medication administration (MRs=4.19±0.971). Nurses acknowledged that the monographs contribute to standardisation of practice (MRS= 4 ± 0.886) and that the monographs had improved their level of knowledge about IV medications (MRS= 3.69 ± 1.001).

Table 3. 17 Feedback Collected About Monographs (N=52)

Statement	Mean	Std. Deviation
Information included within a monograph is concise	4.38	0.867
The monographs assist in overcoming difficulties encountered in IV medication administration	4.37	0.929
The monographs facilitate medication administration	4.19	0.864
I would refer to a monograph when in doubt about a medication administration	4.19	0.971
The structure of a monograph is convenient for using	4.0	1.172
The monographs contributed to standardization of practice	4.0	0.886
The monographs are easy to use	3.73	1.14
The monographs have improved my knowledge about IV medications	3.69	1.001
The monographs contribute to reducing medication administration errors	3.52	1.336
Consulting a monograph is time consuming process	2.62	1.345

$X^2(10) = 95.517, p < 0.001$

Chapter 4: Discussion

4.1 Implications of Introducing Standard Guidance for the Use of IV Medications

Lack of consistent guidelines for reconstitution, dilution and administration of IV medications in paediatric patients at the wards' level poses challenges for nurses to keep up with the quality of care and maintain patient safety (Westbrook et al, 2011; Chedoe et al, 2012). The problem arises when nurses require information quickly to guide the use of the IV medications and they have limited time to search for it. IV medications are error-prone dosage forms with a frequency of errors up to 74% (Kaushal et al, 2001; Anselmi et al, 2007; Westbrook et al, 2011). IV preparation and administration in paediatric population is more complicated and potentially more dangerous compared to adults due to lack of suitable paediatric formulations and the use of adult specific formulations instead for paediatric patients (Taxis and Barber 2003, McDowell et al, 2010). Therefore, preparation includes additional steps such as dilution and weight based calculations of the right volume of IV medications to be administered which would increase the potential for medication errors (Gonzales, 2012; Ameer et al, 2015).

This study led to the development of a manual for medications administered through IV route in the paediatric patients at Mater Dei Hospital (MDH). One of the objectives of the study is to develop and validate IV drug monographs for the paediatric wards at MDH. The drug monographs of the IV manual contain information specific to the brand/generic of a medication being used at the local setting. The information was obtained by reviewing the product updated Summary of Product Characteristics (SmPC), conducting extensive literature review, evidence based practice at MDH and direct communication with the Marketing Authorization Holder (MAH) or the manufacturer of the brand/generic. Specificity of the information about the available products in terms of therapeutics, dose, reconstitution, dilution, displacement values and

special warnings makes it a practical guide that would save time and efforts to search for the necessary information. Despite the availability of different drug monographs from various resources containing theses information, the drug monographs of the IV manual are distinctive in terms of including more specific and various information related to the use of a certain brand/generic of a medication.

British National Formulary for children (BNF-C) drug monographs offer experts advice in all aspects of paediatric prescribing from selecting the best available drug, determining optimum dosing and formulations for neonates to 18 years old (Kowalczuk, 2006). BNF-C is focused on providing detailed information for the licensed and unlicensed indications but it does not provide detailed information with regards to reconstitution and dilution practice or special steps required to follow or sodium content or displacement value and even product specific information. BNF-C monographs cover products that are licensed in the United Kingdom of Britain (UK) and not necessarily all the products that are licensed in Malta.[55]

Injectable Drug Guide (IDG) monographs offer detailed technical advice for the use of injectable medications in terms of preparation, administration, compatibility, stability and monitoring of the medication. Data for each medication are summarized and demonstrated in an easy to use form which makes it convenient for using but the IDG monographs lack specific data for paediatrics. As a result IDG cannot be the reference of choice for administering injectable medications in paediatrics despite the guidance it provides in all aspects of the use of injectable medications such as pH, sodium content,

[55] Medicinescomplete. Paediatric Formulary Committee. BNF for Children [Internet] London: BMJ Group, Pharmaceutical Press, and RCPCH Publications; 2019 [cited 2019 Mar 28]. Available from : http://www.medicinescomplete.com>

excipients, storage conditions, stability after preparation, displacement value, drug interactions, handling of overdose and or adverse drug reactions (ADRs).

Paediatric injectable drug (PID) monographs are an authoritative source of information on the parenteral administration of medications to paediatric patients but they cover mainly products that are licensed in the United States of America (US) and the doses listed are not compliant with the licensed doses in the SmPC or other implemented literature in the local setting such as BNF-C.

Martindale monographs contain general information for the use of medications via parenteral and oral routes for both adult and paediatric patient. Since the data within a monograph is not paediatric specific neither IV oriented, consulting Martindale monograph would be more time consuming compared to other references when searching for specific information. Information such as displacement value, sodium content and monitoring of efficacy and toxicity are not listed within Martindale monographs. [56]

Injectable medicines guide (IMG) Medusa paediatric monographs offer a holistic approach for the parenteral use of medications in paediatrics but lacks detailed dosing information, monitoring and side effects. IMG Medusa monographs are for drugs that are available in UK since it is the national resource for UK National Health Services (NHS) hospitals. [57]

[56] Buckingham R editors. How information is organised. Martindale: The Complete Drug Reference. [Internet] London: Pharmaceutical Press. [cited 2019 Mr 29] Available from: http://www.medicinescomplete.com/

[57] NHS. National Health Services. Injectable Medicines Guide [Internet] NHS Injectable Medicines Guide Group. About Injectable Medicines Guide; July 2016 [cited 28 Mar 2019]. Available from: http://medusa.wales.nhs.uk/HomeAbout.asp

Neofax neonatal and paediatric monographs offer strong guidance for paediatric and neonatal areas on prescribing (particularly off label), administration, side effects and treatment monitoring but has limited information on reconstitution/dilution procedures, displacement value, sodium content and laboratory interference. Neofax monographs are for US Food and Drug Administration (FDA) approved medications therefore they lack information about non-FDA approved medications which are used in the local setting for example teicoplanin and locally available brands/generics.

Lexicomp monographs and the drug information handbook do not provide data related to reconstitution/dilution or compatibility data that is paediatric specific. Both references cover only products that are on the American formulary. The MDH hospital Guideline for Paediatric Intravenous Drug Reconstitution and University of College London (UCL) monographs do not include therapeutic data related to indication, dose, monitoring, side effects and lab interference. These monographs are focused on providing information for the preparation and administration of IV and IM medications.

The availability of drug monographs for the locally available brands/generics is essential when medications of the same active pharmaceutical ingredient vary in the licensed indications or doses for example the use of ranitidine injection in children aged 6 months and older is licensed in the literature and in the SmPC of various brands of ranitidine e.g Zantac® [58] and Ptinolin®[59] but for the locally available brand Pep-rani® [60]

[58] EMA. European Medicines Agency - Find medicine – Zantac Summary of Product Characterisitcs (SmPC) - [Internet]. Ema.europa.eu. 2018 [cited 2019 Mar 28]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000471/human_med_000619.jsp&mid=WC0b01ac058001d124

[59] MMA. Ptinolin –Summary of Product Characteristics (SmPC) - Medicines Databases [Internet] San Gwann: MMA. [cited 2019 Mar 27] Available from: http://www.medicinesauthority.gov.mt/search-medicine-results?modSearch=adv.

[60] MMA. Pep-rani- Summary of Product Characteristics (SmPC) - Medicines Databases [Internet] San Gwann: MMA. [Cited 2109 Mar 28]. Available from: http://www.medicinesauthority.gov.mt/search-medicine-results?modSearch=adv.

the use in children younger than 18 years old is not licensed. Another objective of the study was to develop and administer a questionnaire entitled Assessment of IV medication administration practice questionnaire (AAP-Q). The questionnaire aimed to evaluate the impact of drug monographs on the knowledge, confidence and contributing factors to medication errors from the nurses' perspective in a pre/post-test design. The questionnaire was administered to nurses (n=55) working at the paediatric wards at MDH.

The sample of medications included in this study were the commonly used medications where 12 of the 19 medications were antibiotics. Antibiotics are the most frequent reported class of medications to be associated with MAEs (Cowley et al, 2001; Holdsworth et al, 2003; Ghaleb et al, 2006). Interventions were designed to minimise the risks of MAEs and the impact of the interventions on the safe use of antibiotics and other medications were studied (Chedoe et al, 2012; Niemann, 2015). Antibiotics are commonly used medications in paediatric pateints therefore they are frequently reported with medication errors. Lan et al (2014) and Lu et al (2011) investigated nurses' knowledge and developed educational interventions for the administration and handling of high-alert medications. Hsaio et al (2009) studied a mixed sample containing commonly used medications which were mainly antibiotics and high-alert medications.

The assessment of knowledge of nurses in this study was conducted indirectly by providing real scenarios of medication errors from administration practice. The level of knowledge of nurses was assessed by analysing the answers of whether to proceed or not with the medication administration in the given scenarios. Proceeding with the medication administration indicates that the respondent is unaware of the medication

error associated with it. The responses of proceeding with the scenario versus non-proceeding in pre-test and post-test were compared to each other to study the effect of monographs on enhancing the knowledge of nurses about IV medications and in avoiding errors in reconstitution, dilution, mixing, dose calculations, administration and monitoring of IV medications.

Direct Assement of knowledge in literature was carried out by an examination where nurses answered a written exam of True or False questions or multiple choice questions or even case assessments questions. There is no reported standardised method to assess safe medication administration but calculation questions or mathematical exams were frequently used as an assessment strategy. Calculation and mathematical exams assess only calculation skills and are based on one right of safe medication administration "right dose" (Gonzales, 2012).

Simonsen et al (2011) used a test of multiple-choice questions derived from university tests to assess knowledge of nurses in pharmacology, drug management and drug dose calculations but no assessment of preparation and administration of IV medications was involved. Lu et al (2011) implemented a set of questions in a pre/post-test style to evaluate the effectiveness of an educational intervention at improving nurses' pharmacological knowledge. Ndosi and Nedwell (2009) assessed the knowledge of pharmacology of commonly administered medications. These two studies focused only on one right of safe medication administration which is "right drug".

Lan et al (2014) assessed nurses' knowledge about high-alert medications where nurses were presented a list of True or False questions which were part of an assessment tool

developed by Hsaio et al (2009). Hsaio et al (2009) tool focused on drug delivery routes, dosage, regulation and storage of high-alert medications. Gonzales (2012) utilised Safe Medication Administration (SAM) scale consisting of clinical cases of hospitalized paediatric and adult patients. Participants had to evaluate actions presented in each case and identify if these actions were correct or incorrect based on the five rights of safe medication administration. The tools implemented by Hsaio et al (2009) and Gonzales (2012) are comprehensive involving the five rights but they did not incorporate assessment of knowledge in terms of stability, compatibility, choice of solvent, reconstitution, dilution or even monitoring of IV medications.

Stewart et al (2010) assessed the knowledge of nursing and medical students about prescribing and administration of medications to paediatric patients using "real-life" clinical scenarios which included commonly used medications in paediatric patients. Respondents were allocated to groups of 2 to 3 and were provided with a group of references that could be consulted for answering the questions. The scenarios were about prescribing the appropriate drug, calculating the required dose, preparing the drug for administration and preparing an IV infusion.

Niemann et al (2015) conducted a questionnaire survey and checklist to assess the knowledge of nurses regarding medication use in paediatric patients. Questions were about the appropriateness of routine medication therapy processes for both IV and oral formulations. The survey contained IV specific questions related to preparation and administration such as choice of solvent, volume required for reconstitution and dilution, doses to be administered, stability and storage of reconstituted medications.

Scenarios that were implemented in our study were shorter and less time consuming than the clinical cases of Gonzales (2012) or questions of Niemann et al (2015) survey. The scenarios of APP-Q were set to assess knowledge and administration practice of nurses while Stewart et al (2010) scenarios were designed to assess knowledge of pharmacology and interprofessional team working.

All of the questions of AAP-Q were specific to paediatric patients and focused on knowledge of preparation and administration of IV medications. The baseline nurses' pharmacology knowledge in terms of stability, compatibility, choice of diluent and treatment monitoring was assessed in the pre-test and the impact of the monographs as an intervention was evaluated by comparing pre-test to post-test answers. Implementing scenarios rather than direct questions help in evaluating not only the knowledge of nurses but also the actions taken by nurses for the encountered scenarios throughout IV medication preparation and administration process. The disadvantage about this method is the respondent might not understand the question and choose the option "to proceed" when a medication error was identified as it is his/her attitude not to refer to a healthcare professional or a reference when administering medications.

The introduction of the monographs improved the knowledge of the nurses about compatibility of IV medications in terms of choice of compatible reconstitution fluids/diluents and drug-drug compatibility. The number of nurses who responded in the pre-test to proceed with the orders of "*diluting Ambisome® in NS*" and "*reconstituting co-amoxiclav with D5W*" decreased from 20 and 10 nurses (pre-test) to 6 and 2 nurses respectively (post-test). NS is incompatible with Ambisome® and D5W is incompatible with co-amoxiclav. Ten and 15 nurses managed to identify an error with the following

scenarios respectively: "*Co-infusion of teicoplanin with other antibiotics*" and "*adding cephalosporins/penicillins to an infusion set containing Aminoglycoside*" where they failed to identify it in the pre-test when drug monographs for these medications were not present.

The effect of monographs on knowledge levels of nurses about stability of a reconstituted/diluted medication was demonstrated when 11 nurses changed their answers from proceeding in the pre-test with a reconstituted amoxicillin or co-amoxiclav solutions with developed pink colour or a reconstituted flucloxacillin with developed particles to other options in the post-test. Nurses were made aware of the importance of serum gentamicin level monitoring and the maximum allowed rate of infusion for potassium chloride where around 15 out of 16 nurses changed their answer for these scenarios from "*proceed*" in pre-test to other options in post-test.

Monographs assisted nurses in overcoming their difficulties in administration practice that are related to choice of diluent or solvent and knowledge about pharmacology, where only 7 nurses reported to have difficulties with these areas in the post-test compared to 18 and 20 nurses in the pre-test. Monographs did not assist nurses in encountering difficulties associated with dealing with adverse drug reactions (ADRs) since the monographs lacked information regarding ADR management.

Nurses were asked to rate the level of their knowledge and proficiency about IV preparation and administration and the majority (n=40) identified it as "Good" or "Excellent". This indicates that nurses were confident about their proficiency in administration practice however they considered the need to update their knowledge as

"often" and "always". Only 7 nurses did not consider the need to update their knowledge. These 7 nurses could be the ones who assessed their proficiency and knowledge as "Excellent". In a study by Di Muzio et al (2017) Nurses were asked through a questionnaire to assess their level of knowledge about IV medication preparation and administration where 64.2% nurses rated their knowledge as "Good", 22.8% as "Excellent" and 12.2% as "sufficient".

A study by Davis et al (2009) identified a relationship between level of experience and confidence and need to update knowledge. Nurses who were new to the paediatric nursing area were relatively unconfident with medication administration but introducing nurses to a new field of practice motivated them to update their knowledge. In our study most nurses reported to have more than 10 years of experience thus higher confidence levels were observed.

Implementing monographs had a significant ($p<0.0001$) positive impact on the confidence level of nurses for the use of medications which nurses reported to be unfamiliar with their use such as clarithromycin. The confidence level of nurses increased even with frequently used medication such as Ambisome® and ceftazidime. The availability of brand specific information within a monograph had impacted the confidence level about their use significantly ($p<0.0001$) where the differences in dilution and reconstitution among the available brands were addressed.

Nurses in our study identified reconstitution and dilution of IV medications as the top encountered difficulty in administration practice followed by choice of compatible fluids and dose calculations was the least reported difficulty. In a study by Essani and

Ali (2011) the top difficulty in admninstration practice was reported to be “dosage calculations” (32.68%) followed by drug dilution (26%) and drug compatibility (15%). The difference in level of experience between the group of nurses in our study and nurses in this study might have influenced the difference of the dose calculation skills between the two groups. More than half of the nurses (n= 40) in our study reported to have more than 10 years of experience compared to 53% of nurses of the other study who had less than 2 years of experience (Ali and Essani, 2011). Experience was found to overcome theory-practice gap where more experienced nurses tend to be more practical about dose calculations than nursing students or fresh graduates (Davis et al, 2009; Lan et al, 2014).

The areas of training which nurses deem necessary were pharmacology of IV medications, mixing of IV preparations- related to compatibility and stability of the medications, reconstitution and dilution practice of IV medications. Academic training is necessary to improve safety of IV medication use (You et al, 2015). It was recommended that nurses should undergo intense undergraduate training about pharmacology of medications to be prepared for the clinical setting (Ali and Essani, 2011). Nurses as well have to attend pharmacology courses through their practice years to continuously update their knowledge (Petrova et al, 2010; Simonsen et al, 2011).

Forty-seven nurses considered the need to update their knowledge about IV medication preparation and administration. Similarly 88.6% of nurses in another study considered the need to update the knowledge and agreed that improving knowledge could contribute to reducing MAEs (Di Muzio et al, 2017).

Sources of information nurses refer to when using IV medications included mainly package insert in the pre-test and drug monographs in the post-test. Introducing the drug monographs in the post-test made the nurses shift from using package insert as a source of reference to drug monographs where more complete and detailed reconstitution/dilution data which is directly adapted from SmPC is present. When asked about their choice of sources, nurses selected hardcopy versions of a source over online version as they are more accessible, easier to handle and can be used at bed side.

Following introducing the monographs more nurses tended to consult pharmacists or drug monographs than the doctors with compatibility and stability scenarios such as "*co-infusion of ceftriaxone with Calcium containing fluids*" or "*Development of particles in reconstituted flucloxacillin or clarithromycin*". The opposite was observed in the cases related to tapering and monitoring of treatment such as gentamicin monitoring or tapering of steroids or even infusion rates of potassium chloride. This might be because nurses prefer consulting doctors over pharmacists when it comes to dose tapering and side effects. Results by other studies demonstrated that nurses refer to physicians and colleagues as primary source for information in administration practice compared to other resources (Clarke et al, 2013; Kumaran and Chipanshi, 2015).

The number of nurses referring to drug monographs was variable depending on the scenario where the number ranged from 23 to 35 nurses. Monographs are the choice of reference for drug-drug or drug-fluid compatibility and stability situations. Monographs save the time consumed for searching literature, online and hardcopy resources Monogtaphs also reduce the need to heavily rely on one's own judgment or colleagues'

experience, therefore nurses now have a continuously updated guidance with information gathered from multiple resources and the product SmPC.

Nurses do not have access to the references that were used to develop monographs (Appendix 1) therefore they are not familiar with their use except for online BNF-C and Uptodate. The rest of references are accessible only for pharmacists. Nurses do not prefer to use online resources as they find difficulty interpreting them, consider them very time consuming and misleading due to inconsistency in data related to licensed uses and licensed doses. Nurses were reported to prefer to consult physicians and other nurses or rely on the nursing education received and personal experience than using electronic resources (Kumaran and Chipanshi, 2015; Alving et al, 2018). The reasons for not using online resources frequently were lack of time to search for information, the busy nature of hospital nursing and lack of experience and skills to retrieve and implement evidence based information (Alving et al, 2018). Additionally paediatric specific information in some of these references such as Lexicomp is merged with adult data which makes it harder for nurses to locate paediatric specific information. Identifying and accessing the correct information that guide the appropriate preparation and administration of paediatric medications such as choice of diluent or dosage was reported to be hard by nurses (Dickinson et al, 2010).

The unavailability of online SmPC in the English language for the locally available generics in the platforms like Medicines and Healthcare products Regulatory Agency (MHRA) and Malta Medicines Authority (MMA) websites discourage nurses for consulting online references at the wards. Nurses instead prefer to ask a healthcare professional, read package insert or check a hardcopy reference e.g. BNF-C.

Availability of the monographs in a hardcopy format do not restrict the accessibility to information since access to a computer device or internet connection is required. Establishing adequate computer literacy for nurses and access to devices is important when implementing electronic or online policies and drug information as nurses reported in literature to have difficulties in locating those (Ahmad et al, 2018). In our study it was identified that nurses have inadequate logistics such as computer devices or electronics to access drug information electronically therefore nurses resort to use the hardcopy versions of the references despite being outdated compared to the online versions. The monographs were printed out and distributed to nurses in a hardcopy format to increase the accessibility for drug information for all the staff. Ahmad et al (2018) and Dickinson et al (2010) highlighted the importance to improve the access to medication information at wards' level by ensuring the logistics of accessing electronic information. Nurses as well should be trained and encouraged to implement electronic resources to search evidence based information and not to rely only on their experience or other healthcare professionals (Alving et al, 2018).

A relationship was demonstrated in literature between insufficient knowledge of the nurses, lack of experience in administration practice and higher percentage of medication administration errors (Benner et al, 2002; Lu MC et al, 2011; Lan et al, 2014). Insufficient knowledge, lack of training and being a new staff were all identified to be strong contributing factors to medication errors where the developed monographs were considered to have a significant impact in reducing their contribution ($p < 0.05$). Insufficient knowledge and difficulties with abbreviation were identified to have lower impact on medication errors after implementing monographs since monographs

addressed these problems by providing the necessary terms for the abbreviations and the information required for the appropriate use of IV medications.

The leading causes of medication preparation and administration errors are the lack of practical guidelines and procedures, deviations in practice from the policies (Taxis and Barber, 2003; Stavrodius et al, 2010; Westbrook et al, 2011; Chedoe et al, 2012) and non-compliance with the medications administration protocols (Armitage and Knapman, 2003). In this study inconsistency between references and lack of a standard guide for medication preparation and administration and lack of time to check a reference were regarded to strongly impact safety of medication administration. Other identified factors were inconsistency between healthcare professionals and lack of accessibility to a healthcare professional during shift. The monographs were considered to be a form of standard guide that assisted in addressing these factors by providing standard information adopted from literature, product SmPC and various references. Nurses consulted the monographs when they could not refer to a healthcare professional in particular during late or evening shifts or busy times of the day.

Monographs were developed to include data for the medication that is specific to the brand used and a change in brand would warrant updating the information within the whole monograph. This would reduce risks associated with the use of medications which their brand names was recently changed. A change in brand names was reported by other studies to be contributing factor for error in 18% of medication events (Valentin et al, 2009) but was not investigated in our study.

Factors such as “Unfamiliarity with the medication” , “Being a recent graduate” and “insufficient training” were less contributing to medication errors in the post-test compared to pre-test ($p< 0.05$) since monographs provide the information necessary for preparation and administration of IV medications in an easy to use form. The information within a monograph assisted nurses in particular nurses with inadequate experience or training or nurses who require specific guidelines or protocols to guide their practice or even the experienced nurses when they are using a new medication.

Factors like “similar drug names” ($p<0.001$) and “unclear package insert/label” ($p< 0.001$) are less contributing in the post-test ($p<0.05$) when compared to the pre-test. Monographs assisted nurses in identifying the correct drug names by promoting the use of tall man letters for medication names that are prone to confusion “sound alike”. Monographs provided the necessary information for reconstitution/dilution which nurses often retrieve from checking the package insert in the situations where the package inserts were unclear which contributed to a medication error.

Factors like illegible writing, heavy workload and unfamiliarity with the patient’s condition were not affected by the introduction of drug monographs. The drug monographs of the IV manual provide detailed information and guidance addressing factors that are related to knowledge, experience and training in preparation and administration of IV medications and do not address these issues.

Feedback collected about the monographs indicated that the structure facilitate obtaining information and it is convenient to use. Information within a monograph is clear, concise and using monographs does not consume much time. The

recommendation for developing any medication administration protocol or guidance is to be designed in an easy to use form where nurses would be encouraged to refer to and would not fear consuming much time when checking it (Gill et al, 2012). Nurses often did not adhere to guidelines or protocols if they considered them time consuming or information within is difficult to interpret which stresses the need for developing guidelines that are practical to use in daily practice (Davis et al, 2009; Gill et al, 2012). McLeod and Flowers (2006) developed a practical guide for nurses about diluent selection for subcutaneous infusion. The IV manual covered an area of practice where limited information is available in literature for the nurses and no standard procedures existed. Nurses were encouraged to implement drug monographs as the structure and content facilitated searching for information without consuming a lot of time.

Nurses in this study reported that monographs provided standard information that were lacking in the wards and consulting a healthcare professional or research for this information might be time consuming. Difficulty in accessing paediatric medication resources and the lack of availability of medication information were reported by nurses to interfere with their ability to prepare and administer medications (Dickinson et al, 2010). Readily accessible information is strongly recommended as a safety measure to guide medication administration (Hughes and Blegen, 2008). Providing medication information at ward level is an initiative done in the local setting similar to which was conducted by Campino et al (2016), Neimann (2015) et al and Gill et al (2012).

A study by Campino et al (2016) in neonates developed a standard concentration protocol for preparation of IV medications in neonates to minimise calculation errors associated with the dilution/reconstitution. Additionally, an educational programme

containing a practical teaching session and a theoretical teaching session was carried out. Campino et al (2016) studied the impact of the protocol and teaching sessions in a pre/post-test design where the calculation error rates were measured prior to and after the intervention. In the pre-intervention phase the calculation error rate was 1.35% while no errors were detected in the post-intervention due to standardisation and correct fulfilment of the protocol. In our study the dose calculations were among the least reported difficulties and thus the impact on the dose calculations was not studied directly but rather the impact on facilitating dose calculations. Instructions in form of steps that assist in reconstitution/dilution of the medication were provided in drug monographs while taking into consideration the displacement value.

Niemann et al (2015) developed a three step intervention and assessed their impact in reducing the frequency of medication errors in drug handling in paediatric wards at a hospital. These interventions were: (i) three-page handout that included concise information about drug-handling processes (ii) pharmacist led training course about practical handling guidelines, (iii) a reference book which contained detailed information regarding drug handling. This study involved anti-infective and gastrointestinal medications that are administered through IV and oral routes. The full intervention programme successfully decreased the medication error frequency from 91% to 26 % and the number of affected children from 88% to 49% .The Interventions were not equally successful in reducing the medication errors for example intervention I decreased the frequency of "Incorrect volume of solvent for IV drugs" by 25% by while the other interventions II & III (book and training) did not significantly affect the frequency of this error. This suggest that a set of interventions could address more

medication errors than one intervention where each intervention would address a different cause; knowledge deficits, memory lapses and rule violations.

The multifaceted educational interventions could contribute to reducing MAEs rate but other measures are needed as well to contribute to medication safety (Chedoe et al, 2012). Technical methods that are used to minimise MAEs include computerised medication administration records, barcoding of the patients and medications, smart infusion pumps and automised drug dispensing system (Hardmeier et al, 2014; Ameer et al, 2015; Nguyen et al, 2017). The disadvantages for the technical measures are the cost and the need for technology to implement them which may be difficult to afford in some settings (Raja et al, 2009; Nguyen et al; 2014; Ameer et al, 2015). Monographs are more feasible and can be implemented without the need to develop and utilize large-scale technology provided they will be available in hardcopy. If the drug monographs were uploaded on the intranet of MDH then an access to computer devices and network connections need to be established.

4.2 Limitations

This study is a pilot testing designed to evaluate the impact of developing and introducing drug monographs at the wards' level. Limited number of monographs were developed due to time restrictions while a monograph is needed for each medication used at the paediatric wards. Drug monographs were lacking detailed data regarding drug-drug interactions and drug-drug incompatibility. The administrator was advised to directly consult the pharmacist for drug-drug interactions or incompatibilities cases. Listing information within a monograph might lead to misinterpretation or incorrect assumption of the provided drug interactions or incompatibilities. The dose section in

general was not detailed whereas clinicians require dose specific indication for each age category in paediatric and term/preterm neonatal patients. The main target audience of the monographs are the nurses or administrators of the medications rather than the prescribers who require in certain cases consulting other dose detailed references. Furthermore, availability of the monographs in hardcopy format makes it difficult for the pharmacist to update the information continuously and it would be costly and time consuming to change the whole monograph by withdrawing it from the ward and printing a new one each time there is an update in the information.

The study could have evaluated the impact of drug monographs by developing an incident report system to encourage nurses reporting administration errors associated with the use of study sample prior to using the drug monographs and after implementing them. An analysis of the baseline medication error reports and post-testing medication error reports would have measured the direct impact of drug monographs on the medication errors. Previous studies implemented an intervention or a protocol and assessed its impact on medication administration errors prior to and after introducing the intervention by developing an incident reporting system and or observing medication administration by nurses (Jones, 2009; Okumura et al, 2016). The use of observation technique to evaluate the impact of an intervention on MAEs would result in a more direct approach (Tromp, 2008; Berdot et al, 2013).

An audit tool could have been developed to assess the use and monitor the compliance of the nurses/administrators with the use of drug monographs similar to previous studies which measured level of compliance with administration protocols (Canavan and Sutherland, 2013; Schutijser et al. 2018). Permits were not granted to perform these

types of measurements where the questionnaire and informal interviews were the main method of research to collect the feedback and data regarding impact of drug monographs on the administration practice.

Evaluation of the impact of age, nursing experience and level of position on medication administration practice and compliance with the monographs could have been measured. Age and experience are influential factors for medication administration practice and adherence to policies (Davis et al, 2009). Seniors nurses or nurses with higher level of experience were found to be less adherent to policies and tend to affect the judgement of recent nursing graduates when choosing to act for the best of the child over complying with the policies. Assessing the level of compliance against age and experience of nurses could not be performed in our study as permits were not granted to conduct this type of measurement.

4.3 Recommendations for Future Work

The area of IV administration practice in paediatrics lacks adequate information that is specific to the use of a medication. A monograph is needed for each medication used in the paediatric wards. The content of a monograph could be expanded to include more detailed data such as drug-drug interactions and drug-drug incompatibilities. A detailed dosing section could be added as an appendix to each monograph in a form of a table like in the first draft of monographs to enhance obtaining information and make it a more complete reference for the prescribing.

Other types of intervention in addition to the monographs could be implemented to update the pharmacological knowledge of nurses and healthcare professionals. These

interventions could be in the form of practical teaching sessions (Stewart et at, 2010) or power point presentations (Lu et al, 2013), educational materials (e.g, brochures and presentations) or special protocols (Tromp , 2008) and lectures delivered by pharmacists (Bertsche et al, 2010; Niemann et al, 2015).

Adherence to policies and protocols in the clinical settings should be promoted to ensure standardisation of practice among nurses and healthcare professionals. Adherence can be encouraged not only through educating about the policies (Raja et al, 2009) but also through increasing accessibility to the protocols in the medication preparation area (Ahmad et al, 2018). Examples of increasing accessibility could be by making monographs available as an application on the mobile phones of the nurses or providing more electronic devices (computers, tablets) in the wards to access electronic versions of the monographs and the online medical resources.

The direct impact of drug monographs on MAEs should be studied where baseline MAEs (pre-test) would be measured and compared to MAEs after introducing drug monographs (post-test). The difference in pre-test and post-test MAEs would provide a more reflective measure of the effect of monographs in reducing MAEs.

4.4 Conclusion

Patient safety forms a major part of quality of a healthcare system. Quality cannot be maintained without the work of multidisciplinary team of healthcare professionals. The pharmacist is knowledgeable and uniquely trained to be able to impact medication safety at patient level and medical staff level. Pharmacist role can be expanded from patient counselling and medication therapy management to training, upgrading the

knowledge of healthcare professionals and delivering pharmacological education. Pharmacists can lead patient safety initiatives by developing clinical practice guidelines and protocols which guide the safe use of medications and minimise the risks. Paediatrics are a vulnerable population with high risk for adverse drug events therefore paediatrics could benefit from a focus on medication safety through clinical pharmacy services and interventions that are targeted to reduce risks associated with the use of medications.

Drug monographs of the IV manual serve as guidance for choosing compatible diluents, preparing, administering and monitoring an IV medication — nurses and doctors have to consult different sources to obtain these information. The intention of this guide was to develop practice directions for nurses in obtaining information to direct the safe administration of IV medications and minimize risks and harms associated with this route. It is hoped that in its current form the IV manual will enhance the practice of clinicians and nurses by addressing the gaps in knowledge with use of IV medications and standardizing the administration practice. This could contribute to addressing factors leading to medication errors which would overall promote safer administration practice.

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Appendices

Appendix 1– List of References used for the Monographs

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Appendix 2-Power Point Presentation of Monographs

UOM

CPPU

Parenteral Drug Therapy Manual (PDTM)

PAEDIATRIC MONOGRAPHS

Background

- This manual is document or database that includes information related to administration, reconstitution of medicinal products including dissolution, dilution in infusion bags, compatibility with other medicines and adverse reactions[4] for general paediatrics
- Used as a guidance for preparing and administering medications given via parenteral routes

[4] Council of Europe. Committee of Ministers. Resolution CM/Res (2016)2 on good reconstitution practices in health care establishments for medicinal products for parenteral use [Internet]. Adopted by the Committee of Ministers on 1 June 2016 at the 1258th meeting. Available from https://www.edqm.eu/sites/default/files/resolution_cm_res_2016_1_quality_and_safety_assurance_requirements_for_medicinal_products_prepared_in_pharmacies.pdf

Background

- The use of manuals for drug therapies is adopted in various settings abroad in different countries; Ottawa Hospital PDTM, Vancouver Acute Pharmaceutical sciences PDTM ,London Drug monographs and Alberta Health Services Provincial Parenteral Monographs –Paediatric and Neonatal [5,6,7,8]

[5] The Ottawa Hospital Parenteral Drug Therapy Manual [Internet]. Ottawa: The Ottawa hospital; c2016 [Cited 2017 January 8]. Available from: https://www.ottawahospital.on.ca/wps/portal/Base/TheHospital/ClinicalServices/DeptPgrmCS/Departments/Pharmacy/Publications
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Introduction

- The parenteral manual is a patient safety initiative lead by Clinical Pharmacy Practice Unit (CPPU) at Mater Dei Hospital (MDH)
- The Parenteral Drug Monographs are approved by the pharmacy quality assurance (QA) and are maintained by the CPPU
- MDH healthcare professionals will use the manual as a reference to guide the appropriate and standard preparation and administration of parenteral medications in the wards

Purpose of the manual

- This manual provides a convenient, accessible, reliable reference and guide to healthcare professionals involved with intravenous drug administration
- It is not a complete treatise on intravenous drugs; it is impossible to provide extensive therapeutic or compatibility information in such an abbreviated format
- Designed to provide all essential information on the intravenous administration of a drug once therapeutic and compatibility data have been assessed

Development of a monograph

Fig. 1 Stages of developing a monograph

The prepared monographs were reviewed and validated by pharmacists working at Clinical Pharmacy Practice Unit in a multi-stage process

7

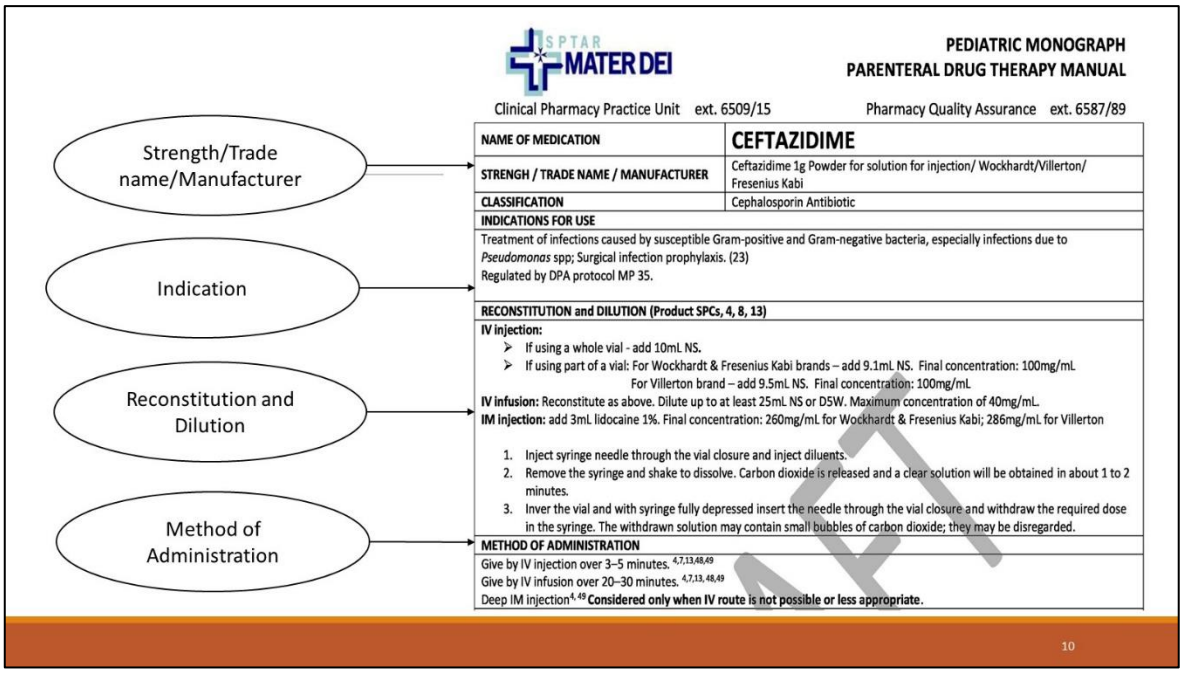
Structure of a monograph

- The template used for the adult monographs of PDTM is used for development of the paediatrics monographs

- The paediatric monographs will be formed for the available brands and strengths of a medication at MDH, where information is based on the relevant updated Summary Of Product Characteristics (SmPC)

Monograph sections

- Indications
- Reconstitution and Dilution
- Method of Administration
- Compatibility and Stability
- Monitoring required
- Potential hazards of administration



SPTAR MATER DEI

PEDIATRIC MONOGRAPH
PARENTERAL DRUG THERAPY MANUAL

Clinical Pharmacy Practice Unit ext. 6509/15 Pharmacy Quality Assurance ext. 6587/89

NAME OF MEDICATION	**CEFTAZIDIME**
STRENGH / TRADE NAME / MANUFACTURER	Ceftazidime 1g Powder for solution for injection/ Wockhardt/Villerton/ Fresenius Kabi
CLASSIFICATION	Cephalosporin Antibiotic

INDICATIONS FOR USE

Treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria, especially infections due to *Pseudomonas* spp; Surgical infection prophylaxis. (23)
Regulated by DPA protocol MP 35.

RECONSTITUTION and DILUTION (Product SPCs, 4, 8, 13)

IV injection:
- If using a whole vial - add 10mL NS.
- If using part of a vial: For Wockhardt & Fresenius Kabi brands – add 9.1mL NS. Final concentration: 100mg/mL
  For Villerton brand – add 9.5mL NS. Final concentration: 100mg/mL

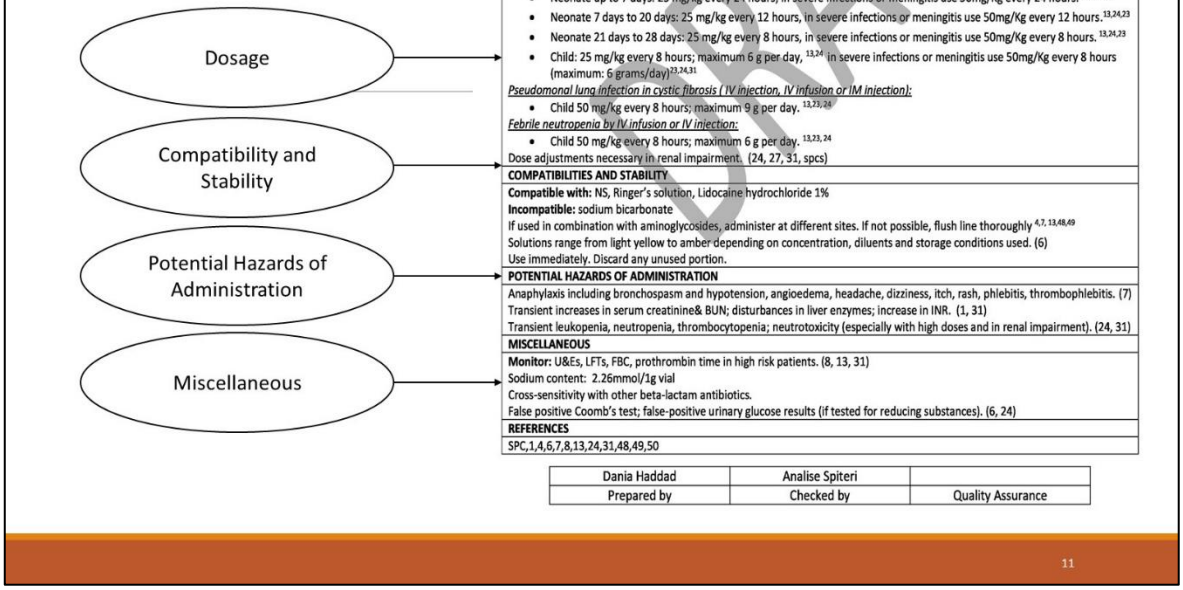
IV infusion: Reconstitute as above. Dilute up to at least 25mL NS or D5W. Maximum concentration of 40mg/mL.
IM injection: add 3mL lidocaine 1%. Final concentration: 260mg/mL for Wockhardt & Fresenius Kabi; 286mg/mL for Villerton

1. Inject syringe needle through the vial closure and inject diluents.
2. Remove the syringe and shake to dissolve. Carbon dioxide is released and a clear solution will be obtained in about 1 to 2 minutes.
3. Inver the vial and with syringe fully depressed insert the needle through the vial closure and withdraw the required dose in the syringe. The withdrawn solution may contain small bubbles of carbon dioxide; they may be disregarded.

METHOD OF ADMINISTRATION

Give by IV injection over 3–5 minutes. [4,7,13,48,49]
Give by IV infusion over 20–30 minutes. [4,7,13, 48,49]
Deep IM injection[4, 49] **Considered only when IV route is not possible or less appropriate.**

10



DOSAGE

Susceptible infections due to sensitive Gram-positive and Gram-negative bacteria (IV injection or IV infusion)
- Neonate up to 7 days: 25 mg/kg every 24 hours, in severe infections or meningitis use 50mg/Kg every 24 hours. [13,24, 23]
- Neonate 7 days to 20 days: 25 mg/kg every 12 hours, in severe infections or meningitis use 50mg/Kg every 12 hours. [13,24,23]
- Neonate 21 days to 28 days: 25 mg/kg every 8 hours, in severe infections or meningitis use 50mg/Kg every 8 hours. [13,24,23]
- Child: 25 mg/kg every 8 hours; maximum 6 g per day, [13,24] in severe infections or meningitis use 50mg/Kg every 8 hours (maximum: 6 grams/day)[13,24,31]

Pseudomonal lung infection in cystic fibrosis (IV injection, IV infusion or IM injection):
- Child 50 mg/kg every 8 hours; maximum 9 g per day. [13,23, 24]

Febrile neutropenia by IV infusion or IV injection:
- Child 50 mg/kg every 8 hours; maximum 6 g per day. [13,23, 24]

Dose adjustments necessary in renal impairment. (24, 27, 31, spcs)

COMPATIBILITIES AND STABILITY

Compatible with: NS, Ringer's solution, Lidocaine hydrochloride 1%
Incompatible: sodium bicarbonate
If used in combination with aminoglycosides, administer at different sites. If not possible, flush line thoroughly [4,7, 13,48,49]
Solutions range from light yellow to amber depending on concentration, diluents and storage conditions used. (6)
Use immediately. Discard any unused portion.

POTENTIAL HAZARDS OF ADMINISTRATION

Anaphylaxis including bronchospasm and hypotension, angioedema, headache, dizziness, itch, rash, phlebitis, thrombophlebitis. (7)
Transient increases in serum creatinine& BUN; disturbances in liver enzymes; increase in INR. (1, 31)
Transient leukopenia, neutropenia, thrombocytopenia; neutrotoxicity (especially with high doses and in renal impairment). (24, 31)

MISCELLANEOUS

Monitor: U&Es, LFTs, FBC, prothrombin time in high risk patients. (8, 13, 31)
Sodium content: 2.26mmol/1g vial
Cross-sensitivity with other beta-lactam antibiotics.
False positive Coomb's test; false-positive urinary glucose results (if tested for reducing substances). (6, 24)

REFERENCES

SPC,1,4,6,7,8,13,24,31,48,49,50

Dania Haddad	Analise Spiteri	
Prepared by	Checked by	Quality Assurance

11

List of Abbreviations used in the monographs

- An updated list of abbreviations was compiled for the abbreviated terms included in the monographs
- This list will be attached along with the release of the monographs
- Only the abbreviations included within this list are considered safe to use by Institute for Safe Medication Practices (ISMP)

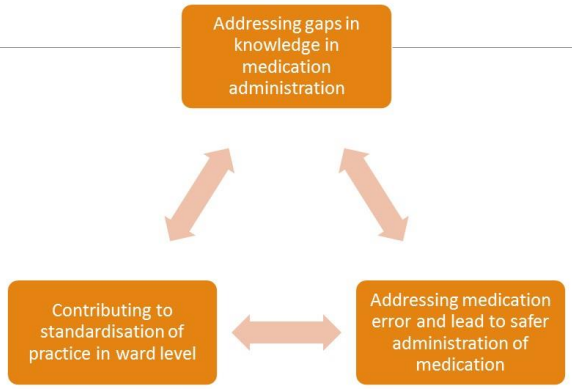
Term	Abbreviation	Term	Abbreviation
Concentration	Conc.	Dextrose 10%	D10W
Compound Sodium Lactate (Hartmann's or lactated Ringer)	Hartmann's	Glucose 10%	
5% dextrose in water	D5W	Full Blood Count	FBC
Glucose 5% and water		Liver function Test	LFT
Dextrose 5%		Microgram	Mcg
Dextrose 5% & sodium chloride 0.9%	D5NS	Milliliter	mL
Glucose 5% & sodium chloride 0.9%		Millimole	mmoL

Table 1 List of Abbreviations

List of References

- A continuously updated list of references was used for the compilation of the monographs
- The number of each reference used in the compiling of information of a monograph is listed in References section
- These references are accessible by CPPU and they are specific for preparation and administration of parenteral medications. Some of these references are specialised for paediatric population

Studies demonstrated a relationship between insufficient knowledge and higher percentage of medication administration errors [9,10,11]



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Appendix 3-Pre-test Assessment of administration practice questionnaire (AAPQ pre)

University of Malta: Department of Pharmacy
Development of a paediatric Intravenous formulations (IV) Manual Questionnaire (Pre-test)

Dear Participant:

I am a Doctorate of Pharmacy student at University of Malta. I am conducting my research on "Development of a Paediatric Intravenous Formulations Manual." This questionnaire is directed to administrators of IV medications in paediatrics. You are kindly invited to participate in this research study by completing the attached questionnaire.

The questionnaire is intended to determine the impact of introducing the drug monographs at wards' level. The results of the questionnaire will be used to measure the impact of introducing Drug monographs at wards' level on the administration practice. The outcome of the questionnaire will be used to identify any arising needs or difficulties encountered in practice when consulting Drug monographs for medications administration in paediatrics.

All information will remain confidential so please do not include your name. If you choose to participate in this project, please answer the questions. Participation is voluntary and you may refuse to participate at any time.

The questionnaire is consisted of 4 different parts (A: Background, B: Self-evaluation, C: Assessment and D: Safe medication administration). The estimated time to answer the questions is 25 minutes. Please take your time when answering questions as the results obtained will be considered in developing the monographs.

Thank you for taking the time to contribute to this research.

Yours sincerely,

Dania

Contact Details:

Name: Dania Al-Haddad
Email: dania.al-haddad.15@um.edu.mt
Mobile: 99444382

Part A: Background and Work related experience

1. **Age**

- □ <25
- □ 25-30
- □ 31-35
- □ 36-45
- □ 46-55
- □ 55+

2. **Education level**

- □ Diploma
- □ Bachelor of Science degree
- □ Master's degree
- □ other

3. **Position**

- □ Staff Nurse
- □ Senior Staff Nurse
- □ Deputy Charge Nurse
- □ Charge Nurse
- □ Paediatric Practice Nurse

4. **For how long have you been practicing as a nurse (years)**

- □ <2
- □ 2-5
- □ 6-10
- □ 11-15
- □ 16-20
- □ >20

5. **In which wards do you work?**

- □ Fairyland
- □ Wonderland
- □ Disneyland
- □ Paediatric Day care
- □ Rainbow
- □ Other……

6. a Have you ever attended training about IV drug preparation and administration in the last five years? If yes pleases tick one or more of the type of the training received and choose the date/s of the training.

- Yes
- No

If yes pleases tick one or more of the type of the training received and choose the year/s of the training.

Training	2017	2016	2015	2014	2013
Undergraduate training					
Postgraduate training					
Continuing professional development					
From work					
Other					

6 b Was the training paediatric patients' oriented?

- Yes
- No

Part B: Self-evaluation

7 In general how would you classify your proficiency and knowledge level of IV medications preparation and administration?

- Poor
- Fair
- Average
- Good
- Excellent

8 How often do you consider the need to continuously update your knowledge about IV preparation and administration? Please tick what is applicable.

- Never
- Rarely
- Sometimes
- Often
- Always

9 What type of training related to IV medications you would like to have?

- Pharmacology training (e.g. Indications, side effects, Dosage…etc)
- IV administration techniques (routes, methods, devices)
- IV preparations (Reconstitution and dilution)
- Mixing of IV preparations (e.g. stability and compatibility of fluids)
- Dose calculations and mathematical skills
- Other ……

Part C- Assessment of administration practice

10 When administering an IV medication what source of information do you refer to? Please circle the options in brackets if applicable.

- A health practitioner (a. Nurse b. Pharmacist c. Doctor)
- Package inserts/label
- BNF-Children (a. Online b. Hardcopy)
- Summary of product characterises
- Online medical resources
- Drug monographs of the IV manual
- Other …….

11 What sources of information related to IV administration of medications do you prefer to have in the wards

- Medication administration charts
- BNF-Children (a. Online b.Hardcopy)
- Online medical resources
- Drug monographs of the IV manual
- Other …….

12 What are the type of difficulties encountered when administering IV medications

- Dose calculations
- Infusion rate calculations
- IV administration technique
- Knowledge of IV medications
- Dealing with adverse reactions
- Reconstitution and dilution practice
- Choice of compatible fluids

13 The following statements are scenarios that might be encountered in practice. Kindly choose from the statements below how would you act in each scenario?

Proceed with the prescription/order without checking (Proceed)
Consult a colleague (**Nurse**)
Refer to a doctor (**Dr**)
Refer to a pharmacist (**Pharmacist**)
Check online medical resource (**Online resource)**
Check Drug monographs of IV manual (**Drug monograph)**

		Proceed	**Refer to**			**Check**	
No	**Statement**		**Nurse**	**Dr**	**Pharma -cist**	**Online resourc e**	**Drug monogra ph**
1	Receiving a prescription where the strength of doses is expressed as *U*.						
2	An order to dilute Ambisome® in 0.9% normal saline for administration as IV infusion.						
3	An order to co- infuse Ceftriaxone with calcium containing infusion fluids (e.g nutrition fluids).						
4	Development of a cloudy solution after reconstitution of Aciclovir injection.						
5	A paediatric patient who is receiving IV Gentamicin and no order for serum level monitoring was initiated.						
6	An order for Potassium chloride 20% w/v to be infused at a rate 0.5 mmol/kg/hour peripherally.						
7	An order to administer Co-amoxiclav as IM injection.						
8	An order for abrupt discontinuation of Hydrocortisone Sodium Succinate after long term therapy.						
9	An order to administer Co-amoxiclav as IV infusion diluted in 5% dextrose in water.						
10	An order to administer Teicoplanin simultaneously with other antibiotics.						
11	An Administration order of reconstituted Clarithromycin undiluted.						
12	Development of a pink colour solution when reconstituting Co-amoxiclav and Amoxicillin.						
13	An order to add a Cephalosporin or Penicillin antibiotic to an infusion set/bag containing Aminoglycoside.						
14	Development of particles in a reconstituted solution of Flucloxacillin and a reconstituted solution of Clarithromycin.						

14 How confident from a scale of 1 to 5 do you feel about the use of the following medications in paediatric patients .Please answer if applicable.

(1= very unconfident at all, 2= slightly unconfident, 3= Neutral, 4= slightly confident, 5= Very confident)

No	Medication	1	2	3	4	5
Antibiotics						
1	Aciclovir					
2	Amphotricin B (liposomal)					
3	Amoxicillin					
4	Benzylpenicillin					
5	Cefotaxime					
6	Ceftazidime					
7	Ceftriaxone					
8	Cefuroxime					
9	Clarithromycin					
10	Co-amoxiclav					
11	Flucloxacillin					
12	Gentamicin					
13	Metronidazole					
14	Teicoplanin					
15	Piperacillin/Tazobactam					
Sedatives/Analgesics						
16	Paracetamol					
Corticosteroids						
17	Hydrocortisone					
High alert medications						
18	Potassium Chloride					
Antiemetics						
19	Ondansetron					
20	Ranitidine					

Part D- Safe medication administration

15 On a scale of 1 to 5 how much do these factors contribute to medication errors in administration practice?

(1= not contributing at all, 2= slightly contributing, 3= Neutral, 4= contributing, 5=highly contributing)

No.	Factors	1 Not Contributing	2	3	4	5 Highly Contributing
1.	Personal neglect					
2.	Being a new staff					
3.	Being a recent graduate					
4.	Heavy workload					
5.	Unfamiliarity with patient's condition					
6.	Unfamiliarity with the medication					
7.	Similar drug names					
8.	Similar drug packages					
9.	Unclear labelling of medication					
10.	Illegible writing					
11.	Unclear expressions in a prescription					
12.	Complicated calculations					
13.	Complicated method of administrations					
14.	No warning included in the instruct ions					
15.	Insufficient training					

16 On a scale 1 to 5, how much do you agree that these following scenarios will affect safe administration of IV medications in paediatric patients?

(1=strongly disagree, 2=Disagree, 3=neither agree/neither disagree, 4=Agree, 5=strongly agree)

No.	Scenario	1 Strongly disagree	2	3	4	5 Strongly agree
1.	Insufficient knowledge					
2.	Prescription full of abbreviations					
3.	Lack of availability of standard guide for administration					
4.	Lack of time to check a reference for administration					
5.	Inconsistencies between different resources and references					
6.	Inconsistent opinions between healthcare professionals					
7.	No accessibility to a pharmacist or a medical practitioner during shift					
8.	Other (please specify) …… …… …… …… …… …… …… …… …… …… …… ……					

Appendix 4-Post-test Assessment of administration practice questionnaire (AAPQ post)

University of Malta: Department of Pharmacy
Development of a paediatric Intravenous formulations (IV) Manual Questionnaire (Post-test)

Dear Participant:

I am a Doctorate of Pharmacy student at University of Malta. I am conducting my research on "Development of a Paediatric Intravenous Formulations Manual." This questionnaire is directed to administrators of IV medications in paediatrics. You are kindly invited to participate in this research study by completing the attached questionnaire.

The questionnaire is intended to determine the impact of introducing the drug monographs at wards' level. The results of the questionnaire will be used to measure the impact of introducing Drug monographs at wards' level on the administration practice. The outcome of the questionnaire will be used to identify any arising needs or difficulties encountered in practice when consulting Drug monographs for medications administration in paediatrics.

All information will remain confidential so please do not include your name. If you choose to participate in this project, please answer the questions. Participation is voluntary and you may refuse to participate at any time.

The questionnaire is consisted of 4 different parts (A: Background, B: Self-evaluation, C: Assessment and D: Safe medication administration). The estimated time to answer the questions is 25 minutes. Please take your time when answering questions as the results obtained will be considered in developing the monographs.

Thank you for taking the time to contribute to this research.

Yours sincerely,

Dania

Contact Details:

Name: Dania Al-Haddad
Email: dania.al-haddad.15@um.edu.mt
Mobile: 99444382

Part A: Background and Work related experience

6. Age

- □ <25
- □ 25-30
- □ 31-35
- □ 36-45
- □ 46-55
- □ 55+

7. Education level

- □ Diploma
- □ Bachelor of Science degree
- □ Master's degree
- □ other

8. Position

- □ Staff Nurse
- □ Senior Staff Nurse
- □ Deputy Charge Nurse
- □ Charge Nurse
- □ Paediatric Practice Nurse

9. For how long have you been practicing as a nurse (years)

- □ <2
- □ 2-5
- □ 6-10
- □ 11-15
- □ 16-20
- □ >20

10. In which wards do you work?

- □ Fairyland
- □ Wonderland
- □ Disneyland
- □ Paediatric Day care
- □ Rainbow
- □ Other……

6. a Have you ever attended training about IV drug preparation and administration in the last five years? If yes pleases tick one or more of the type of the training received and choose the date/s of the training.

- □ Yes
- □ No

If yes pleases tick one or more of the type of the training received and choose the year/s of the training.

Training	2017	2016	2015	2014	2013
□ Undergraduate training					
□ Postgraduate training					
□ Continuing professional development					
□ From work					
□ Other					

6 b Was the training paediatric patients' oriented?

□ Yes
□ No

Part B: Self-evaluation

7 In general how would you classify your proficiency and knowledge level of IV medications preparation and administration?

□ Poor
□ Fair
□ Average
□ Good
□ Excellent

8 How often do you consider the need to continuously update your knowledge about IV preparation and administration? Please tick what is applicable.

□ Never
□ Rarely
□ Sometimes
□ Often
□ Always

9 What type of training related to IV medications you would like to have?

□ Pharmacology training (e.g. Indications, side effects, Dosage…etc)
□ IV administration techniques (routes, methods, devices)
□ IV preparations (Reconstitution and dilution)
□ Mixing of IV preparations (e.g. stability and compatibility of fluids)
□ Dose calculations and mathematical skills
□ Other ……

Part C- Assessment of administration practice

10 When administering an IV medication what source of information do you refer to? Please circle the options in brackets if applicable.

- A health practitioner (a. Nurse b. Pharmacist c. Doctor)
- Package inserts/label
- BNF-Children (a. Online b. Hardcopy)
- Summary of product characterises
- Online medical resources
- Drug monographs of the IV manual
- Other …….

11 What sources of information related to IV administration of medications do you prefer to have in the wards

- Medication administration charts
- BNF-Children (a. Online b.Hardcopy)
- Online medical resources
- Drug monographs of the IV manual
- Other …….

12 What are the type of difficulties encountered when administering IV medications

- Dose calculations
- Infusion rate calculations
- IV administration technique
- Knowledge of IV medications
- Dealing with adverse reactions
- Reconstitution and dilution practice
- Choice of compatible fluids

13 The following statements are scenarios that might be encountered in practice. Kindly choose from the statements below how would you act in each scenario?

Proceed with the prescription/order without checking
Consult a colleague (**nurse**)
Refer to a doctor (**Dr**)
Refer to a pharmacist (**Pharmacist**)
Check online medical resource (**Online resource**)
Check Drug monographs of IV manual (**Drug monograph**)

		Proceed	**Refer to**			**Check**	
No	**Statement**		**Nurse**	**Dr**	**Pharma -cist**	**Online resourc e**	**Drug mono graph**
1	Receiving a prescription where the strength of doses is expressed as *U*.						
2	An order to dilute Ambisome in 0.9% normal saline for administration as IV infusion.						
3	An order to co- infuse Ceftriaxone with calcium containing infusion fluids (e.g nutrition fluids).						
4	Development of a cloudy solution after reconstitution of Aciclovir injection.						
5	A paediatric patient who is receiving IV Gentamicin and no order for serum level monitoring was initiated.						
6	An order for Potassium chloride 20% w/v to be infused at a rate 0.5 mmol/kg/hour peripherally.						
7	An order to administer Co-amoxiclav as IM injection.						
8	An order for abrupt discontinuation of Hydrocortisone Sodium Succinate after long term therapy.						
9	An order to administer Co-amoxiclav as IV infusion diluted in 5% dextrose in water.						
10	An order to administer Teicoplanin simultaneously with other antibiotics.						
11	An Administration order of reconstituted Clarithromycin undiluted.						
12	Development of a pink colour solution when reconstituting Co-amoxiclav and Amoxicillin.						
13	An order to add a Cephalosporin or Penicillin antibiotic to an infusion set/bag containing Aminoglycoside.						
14	Development of particles in a reconstituted solution of Flucloxacillin and a reconstituted solution of Clarithromycin.						

14 How confident from a scale of 1 to 5 do you feel about the use of the following medications in paediatric patients .Please answer if applicable.

(1= very unconfident at all, 2= slightly unconfident, 3= Neutral, 4= slightly confident, 5= Very confident)

No	Medication	1	2	3	4	5
Antibiotics						
1	Aciclovir					
2	Amphotricin B (liposomal)					
3	Amoxicillin					
4	Benzylpenicillin					
5	Cefotaxime					
6	Ceftazidime					
7	Ceftriaxone					
8	Cefuroxime					
9	Clarithromycin					
10	Co-amoxiclav					
11	Flucloxacillin					
12	Gentamicin					
13	Metronidazole					
14	Teicoplanin					
15	Piperacillin/Tazobactam					
Sedatives/Analgesics						
16	Paracetamol					
Corticosteroids						
17	Hydrocortisone					
High alert medications						
18	Potassium Chloride					
Antiemetics						
19	Ondansetron					
20	Ranitidine					

Part D- Safe medication administration

15. **On a scale of 1 to 5 how much do these factors contribute to medication errors in administration practice after availability of IV manual?**

(1= not contributing at all, 2= slightly contributing, 3= Neutral, 4= contributing, 5=highly contributing)

No.	Factors	1 Not Contributing	2	3	4	5 Highly Contributing
1.	Personal neglect					
2.	Being a new staff					
3.	Being a recent graduate					
4.	Heavy workload					
5.	Unfamiliarity with patient's condition					
6.	Unfamiliarity with the medication					
7.	Similar drug names					
8.	Similar drug packages					
9.	Unclear labelling of medication					
10.	Illegible writing					
11.	Unclear expressions in a prescription					
12.	Complicated calculations					
13.	Complicated method of administrations					
14.	No warning included in the instruct ions					
15.	Insufficient training					

16. On a scale 1 to 5, how much do you agree that these following scenarios will affect safe administration of IV medications in paediatric patients after availability of IV manual?
(1=strongly disagree, 2=Disagree, 3=neither agree/neither disagree, 4=Agree, 5=strongly agree)

No.	Scenario	1 **Strongly disagree**	2	3	4	5 **Strongly agree**
1.	Insufficient knowledge					
2.	Prescription full of abbreviations					
3.	Lack of availability of standard guide for administration					
4.	Lack of time to check a reference for administration					
5.	Inconsistencies between different resources and references					
6.	Inconsistent opinions between healthcare professionals					
7.	No accessibility to a pharmacist or a medical practitioner during shift					
8.	Other (please specify) …… …… …… …… …… …… …… …… …… …… …… …… ……					

Appendix 5- Approvals

L-Università ta' Malta

Faculty of
Medicine & Surgery

University of Malta
Msida MSD 2080, Malta

Tel: +356 2340 1879/1891/1167
umms@um.edu.mt

www.um.edu.mt/ms

Ref No: **44/2017**

Tuesday 17th October 2017

Ms. Dania Al-Haddad
96, Flat 2, Debono Flats
Triq E.B Vella
Mosta MST3153

Dear Ms. Dania Al-Haddad,

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

Development of a paediatric intravenous formulations manual

The University Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Dr. Mario Vassallo
Chairman
Research Ethics Committee

Dear Mr Falzon,

I am Dania Haddad, a pharmacist and a second year Doctorate of Pharmacy student. I am working on a dissertation entitled "Development of a Paediatric intravenous formulations manual ". This research is being carried out under the supervision of Professor Anthony Serracino Inglott and Dr. Nicolette Sammut Bartolo.

The aim of this dissertation is to develop an intravenous formulations manual for the medications administered in the Paediatric wards and to test the impact of the manual on the administration practice.

The Paediatric manual will be based on the template used for the Parenteral Drug Therapy Manual for adults at Mater-Dei Hospital. Information included in the monographs for the paediatric manual will be accroding to the latest Summary of product characteristic (SmPC) and each monograph reviewed and validated by the Pharmacy Department at Mater Dei Hospital. The monographs will be released through MDH Pharmacy Department at a later stage. The impact of monographs will be tested using a validated questionnaire developed to assess the knowledge and potential impact of the manual on the intravenous medication administration practice in the Paediatric wards . In the post stage feedback will be collected regarding the introduced monographs as the preferred source of information consulted for administering IV medications in the paediatric wards.

In order to be able to proceed, I need your approval as Head of the Pharmacy to give me the permits to work on the monographs in collaboration with the pharmacists and to use the references and resources within the Medicines Information unit for the purpose of developing the monographs.

For your consideration and approval please

Dania 15/06/2017

Name	Signature	Date
	Stephen Falzon Head of Pharmacy Department Managing Pharmacist Reg. No. 474 Mater Dei Hospital 15/6/2017	

Dear Dr Cutajar,

I am Dania Haddad, a pharmacist and a second year Doctorate of Pharmacy student. I am working on a dissertation entitled "Development of a Paediatric intravenous formulations manual ". This research is being carried out under the supervision of Professor Anthony Serracino Inglott and Dr. Nicolette Sammut Bartolo.

The aim of this dissertation is to develop an intravenous formulations manual for the medications administered in the Paediatric wards and to test the impact of the manual on the administration practice.

The paediatrics manual will be based on the template used for the Parenteral Drug Therapy Manual for adults at Mater-Dei Hospital. Information included in the monographs for the paediatric manual will be accroding to the latest Summary of product characteristics (SmPC) and each monograph reviewed and validated by the pharmacy department at Mater Dei Hospital. The monographs will be released through the pharmacy department in a later stage. The impact of monographs will be tested using a validated questionnaire developed to assess the knowledge and potential impact of the manual on the intravenous medication administration practice in the Paediatric wards . In the post stage feedback will be collected regarding the introduced monographs as the prefferd source of information consulted for administering IV medications in the paediatric wards.

In order to be able to proceed, I need the approval of the Head of the Clinical Pharmacy Practice Unit (CPPU) to give me the permits to work on the monographs in collaboration with CPPU and to use the references and resources within the Medicines Information unit for the purpose of developing the monographs.

I, undersigned grant the permission to the Pharm.D student Dania Haddad to approach CPPU and work on the monographs in collaboration with the pharmacists enabling her to conduct the study with her dissertation entitled "Development of a paediatric intravenous formulations manual".

Anthony Cutajar
Senior Principal Pharmacist
Reg. No. 544

Name

Signature

15/06/2017.

Date

Dear Dr Sultana,

I am Dania Haddad, a pharmacist and a second year Doctorate of Pharmacy student. I am working on a dissertation entitled "Development of a paediatric intravenous formulations manual ". This research is being carried out under the supervision of Professor Anthony Serracino Inglott and Dr. Nicolette Sammut Bartolo.

The aim of this dissertation is to develop an intravenous formulations manual for the medications administered in the paediatric wards and to test the impact of the manual on the administration practice.

The paediatrics manual will be based on the template used for the Parenteral Drug Therapy Manual for adults at Mater-Dei Hospital. Information included in the monographs for the paediatric manual will be accroding to the latest Summary of product characteristic (SmPC) and each monograph will be reviewed and validated by the pharmcay department at Mater Dei Hospital. The monographs will be released through the pharmacy department in a later stage. The impact of monographs will be tested using a validated questionnaire developed to assess the knowledge and potential impact of the manual on the intravenous medication administration practice in the paediatric wards . Questionnaires will be distributed prior to and after introducing the monographs to identify the effect of monographs on the difficulties encountered in administration practice and on safe medication administration. In the post stage feedback will be collected regarding the introduced monographs as well as suggestions for improvement.

In order to be able to proceed, I need the help of the Director of nursing and other healthcare professionals to give me the permits to approach healthcare professionals including nurses working in the paediatric wards.

I, undersigned grant the permission to the Pharm.D student Dania Haddad to approach nurses within the paediatric wards enabling her to conduct the study with her dissertation entitled "Development of a paediatric intravenous formulations manual".

Name	Signature	Date
Dr. Victoria Sultana Director Nursing & Midwifery Services Mater Dei Hospital Tel. 2545 4202		

Dear Mr Buttigieg,

I am Dania Haddad, a pharmacist and a second year Doctorate of Pharmacy student. I am working on a dissertation entitled "Development of a paeditaric intravenous formulations manual ". This research is being carried out under the supervision of Professor Anthony Serracino Inglott and Dr. Nicolette Sammut Bartolo.

The aim of this dissertation is to develop an intravenous formulations manual for the medications administered in the paediatric wards and to test the impact of the manual on the administration practice.

The paediatrics manual will be based on the template used for the Parenteral Drug Therapy Manual for adults at Mater-Dei Hospital. Information included in the monographs for the paediatric manual will be accroding to the latest Summary of product characteristic (SmPC) and each monograph is reviewed and validated by the pharmacy department at Mater Dei Hospital. The monographs will be released through the pharmacy department in a later stage. The impact of monographs will be tested using a validated questionnaire developed to assess the knowledge and potential impact of the manual on the intravenous medication administration practice in the paediatric wards. Questionnaires will be distributed prior to and after introducing the monographs to identify the effect of monographs on the difficulties encountered in administration practice and on safe medication administration. In the post stage, feedback will be collected regarding the introduced monographs as well as suggestions for improvement.

In order to be able to proceed, I need the help of the Nursing manager and other healthcare professionals to give me the permits to approach healthcare professionals including nurses working in the paediatric wards.

I, undersigned grant the permission to the Pharm.D student Dania Haddad to approach nurses within the paediatric wards enabling her to conduct the study with her dissertation entitled "Development of a paediatric intravenous formulations manual".

PAUL BUTTIGIEG
Name

Paul Buttigieg
Chief Nursing Manager
Mater Dei Hospital
Signature

15/6/17
Date

Dear Dr Soler,

I am Dania Haddad, a pharmacist and a second year Doctorate of Pharamcy student. I am working on a dissertation etitled "Development of a peaditaric intravenous formulations manual ". This research is being carried out under the supervision of Professor Anthony Serracino Inglott and Dr. Nicolette Sammut Bartolo.

The aim of this dissertation is to develop an intravenous formulations manual for the medications administered in the peadiatric wards and to test the impact of the manual on the administration practice.

The paediatric manual will be based on the template used for the Parenteral Drug Therapy Manual for adults at Mater-Dei Hospital. Information included in the monographs for the paediatric manual will be accroding to the latest Summary of product characteristic (SmPC) and each monograph reviewed and validated by the Pharmacy Department at Mater Dei Hospital. The monographs will be released through the Pharmacy Department at a later stage. The impact of monographs will be tested using a validated questionnaire developed to assess the knowledge and potential impact of the manaul on the intravenous medication administration practice in the peadaitric wards. Questionnaires will be disseminated prior to and after introducing the monographs to identify the effect of monographs on the difficulties encountered in administration practice and on safe medication administration. In the post stage feedback will be collected regarding the introduced monographs as well as suggestions for improvement.

In order to be able to proceed, I need the help of the Chairman of paediatrics and other healthcare professionals to give me the permits to approach healthcare professionals including nurses working in the paediatric wards.

I, undersigned grant the permission to the PharmD student Dania Haddad to approach healthcare professionals within the paediatric ward enabling her to conduct the study with her dissertation entitled "Development of a paediatric intravenous formulations manual ".

21.6.2017

Name | Signature | Date

Dr. Paul Soler (MD MRCPCH MRCP)
Chairman
Dept. of Child & Adolescent Health

Appendix 6- Publications

Abstract for the 78th FIP World Congress of Pharmacy and Pharmaceutical Sciences

Developing a standard guidance for IV medications at wards' level

Dania Al-Haddad, Msc[1], Anthony Cutajar, Msc[2], Nicolette Sammut Bartolo, Phd[1] and Anthony Serracino-Inglott Phd[1]

(1) University of Malta, Msida, Malta

(2) Mater Dei Hospital, Msida, Malta

Introduction: Safe and effective administration of IV medications is key to patient safety. There is a need within an organization for a guidance to standardise use of IV medications. In the local setting preparation of IV medications is carried at wards' level and no special unit or guidelines are present to aid in this practice.

Purpose: To introduce a standard guidance for the appropriate preparation and administration of IV medications.

Method: Drug monographs were designed to include therapeutic information and detailed information about reconstitution, dilution, compatibility and stability. Published literature, evidence based local practice, latest updated SmPC (Summary of Product Characteristics) and manufacturers of the medications were all consulted to develop monographs which were sent to hospital pharmacists for review and approval as hospital guidance. Questionnaires were developed to evaluate the impact of the monographs on the administration practice by nurses.

Results: Monographs were developed for the commonly used IV medications in paediatric wards at the hospital. Reconstitution and dilution according to each available strength and brand of a medication is explained where displacement value and volume of diluent to be used is specified. Method of administration, stability and appearance of a solution and critical monitoring parameters were all provided. Feedback collected indicated that 32 out of 55 paediatric nurses prefer to use a monograph as a reference in the administration practice.

Conclusion: Availability of a standard guidance has shown to have a positive impact in administration practice by promoting the safe use of IV medications.

Abstract for the 10th Malta Medical School Conference

Development of paediatric Intravenous formulation Manual

Dania Haddad, Anthony Cutajar, Nicolette Sammut Bartolo, Anthony Serracino-Inglott

Introduction: Safe and effective administration of injectable medications is key to patient safety. A Parenteral Drug Therapy Manual (PDTM) is a document or database that includes information related to administration, reconstitution of medicinal products, compatibility with other medicines and adverse reactions. The PDTM is used as a guidance for the preparation and administration of medications via parenteral routes. In the acute general hospital of Malta, currently there is no PDTM for paediatrics.

Research question: Will introducing a standardised guide for medication administration contribute to safer practice and have the potential to reduce preventable medication administration errors?

Study design: Cross-sectional study**.**

Method: Monographs were designed to include the drug indication, reconstitution, preparation and administration method and any monitoring that may be required during and after administering the therapy. Pre- and post-testing questionnaires were developed and validated by eleven panellists to evaluate the impact of the monographs on the administration practice of IV medications by nurses.

Results: Fifty-six paediatric nurses out of 62 participated in the study. Reconstitution and dilution practice and choice of compatible fluids when preparing an IV medication were identified as main difficulties encountered in administration practice by forty nurses. Lack of standardised guide for medication administration and inconsistency between different resources and references were considered by 49 nurses as the main factors that contribute to medication errors. Feedback collected indicated that 49 nurses prefer to consult the monographs as a reference of information when they administer medications**.**

Conclusion: The developed monographs were considered to have a positive impact on the safety of medication administration by contributing to standardisation of practice and providing an easy-to-use reference at the bed side.

Abstract for the 79th FIP World Congress of Pharmacy and Pharmaceutical Sciences

Nurses perception of intravenous medication administration errors in paediatrics

Dania Al-Haddad[1], Anthony Cutajar[2], Nicolette Sammut Bartolo[1], Anthony Serracino-Inglott[1]

[1]Department of Pharmacy, University of Malta, Msida, Malta

[2]Mater Dei Hospital, Msida, Malta

Background information: Paediatric nurses activities may be challenging since paediatric patients may be more prone to intravenous (IV) medication administration errors (MAEs) and continuous training is pertinent.

Purpose: (i) To identify difficulties encountered in medication administration, (ii) To assess the perception of nurses about factors that contribute to MAEs and (iii) To investigate possible preventive measures.

Method: A questionnaire was developed, validated and distributed to nurses working in paediatric wards. Nurses were asked using a 5-point Likert scale to assess the impact of contributing factors and encountered difficulties, on the safety of IV medication administration and to identify preventive measures related to MAEs.

Results: Fifty-five nurses answered the questionnaire. Reconstitution and dilution practice and choice of compatible fluids when preparing and administering an IV medication, were identified as main difficulties encountered (n=40) in medication administration. Insufficient knowledge about IV medications and their administration (n=49), lack of specialised training in paediatric nursing (n=49), lack of accessibility to a pharmacist during shift (n=45) and lack of availability of a standard guide for administration (n=43) were rated as the highest (>4) contributing factors for MAEs. Need for

specialised training in IV medication preparation and administration (n=36), pharmacological education (n=36) and use of a standard guide for IV administration (n=32) were identified as preventive measures related to MAEs.

Conclusion: Developing a standard guidance for administration of IV medication in paediatric patients and introducing regular educational sessions may contribute to reduce preventable MAEs.

Appendix 7- Quantities of IV Medications Consumed Per Ward (2007-2016)

Medication	Ward							Total
	Disneyland	Fairyland	Wonderland	Paediatric day-care	Rainbow	Paediatric outpatient	Paediatric emergency	
Cefotaxime 1g injection	14,168	1,324	8,413	37	86	-	7	24,035
Co-amoxiclav 600mg, 1.2g injection	9,165	7,367	5,475	1,428	391	-	97	23,923
Heparin Sodium injection	3,325	3,863	1,323	5,530	3,949	159	95	18,244
Cefuroxime 250mg, 750mg injection	5,028	8,155	3,446	466	548	-	35	17,678
Tazobactam e` Piperacillin 2.25g, 4.5g injections	1,936	1,575	972	3,117	6,571	30	12	14,213
Ceftriaxone 500mg, 1g injection, 2g inject,	4,584	2,364	1,947	2,316	290	-	1	11,502
Ondansetron 4mg, 8mg injection	366	196	225	21	10,054	-	242	11,104
Gentamicin 80mg injection	1,769	2,398	1,045	1,452	3,688	20	10	10,382
Hydrocortisone 100mg injection	4,266	250	2,882	1,141	1,150	-	160	9,849
Potassium chloride injections	2,050	917	1,550	326	4,605	-	35	9,483
Metronidazole 500mg injection	610	6,707	193	304	240	-	5	8,059
Ranitidine 50mg / 2mls injections	2,440	2,100	1,733	245	1,173	-	255	7,946
Flucloxacillin 250mg,1g injection	3,092	3,017	1,132	78	203	-	4	7,526
Paracetamol 10mg/ml x 100mls	1,110	2,880	418	363	1,471	-	640	6,882

Medication	Ward							Total
	Disneyland	Fairyland	Wonderland	Paediatric day-care	Rainbow	Paediatric outpatient	Paediatric emergency	
Teicoplanin 200mg injections	1,401	641	511	354	2,992	8	-	5,907
Amoxicillin 250mg , 500mg injection	3,024	1,092	1,291	110	90	-	20	5,627
Ceftazidime 1g injection	1,465	927	360	1,091	1,321	20	-	5,184
Ciprofloxacin 100mg/50ml, 200mg/100ml injection	172	532	42	338	3,975	2	4	5,065
Furosemide 20mg/2ml, 250mg/25ml injection	780	121	2,693	1,382	60	-	-	5,036
Meropenem 500mg, 1g injection	1,209	1,206	487	253	1,267	-	-	4,422
Enoxaparin 10000iu,2000,4000,6000,8000 Injection	266	127	176	2,417	685	-	-	3,671
Clindamycin 300mg / 2ml Injection	980	1,693	220	275	218	5	-	3,391
Aciclovir 250mg Injection	1,906	45	850	-5	237	-	-	3,033
Dexamethasone 8mg/2ml ,4mg/Ml In 1ml Injection	261	203	191	100	1,172	-	1,105	3,032
Chlorpheniramine 10mg/Ml Injection	470	-55	288	215	1,651	-	57	2,626
Midazolam 10mg/5ml Injections	151	1,444	133	487	45	30	25	2,315
Morphine Sulphate 10mg/Ml, 20mg/Ml Injections	40	143	69	-	1,893	4	53	2,202
Vancomycin 500mg Injections	577	1,053	63	10	1	-	-	1,704

Medication	Ward							Total
	Disneyland	Fairyland	Wonderland	Paediatric day-care	Rainbow	Paediatric outpatient	Paediatric emergency	
Adrenaline 1:1000 , 1:10000 Injection IV, IM	504	21	265	428	122	12	310	1,662
Immunoglobulin Normal 5g Iv Injection	395	6	313	724	55	8	-	1,501
Methotrexate 1g/10mL, 50mg/2ml, 5mg/2ml Injection	-	-	-	421	870	171	-	1,462
Infliximab 100mg Injection (Remicade)	52	-	10	1,068	-	48	-	1,178
Benzylpenicillin 1000000 IU Injection	452	200	336	67	-	-	7	1,062
Lidocaine 1% Or 2% Injection, In 20ml Or In 5 mL	284	79	91	171	50	-	289	964
Bumetanide 0.5mg /mL *4mL Injection	-6	-	6	845	-	-	20	865
Amphotericin Liposomal Injections	158	34	56	86	485	-	-	819
Methylprednisolone Succ. 40mg,500mg IV/IM Injection	372	16	239	48	96	-	-	771
Calcium Gluconate Injection	40	82	63	123	380	-	-	688
Hyoscine Butylbromide 20mg Injection	160	135	124	170	20	-	65	674
Clonidine 150mcg/mL Injection	431	27	160	-	40	-	-	658
Glycopyrolate 600mcg/3mL Injection	547	-	85	3	-	-	-	635
Esomeprazole 40mg Inj/Infusion	153	136	171	95	28	-	5	588
Metoclopramide 10mg / 2mls Injection	60	103	132	230	22	-	32	579

Medication	Ward							Total
	Disneyland	Fairyland	Wonderland	Paediatric day-care	Rainbow	Paediatric outpatient	Paediatric emergency	
Diclofenac 75mg Injection	70	5	227	45	20	-	210	577
Pamidronate 15mg Injection	12	-	29	498	-	6	-	545
Sodium Valproate 400mg Injections	261	19	216	-	2	-	10	508
Amikacin 500mg Injection	112	42	2	-	324	-	-	480
Co-Trimoxazole 480mg/5mL Injection	106	297	-	-	55	-	-	458
Imipenem/Cilastatin 500mg Injection	20	259	85	14	80	-	-	458
Vincristine 2mg/2mLs Injections	-	-	-	-	418	-	-	418
Actinomycin -D 500mcg Injections	-	-	-	-	412	-	-	412
Pethidine Hcl 100mg/2mL, 50mg/mL Injections	10	288	10	64	-	-	3	375
Cytosine Arabinase 500mg, 100mg Injection	-	-	-	-	370	-	-	370
Levofloxacin 500mg Injection	10	152	12	159	5	15	-	353
Diazepam 10mg/2mL Injections	132	57	98	9	14	2	29	341
Filgrastim -Gcsf Injection	77	8	0	1	248	1	-	335
Hydroxycobalamin 1mg/2mL Injection	97	105	20	50	15	-	45	332

Medication	Ward							Total
	Disneyland	Fairyland	Wonderland	Paediatric day-care	Rainbow	Paediatric outpatient	Paediatric emergency	
Atropine So4 600mcg Injection	11	157	68	70	-	-	20	326
Acetylcysteine 200mg/mL Injection	245	42	1	-	17	-	20	325
Phytomenadione 10mg, 2mg/0.2mL Injections	64	13	39	70	25	-	70	281
Clarithromycin 500mg Injection	79	9	35	4	145	-	-	272
Omalizumab 150mg Injection	4	-	4	254	-	9	-	271
Aminophylline 250mg Injection	135	-3	102	9	5	-	8	256
Phenytoin Sodium 250mg Injections	132	-	96	-	1	-	23	252
Prochlorperazine 12.5mg/mL Injections	40	50	10	40	40	-	35	215
Glucagon 1mg Injection	26	-	29	140	-	1	12	208
Aspariginase (Crisantaspass) 10,000 Units Injection	-	-	-	-	186	-	-	186
Fentanyl injections x2mL (50mcg/mL)	-	75	-	3	100	-	5	183
Promethazine 25mg/mL Injections	10	-	-	20	70	-	75	175
Etoposide 100mg Injection	-	-	-	-	173	-	-	173
Tobramycin 40mg/Ml (80mg/2ml) Injections	150	-	16	-	-	-	-	166

Medication	Ward							Total
	Disneyland	Fairyland	Wonderland	Paediatric day-care	Rainbow	Paediatric outpatient	Paediatric emergency	
Haloperidol (5mg Or 50mg) Injection	6	-	4	134	-	18	-	162
Clonazepam 1mg/mL Injections	42	-	119	-	-	-	-	161
Intralipid Fat Emulsion 20% *100mls, 500ml Injection	38	29	89	-	-	-	-	156
Tranexamic Acid 500mg/5mL Injections	22	48	5	27	52	-	_	154
Urokinase 10,000 Or 50,000 Iu Injections	78	2	14	23	26	4	-	147
Gonadorelin -Lhrh 100mcg Injection	1	-	4	136	-	3	-	144
Anti Haemophiliac Factor 8 500iu,1000u	34	84	8	-	-	-	-	126
Mesna 100mg/mL In 10ml Injection	-	-	-	-	120	-	-	120
Multivitamins Injection Pabrinex	20	-	-	90	-	-	10	120
Vitalipid N Infant Injections	-	-	115	-	-	-	-	115
Levetiracetam 100mg/mL x 5mL injection	64	-	49	-	-	-	-	113
Fluconazole 2mg/mL In 100mL Injection	60	42	2	4	-	-	-	108
Erythromycin 1g Injection	50	14	19	20	-	-	-	105
Flecainide 150mg/15mL Injection	-	-	3	-	-	-	100	103

Medication	Ward							Total
	Disneyland	Fairyland	Wonderland	Paediatric day-care	Rainbow	Paediatric outpatient	Paediatric emergency	
Calcium Folinate 50mg/5mL Injection	8	-	34	-	60	-	-	102
Dacarbazine 200mg Injection	-	-	-	_	99	-	-	99
Aztreonam 1g, 2g Injection	43	54	-	-	-	-	-	97
Naloxone 400mcg/1mL Injection	7	12	-1	17	20	-	40	95
Flucytosine 2.5g Injection	46	45	-	-	-	-	-	91
Propofol 10mg/mL X 20mL Injections	5	-15	-	1	85	-	15	91
Dipyridamole 10mg/2mL Injection	-	-	90	-	-	-	-	90
Salbutamol 5mg/5mL Injections	-	2	28	25	-	-	30	85
Carnitine 1g/5mL Injection	16	21	44	-	-	-	-	81
Vinblastine 10mg Injections	-	-	-	-	77	-	-	77
Doxorubicin 10mg, 50mg Injection	-	-	-	-	76	-	-	76
Adenosine 6mg Injection	13	-	3.2	8	-	-	50	74.2
Omeprazole 40mg Injection For IV Use	4	33	20	-	-	-	15	72
Ganciclovir 500mg Injection	1	-	-	1	69	-	-	71

Medication	Ward							Total
	Disneyland	Fairyland	Wonderland	Paediatric day-care	Rainbow	Paediatric outpatient	Paediatric emergency	
Rasburicase 1.5mg, 7.5mg Injection	-	-	-	-	70	-	-	70
Magnesium Sulphate 20%, 50% In 10mL Injection	15	5	-1	9	30	-	9	67
Colistimethate Sodium (Colistin Sulphomethate) 1000000 Injection	66	-	-	-	-	-	-	66
Amiodarone 50mg/mL Injection	6	3	7	33	4	-	12	65
Sodium Fusidate 500mg Injections	-	43	-	20	-	-	-	63
Hyoscine Hydrobromide 400mcg Injection	-	-	-	-	60	-	-	60
Rituximab 100mg, 500mg Injections	6	-	6	18	30	-	-	60
Iron Sucrose 20mg/mL Injection	31	-	-	28	-	-	-	59
Procyclidine 10mg/2mL Injections	25	-	7	2	10	-	14	58
Bupivacaine 0.25%, 0.5% Injection	-	-	-	10	40	-	-	50
Atracurium 25mg Injection	-	-	-	-	25	-	25	50
Caspofungin 50mg,70mg Injection	-	52	-	-	-3	-	-	49
Dehydrated Alcohol Injection	-	-	40	8	-	-	-	48
Erythropoetin 500,2000,3000, 4000 IU Prefilled IV/SS	40	-	5	-	-	-	-	45

Medication	Ward							Total
	Disneyland	Fairyland	Wonderland	Paediatric day-care	Rainbow	Paediatric outpatient	Paediatric emergency	
Mivacurium 2mg/mL Injection	-	-	-	-	15	-	30	45
Daunorubicin 20mg Injection	-	-	-	-	42	-	-	42
Tetracosactide (Tetracosactrin) Inj 250mcg	3	-	15	22	-	1	-	41
Ifosphamide 2g Injection	-	-	-	-	37	-	-	37
Carboplatin 150mg/15mL Injection	-	-	-	-	35	-	-	35
Flumazenil 0.5mg/5mL Injection	8	10	6	-2	10	-	-	32
Anti Haemophiliac Factor 9 (Replenine) 500 IU	31	-	-	-	-	-	-	31
Chlorpromazine 50mg/2mL Injection	-	26	-	5	-	-	-	31
Hydralazine 20mg Injection	5	-	25	-	-	-	-	30
Etomidate 20mg Injection	-	4	2	-1	10	-	15	30
Vecuronium Bromide 10mg Injections	2	-	-	-1	10	-	17	28
Biphasic Isophane Insulin Injection	3	-	4	17	1	1	1	27
Erythropoetin Beta 500iu	-	-	26	-	-	-	-	26
Chloramphenicol 1g Injection	-	2	-	20	-	-	-	22

Medication	Ward							Total
	Disneyland	Fairyland	Wonderland	Paediatric day-care	Rainbow	Paediatric outpatient	Paediatric emergency	
Cyclizine 50mg Injections	-	-	-	-	10	10	-	20
Desmopressin 4mcg/mL Injection	1	2	1	16	-	-	-	20
Phenobarbital 200mg/mL, 30mg/mL Injections	15	-	-	1	-	-	3	19
Gemcitabine 1000mg Injection	-	-	-	-	18	-	-	18
Rifampicin 600mg/10mL Injections	2	15	-	-	-	-	-	17
Testosterone Depot 100mg Injections, 50mg/mL X 2mL Injections	-	8	2	6	-	-	-	16
Dopamine 200mg /5mL Injection	-1	-1	9	-2	-	-	10	15
Azacitidine 100mg Sc Injection	-	-	-	-	14	-	-	14
Interferon Gamma Injection Recombinant	6	-	-	6	-	-	-	12
Pentamidine 300mg Injections	-	-	-	-	12	-	-	12
Ketamine 10mg/mL X 20mL Injections	2	-	-	1	-	-	9	12
Neostigmine 2.5mg/mL Injection	-	-	1	-	10	-	-	11
Carboprost 250mcg/mL Injection	10	-	-	-	-	-	-	10
Doxapram 100mg Injection	-	-	-	-	10	-	-	10

Medication	Ward							Total
	Disneyland	Fairyland	Wonderland	Paediatric day-care	Rainbow	Paediatric outpatient	Paediatric emergency	
Lorazepam 4mg/mL Injections	-	-	5	2	-	-1	4	10
Dobutamine 250mg / 20mL Injection	3	-2	3	1	-	-	5	10
Ephedrine 30mg Injection	-	-	-	-	-	-	10	10
Anakinra 100mg/0.67ml Prefilled Syringes	9	-	-	-	-	-	-	9
Cisplatin 50mg Injection	-	-	-	-	8	-	-	8
Palivizumab 50mg, 100mg IM	-	-	-	-	-	8	-	8
Iloprost 100mcg Injection	7	-	-	-	-	-	-	7
Atenolol 500mcg/ Injection	-	2	3	-	1	-	-	6
Doxycycline 100mg Injection	-	6	-	-	-	-	-	6
Isoprenaline 200mcg/Ml Injection	-	5	-	-	-	-	-	5
Aspirin 500mg Injection	-	4	-	-	-	-	-	4
Colecalciferol 300 IU Oral Solution X 100mL	-	-	4	-	-	-	-	4
Dextran 40,70 In Normal Saline Injection	-	4	-	-	-	-	-	4
Ertapenem 1g Powder For Solution For Infusion	-	-	-	-	-	4	-	4

Medication	Ward							Total
	Disneyland	Fairyland	Wonderland	Paediatric day-care	Rainbow	Paediatric outpatient	Paediatric emergency	
Insulin Aspart 100 IU/mL Injection	4	-	-	-	-	-	-	4
Mitoxantrone 20mg Injection	-	-	-	-	4	-	-	4
Bleomycin 15000 IU Injection	-	3	-	-	-	-	-	3
Digoxin 0.5mg Injection	-	2	1	-	-	-	-	3
Glyceryl Trinitrate 5mg/mL In 10mL Injection	3	-	-	-	-	-	-	3
Labetolol 5mg/mL X 20ml Injection	1	2	-	-	-	-	-	3
Methylthioninium Chloride (Methylene Blue) Injection	-	3	-	-	-	-	-	3
Benzathine Penicillin 1.2million Units Injection	-	-	-	-	-	1	1	2
Thiopental 0.5g Injections	-	-	1	-1	-	-	2	2
Edrophonium 10mg Injection	1	-	-	-	-	-	-	1
Erythropoetin Zeta 1000i.E. In 0.3mls Prefiled	-	-	1	-	-	-	-	1
Etanercept 25mg Prefilled Syringe	1	-	-	-	-	-	-	1
Feiba - Factor 8 Inhibitor Bypassing Fraction 500iu Or 1000 Iu	-	1	-	-	-	-	-	1
Insulin Glargine 100iu/Ml Injection	1	-	-	-	-	-	-	1
Isophane Insulin Cartridge -Humulin I	-	-	-	-	-	1	-	1
Verapamil 5mg / 2mls Injections	-2	-2	-1	-1	-	-	-	-6

Appendix 8 -Quanitites of Consumption per Ward for the selected sample (2007-2016)

Medication	Ward							Total
	Disneyland	**Fairyland**	**Wonderland**	**Paediatric day-care**	**Rainbow**	**Paediatric outpatient**	**Paediatric emergency**	
Cefotaxime 1g injection	14,168	1,324	8,413	37	86	-	7	24,035
Co-amoxiclav 600mg, 1.2g injection	9,165	7,367	5,475	1,428	391	-	97	23,923
Cefuroxime 250mg, 750mg injection	5,028	8,155	3,446	466	548	-	35	17,678
Tazobactam e` Piperacillin 2.25g, 4.5g injections	1,936	1,575	972	3,117	6,571	30	12	14,213
Ceftriaxone 500mg, 1g injection, 2g inject,	4,584	2,364	1,947	2,316	290	-	1	11,502
Ondansetron 4mg, 8mg injection	366	196	225	21	10,054	-	242	11,104
Gentamicin 80mg injection	1,769	2,398	1,045	1,452	3,688	20	10	10,382
Hydrocortisone 100mg injection	4,266	250	2,882	1,141	1,150	-	160	9,849
Potassium chloride injections	2,050	917	1,550	326	4,605	-	35	9,483
Metronidazole 500mg injection	610	6,707	193	304	240	-	5	8,059
Ranitidine 50mg / 2mls injections	2,440	2,100	1,733	245	1,173	-	255	7,946
Flucloxacillin 250mg,1g injection	3,092	3,017	1,132	78	203	-	4	7,526
Paracetamol 10mg/ml x 100mls	1,110	2,880	418	363	1,471	-	640	6,882
Teicoplanin 200mg injections	1,401	641	511	354	2,992	8	-	5,907
Amoxicillin 250mg , 500mg injection	3,024	1,092	1,291	110	90	-	20	5,627
Ceftazidime 1g injection	1,465	927	360	1,091	1,321	20	-	5,184
Aciclovir 250mg Injection	1906	45	850	-5	237	0	0	3033
Benzylpenicillin 1000000iu Injection	452	200	336	67	0	0	7	1062
Amphotericin Liposomal Injections	158	34	56	86	485	0	0	819
Clarithromycin 500mg Injection	79	9	35	4	145	0	0	272

Appendix 9- Drug Monographs First Draft

NAME OF MEDICATION	ACICLOVIR
STRENGH / TRADE NAME / MANUFACTURER	Each vial contains 250mg of Aciclovir as the sodium salt- Wockhardt UK Ltd
CLASSIFICATION	Antiviral agent

INDICATIONS FOR USE

-Treatment of Herpes simplex infections in neonate and infant up to three months of age , in immunocompromised patients and severe initial genital herpes in the non-immunocompromised.
-Prophylaxis of Herpes simplex infections in immunocompromised patients.
-Treatment of Varicella zoster infections.
-Treatment of herpes encephalitis.

RECONSTITUTION and DILUTION

Aciclovir 250mg for infusion should be reconstituted using 10ml of either WFI or NS IV Infusion to provide a solution containing 25mg aciclovir per ml. To reconstitute each vial add the recommended volume of infusion fluid and shake gently until the contents of the vial have dissolved completely. The reconstituted solution appears light yellow and slightly opalescent. It may be further diluted on the basis of 4ml (100mg aciclovir) reconstituted solution added to 20 ml of infusion fluid to give aciclovir concentration of not greater than 5 mg/ml (0.5% w/v). For dilution, add the required volume of reconstituted solution to the chosen infusion solution, and shake well to ensure adequate mixing occurs.

METHOD OF ADMINISTRATION

-The required dose of aciclovir for infusion should be administered by slow IV infusion over a one-hour period. Rapid IV administration and administration by other routes must be avoided.
-After reconstitution aciclovir for infusion may be administered by a controlled-rate infusion pump. It can be further diluted to a concentration of not greater than 5 mg/ml (0.5% w/v) for administration by infusion.

DOSAGE

For children aged between three months and 12 years the dose is calculated on the basis of body surface area.
In neonates and infants up to three months of age the dose is calculated on the basis of BW.

Indication	Age	Dose
Herpes Simplex infections	Birth to 3 months of age	30-60 mg/kg/day divided q 8 hr for 10-21 day. 20 mg/kg every 8 hours for 10-14 days (for at least 21 days if disseminated disease and CNS disease).
	3 months to 12 years	60 mg/kg/day divided q 8 hr for 10-21 days; some experts recommend 45 mg/kg/day divided q 8 hr for 14-21 days. 250 mg/m2 every 8 hours usually for 5 days or 500mg/m2 in immunocompromised and given for at least 21 days in encephalitis.
	12-17 years	5 mg/kg every 8 hours for 5 to 7 days or 10mg/Kg in immunocompromised for at least 14 days in encephalitis.
Zoster infections	Birth to 3 months	10-20mg/Kg every 8 hours for at least 7 days, or for 10-14 days if encephalitis.
	3 months to 12 years	250 mg/m2 every 8 hours usually for 5 days or 500mg/m2 for 5 days if immunocompromised given for 10 to 14 days in encephalitis and possibly longer if immunocompromised and encephalitis. 10–20 mg/kg every 8 hours for at least 7 days.
	12 -17 years	5 mg/kg every 8 hours given for 5 days , or 10mg/Kg for 5-7 days if immunocompromised and given for 10–14 days in encephalitis.

COMPATIBILITIES AND STABILITY
-**When diluted in accordance with the recommended schedules, aciclovir for infusion is known to be compatible with the following infusion fluids: NS, D5W, D5NS, NS 0.45%.** -Incompatible with Dobutamine, Dopamine, Foscarnet, Meropenem, Morphine, Phenytoin, Piperacillin with Tazobactam, Tacrolimus. -Intact vials of aciclovir sodium should be stored at controlled room temperature. The reconstituted solution should be used within 12 hours at 25°C if **not used immediately and not be longer than 24 hours at 2-8°C.** -Refrigeration of the reconstituted solution may cause a precipitate, but this precipitate will dissolve at room temperature, apparently without affecting potency.
POTENTIAL HAZARDS OF ADMINISTRATION
-Hypersensitivity reactions, including maculopapular rash and itching, anaphylaxis and angioedema have been associated with the use of aciclovir. -The most frequent adverse effects of IV acyclovir are local reactions at the injection site with inflammation and phlebitis. These reactions, including tissue necrosis, can occur following infusion of acyclovir into extravascular tissues. It is recommended to rotate infusion site. -Other undesirable effects include Headache, nausea, vomiting, rash, pruritus, urticaria and reversible increase in liver enzymes. -**Inadequate hydration or too-rapid administration can cause crystalluria, renal tubular damage and acute renal failure.**
MISCELLANEOUS
-Maintain adequate hydration and urine output before and during infusion. -Monitor urinalysis, BUN, serum creatinine, CBC, renal and liver function tests. -In case of overdose, Aciclovir crystals may precipitate in renal tubules and the maximum urine concentration occurs within the first few hours of infusion; therefore, adequate urine flow during that period (with good hydration) should be ensured. -Renal impairment is usually reversible and is reported to respond to hydration and/or dosage reduction or withdrawal, but may progress to acute renal failure. -Cross-sensitivity to famciclovir and to the prodrug valaciclovir may occur.
REFERENCES
1, 2,3, 4,5,7,13, 23,24,28,31,38,39,40

NAME OF MEDICATION	AMOXICILLIN
STRENGH / TRADE NAME / MANUFACTURER	250mg powder for solution for injection or infusion/Bowmed Ibisqus 500 mg powder for solution for injection / Wockhardt
CLASSIFICATION	Antibiotic-Aminopenicillin

INDICATIONS FOR USE

- Treatment of susceptible infections (**including urinary-tract infections**, **otitis media**, **sinusitis**, **uncomplicated CAP**, salmonellosis, **oral infections**)
- Prohylaxis and treatment of Bacterial Endocarditis Prophylaxis
- **Lyme Disease localized or early disseminated.**
- Skin and Skin Structure Infections including cutaneous anthrax caused by susceptible microorganisms.
- **Treatment of meningitis and bacteraemia associated with above infections.**
- Treatment of Cystic fibrosis (treatment of asymptomatic H.inf carriage or mild exacerbation).
- **Severe dental abscess with spreading cellulites.**

RECONSTITUTION and DILUTION

IV injection:

- Reconstitute 250mg vial with 5mL WFI (final volume 5.2 mL). Displacement value 0.2mL. For Dilution dilute up to 10mL using NS, D5W, and D10W.
- Reconstitute each 500-mg vial with 10 mL WFI (final volume 10.4 mL). Displacement value 0.4mL. For dilution dilute up to 20mL using NS, D5W, and D10W.

For neonates : reconstitute 250mg vial with 2.3mL WFI and 500mg vial with 4.6mL WFI to give a concentration of 100mg/mL.

IV infusion:

- Add the 250mg reconstituted solution as prepared above to 50mL of infusion fluid.
- Add the 500mg reconstituted solution as prepared above to 100mL of infusion fluid.

IM injection

- Add 1.5 mL WFI and shake vigorously (final volume 1.7 mL).
- Add 2.5 mL WFI and shake vigorously (final volume 2.9 mL).

METHOD OF ADMINISTRATION

IV injection (doses less than or equal to 30mg/kg) over 3-4 minutes directly into a large vein or infusion line.
IV infusion (doses over 30mg/kg) over 30-60 minutes for children into the drip tubing.
IV infusion over 30 minutes via syringe pump for neonates. Use a 'Category A therapy' infusion pump.
IM injection within 30 min of reconstitution.
Preferably administer via a central venous access, if unavailable use a large peripheral vein.

DOSAGE

Treatment of susceptible infections (including urinary tract infections, otitis media, sinusitis, uncomplicated CAP, salmonellosis and oral infections.

- Neonate up to 7 days
  - (i) 30 mg/kg every 12 hours, increased if necessary to 60 mg/kg every 12 hours, increased dose used in severe infection, CAP or salmonellosis.
  - (ii) If less than 4 Kg: 20 to 100 mg/kg/day given in 2 equally divided doses of up to 25 mg/kg or infusions of up to 50 mg/kg.
- Neonate 7 to 28 days :25-30 mg/kg every 8 hours, increased if necessary to 50-60 mg/kg every 8 hours, increased dose used in severe infection, CAP or salmonellosis.
- Child: 20–30 mg/kg every 8 hours (max. per dose 500 mg), increased if necessary to 40–60 mg/kg every 8 hours (max. per dose 1 g every 8 hours), increased dose used in severe infection.

Listerial meningitis and Enterococcal endocarditis (in combination with another antibiotic)

- Neonate up to 7 days: 50–100 mg/kg every 12 hours.
- Neonate 7 to 28 days: 50–100 mg/kg every 8 hours.
  Child: 50 mg/kg every 4–6 hours (max. per dose 2 g every 4 hours).

Lyme disease

- Neonates up to 3 months to children <40 Kg

(i) Early stage: 25 to 50 mg/kg/day in three divided doses for 10 days (range 10 to 21 days)
(ii) Late stage (systemic involvement): 50 mg/kg/day in two divided doses
(iii)For premature neonates <4 Kg (in two divided doses).

Bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed

- Neonates up to 3 months to children <40 Kg

(i) Usual daily dose of 50 to 150 mg/kg/day given in 3 equally divided doses of up to 25 mg/kg or infusions of up to 50 mg/kg.
(ii) For premature neonates <4 kg in two divided doses).

COMPATIBILITIES AND STABILITY
Compatible with: WFI, NS, D5W, D5NS. Sodium lactate, Ringer sodium lactate, Ringer NaCl. Flush with NS or D5W. **Incompatible** with: D5W, KCL, Ciprofloxacin, Impinem-Cilastatin, Midazolam. Ringer Lactate Solution and Sodium Bicarbonate. **If used in combination with an aminoglycoside (e.g. amikacin, gentamicin, tobramycin), preferably administer at a different site.** If this is not possible then flush the line thoroughly with a compatible solution between drugs. **Amoxicillin is less stable in infusions containing carbohydrate.** **Reconstituted vials should be used immediately**. **Prepared infusions should be used immediatel**y; however, they may be stored at 2–8°C and infused (at room temperature) within 24 hours.
POTENTIAL HAZARDS OF ADMINISTRATION
-Infusion-related adverse events: nausea, vomiting, hypersensitivity reactions including rash (urticarial, erythematous, morbilliform), fever, joint pain and angioedema. - Extravasation may cause tissue damage due to high pH. **-Convulsion in patients with impaired renal function or in those who receive high doses or in patients with predisposing factors (e.g. history of seizures, treated epilepsy or meningeal disorders.**
MISCELLANEOUS
- Monitor: RFT periodically, reaction at the site of lesions. **-Sodium content: 3.3 mmol sodium per gram.** **-Risk of crystalluria with high doses and reports of precipitation in bladder catheters.** **- Maintain adequate fluid intake and urinary output.** **-Amoxicillin can be removed by haemodialysis.** -Lidocaine or benzyl alcohol may be used only when administering amoxicillin by the IM route if it is painful.
REFERENCES
SPC, 1,4,6,7,8,13,23,24,28,40

NAME OF MEDICATION	**Amphotericin B Liposomal**
STRENGH / TRADE NAME / MANUFACTURER	50mg (50 000IU) amphotericin encapsulated in liposomes, powder for solution for infusion for IV only/ Ambisome®/ Gilead Sciences International Ltd
CLASSIFICATION	Polyene antifungal

INDICATIONS FOR USE

- Treatment of severe systemic fungal infections; endocarditis, meningitis, peritonitis, or severe respiratory tract infections
- The empirical treatment of presumed fungal infections in febrile neutropenic patients, where the fever is resistant to treatment with broad spectrum antibiotics and appropriate investigations excluded bacterial or viral cause.
- Treatment of visceral leishmaniasis in immunocompetent patients. AmBisome should not be used to treat the common clinically inapparent forms of fungal disease which show only positive skin or serologic tests.

RECONSTITUTION and DILUTION

Reconstitute each 50mg vial with 12mL sterile WFI (without a bacteriostatic agent). Immediately shake the vial vigorously for 30s to completely disperse; resultant preparation contains 4mg/mL. The resultant solution is yellow and translucent, visually inspect for particulate matter & continue shaking if necessary.

Withdraw the required dose & add (via the 5micron filter provided) to a suitable volume of D5W or D10W to give a solution of concentration 0.2 – 2mg/mL.

The infusion solution is obtained by dilution of the reconstituted AmBisome with between one (1) and nineteen (19) parts of D5W, D10W for infusion by volume, to give a final concentration in the recommended range 0.2 mg/mL to 2 mg/mL amphotericin e.g if the required dose is 30 mg then 7.5 mL of the reconstituted Ambisome will provide this dose. It can be further diluted by adding 142.5 mL of D5W up to a final volume of 150 mL to provide a concentration of 0.2 mg/mL (1 in 20 dilution) OR 7.5 mL of D5W added up to final volume of 15 mL to provide a concentration of 2mg/mL (1 in 2 dilution).

The volume of D5W for the final infusion will also depend on the individual fluid requirements, e.g. doses of less than 100mg/day can be diluted with 100mL D5W; doses between 100mg – 500mg can be diluted with 250 – 500mL D5W

METHOD OF ADMINISTRATION

IV infusion over a 30 - 60 minute period. For doses greater than 5mg/kg/day, IV infusion over a 2 hour period is recommended. *Initial test dose (prior to first dose only):* give 1mg *by IV infusion over 10min via a volumetric infusion device*; stop infusion for 30min & observe patient carefully for signs of allergic reactions; if no adverse effects are seen give the remainder of the infusion. Stop the infusion immediately if severe allergic reaction occurs at any point during administration. If the patient experiences discomfort, the infusion can be given more slowly, e.g. over 2 hours.

Flush the existing IV line with D5W prior to and after administration (or use separate line).

DOSAGE

Indication	Age	Dose
Severe systemic or deep mycoses. Suspected or proven infection in febrile neutropenic patients unresponsive to broad-spectrum antibacterials	Neonates	1 mg/kg once daily, increased if necessary to 3 mg/kg once daily; max 5 mg/kg per day.
	Child	Test dose 100 mcg/kg (max. per dose 1 mg), to be given over 10 minutes, then 3 mg/kg once daily; max 5 mg/kg per day.
Visceral leishmaniasis (unresponsive to the antimonial alone)	Child	1–3 mg/kg daily for 10–21 days to a cumulative dose of 21–30 mg/kg, alternatively 3 mg/kg for 5 consecutive days, followed by 3 mg/kg after 6 days for 1 dose.

Renal impairment: No dose adjustment is required. If clinically significant reduction in renal function or worsening of other parameters occurs, consideration should be given to dose reduction, treatment interruption or discontinuation.

Hepatic Impairment: No data are available on which to make a dose recommendation for patients with hepatic impairment.

COMPATIBILITIES AND STABILITY

Incompatible with: NS & all electrolyte solutions; most drugs; care must be taken to avoid inadvertent contact in infusion lines.

Compatible with: D5W, D10W.

Do NOT mix AmBisome with other drugs or electrolytes.

Stability after preparation: should be used immediately, however reconstituted vials are single use only but may be stored at 2 – 8°C for 24hours or less at the responsibility of the user; prepared infusions may be stored at 2 – 8°C & infused (at room temperature) within 24hours.

Store below 25°C in original packaging. Do not freeze.

POTENTIAL HAZARDS OF ADMINISTRATION
Avoid rapid infusion (risk of arrhythmias); when given parenterally, toxicity common (close supervision necessary & close observation required for at least 30min after test dose). *Immediate:* anaphylactoid reactions. Stop infusion immediately in cases of severe anaphylactic reaction. *Infusion-related:* local: pain & thrombophlebitis at injection site .Fever and chills/rigors chest tightness or pain, dyspnoea, bronchospasm, flushing, tachycardia, hypotension and musculoskeletal pain. These resolve when infusion is discontinued and may not occur with every subsequent dose. Slow infusion rate can prevent their occurrence. (Can be prevented by premedication). Other side effects: Headache, hyperglycaemia, hypokalaemia, hyponatremia, hyperbilirubinaemia, tachycardia, hypocalcaemia .
MISCELLANEOUS
Amphotericin is available in various commercial forms & these preparations are NOT interchangeable. They each have specific instructions for reconstitution, test dosing (to check for potential anaphylaxis) & dosing. Monitor: renal function & serum Mg and k – daily initially, then 2 – 3 times weekly; LFTs & FBC – weekly; observe with each infusion for chills, fever, rigor, nausea & other infusion-related reactions. Monitor cardiac function if used concurrently with corticosteroids. Concomitant administration of nephrotoxic drugs or anti-neoplastics should be avoided. The hypokalaemia following amphotericin B therapy may potentiate the toxicity of digoxin; corticosteroids & corticotrophin (ACTH) may ↑K loss due to amphotericin B Appropriate potassium supplementation may be required during the course of AmBisome administration if there is a risk of hypokalaemia. Amphotericin liposomal (Ambisome®) reconstituted with WFI (4mg/mL) has a pH of 5 to 6.
REFERENCES
1, 4,7, 8, 13, 24,28,31,39,40

NAME OF MEDICATION	BENZYLPENICILLIN SODIUM
STRENGH / TRADE NAME / MANUFACTURER	Each vial contains 1,000,000 U of Benzylpenicillin sodium (equivalent to 600mg) as powder for solution for injection/Cooper
CLASSIFICATION	Antibiotic-Penicillin

INDICATIONS FOR USE

- Most wound infections, pyogenic infections of the skin, soft tissue infections and infections of the nose, throat, nasal sinuses, respiratory tract and middle ear, etc.[13,24,28,31]
- Infections caused by penicillin-sensitive microorganisms: Generalised infections, septicaemia from susceptible bacteria. Acute and chronic osteomyelitis, sub-acute bacterial endocarditis and meningitis caused by susceptible organisms. Suspected meningococcal disease. [13,24,28,31]

RECONSTITUTION and DILUTION

IM injection: 1 vial 1.000.000 I.U. (=600 mg) is usually dissolved in 1.6 to 2.0 ml of WFI. If using part of a vial add 2 mL WFI or NS to the vial.
IV Injection: 1 vial 1.000.000 I.U. (=600 mg) dissolved in 4 to 10 ml of WFI or NS. Can be further diluted with NS, WFI, D5W. If using part of a vial add 3.6 mL WFI or NS to each vial.
IV Infusion: 1 vial 1.000.000 I.U. (=600 mg) should be dissolved in at least 10 ml NS or WFI.
IV infusion via a syringe pump:
For continuous IV infusion, reconstituted solutions of penicillin G potassium or sodium generally should be added to 1–2 L of a compatible IV solution.

METHOD OF ADMINISTRATION

IM: doses ≤100,000 units/mL can be administered through this route.
IV injection: doses ≤1.2 g administer slowly over 3-5 minutes. For doses greater than 1.2 g max rate of administration is 300mg/min.
IV infusion: doses over 1.2 g (50mg/Kg) administer over 30-60 min.
IV push not recommended. Rapid administration of large doses may cause electrolyte imbalances due to the potassium content. Sensitization may be increased with continous infusion over 6-24 hours.
Alternate sites should be used for repeated injections
The max. concentration recommended for peripheral administration is 600mg in 10mL; higher concentrations are irritant due to high osmolality and may cause tissue damage if extravasation occurs. If a higher concentration is needed a central line should be used for administration. If extravasation occurs, refer to local treatment guidelines.

DOSAGE		
Indication	**Age**	**Dose**
Throat infections Otitis media Cellulitis Pneumonia By IM injection, or by slow IV injection, or by IV infusion. IV route recommended in infants and neonates.	Neonate up to 7 days	25 mg/kg every 12 hours; increased if necessary to 25 mg/kg every 8 hours.
	Child 7 days–28 days	25 mg/kg every 8 hours; increased if necessary to 50 mg/kg every 8 hours in severe infection.
	Child	25 mg/kg every 6 hours; increased if necessary to 50 mg/kg every 4–6 hours (max. per dose 2.4 g every 4 hours) in severe infection.
Endocarditis (in combination with another antibacterial if necessary)	Child	By slow IV injection, or by IV infusion 25 mg/kg every 4 hours; increased if necessary to 50 mg/kg every 4 hours (max. per dose 2.4 g every 4 hours).
Meningococcal disease	Neonate up to 7 days	50 mg/kg every 12 hours.
	Child 7 days–28 days	50 mg/kg every 8 hours.
	Child 1 month-1 year	50 mg/kg every 4–6 hours (max. per dose 2.4 g every 4 hours).
	Children over 12 years	2.4 g every 4 hours.
Suspected meningococcal disease single dose prior to urgent transfer to hospital so long as does not delay transfer.	Child 1-11 months	300 mg IV or IV.
	Child 1-9 years	600 mg IV or IM.
	Child 10-17 years	1,200 mg IV or IM.

Dose adjustment:

- In premature babies/infants: Dosing should not be more frequent than every 8 or 12 hours in this age group, since renal clearance is reduced at this age.
- Renal impairment:
- For doses of 0.6-1.2 g (1-2 vials) the dosing interval should be no more frequent than every 8 to 10 hours.
- Hepatic impairment:
- Dose of 300mg should be reduced to every 8 hours if liver failure is associated with severe renal failure.
- If haemodialysis is required, an additional dose of 300 mg (0.5 vials) should be given 6 hourly during the procedure.

COMPATIBILITIES AND STABILITY

Incompatible with: Amphotericin B, aminophylline, cimetidine, cytarabine, flucloxacillin, hydroxyzine, methylprednisolone promethazine and solutions containing metal ions. Benzylpenicillin sodium and solutions that contain metal ions should be administered separately.
Reconstituted product should be used immediately, if not the product would not be stable more than 24 hours at 2 to 8^0C.
Compatibilities: NS, D5W.

POTENTIAL HAZARDS OF ADMINISTRATION

- Hypersensitivity to penicillin in the form of rashes (all types); fever, anaphylaxis, angioedema, serum sickness. Observe for 30 min after administration if an allergic reaction occurs withdraw the drug and give treatment. These may be treated with antihistamines.
- Diarrhoea, urticaria, joint pain. Large doses can cause hypokalaemia and hypernatraemia.
- Patients treated for syphilis or neurosyphilis may develop a Jarisch–Herxheimer reaction (occurs 2–12 hours after initiation of therapy – headache, fever, chills, sweating, sore throat, myalgia, arthralgia, malaise, ↑pulse and ↑BP followed by a ↓BP. Usually subsides within 12–24 hours. Corticosteroids may ↓incidence and severity).
- Neurotoxic effects (e.g., lethargy, confusion, twitching, seizures) may occur with large doses, especially in patients with renal insufficiency.

MISCELLANEOUS

- 1 vial of benzylpenicillin contains 1.68 mmol of sodium. Massive doses of Benzylpenicillin sodium can cause hypokalaemia and sometimes hypernatraemia.
- Displacement value is 0.4mL.
- Monitor CBC, renal function test, LFT, electrolyte balance in patients undergoing high-dose treatment.
- Intrathecal injection of benzylpenicillin is not recommended.
- Avoid reconstitution in sodium containing liquids such as NS Injection or Ringer's solution in patients with heart failure, renal failure or sodium overload.
- Penicillins may interfere with: Urinary glucose test, coomb's tests, tests for urinary or serum proteins, tests which use bacteria e.g. Guthrie test.

REFERENCES

1,4,7,8,13,24,28,31,39,40

NAME OF MEDICATION	CEFTRIAXONE
STRENGH / TRADE NAME / MANUFACTURER	Each vial contains 1g of Ceftriaxone as powder for solution for injection- Wockhardt UK Ltd, Fresenius Kabi Each vial contains 500mg Ceftriaxone as sterile crystalline powder in glass vial, Hospira.
CLASSIFICATION	Antibiotic-Cephalosporin

INDICATIONS FOR USE

-Treatment of pneumonia(HAP, CAP).
-Peri-operative prophylaxis associated with surgery.
-Treatment of septicaemia, infections in neutropenic patients.
-Treatment of meningitis, gonorrhoea.
-Treatment of complicated skin and soft tissue infections , infections of bone and joints.
-Treatment of intra-abdominal infections , complicated urinary tract infections.
-Disseminated Lyme borreliosis (early [Stage II] and late [Stage III])
Treatment may be started before the results of susceptibility tests are known, Consideration should be given to official guidance on the appropriate use of antibacterial agents.

RECONSTITUTION and DILUTION

Powder for solution for injection (Powder for injection). White to pale yellow crystalline powder.
IV injection: Reconstitute each 1g vial with 10mL water for injections. Final volume of reconstitution is 10.8 mL.
500mg ceftriaxone should be reconstituted in 4.8 mL of water for injections.
IM injection: 1g ceftriaxone should be dissolved in 3.5mL of 1% Lidocaine injection BP.
500mg ceftriaxone should be reconstituted in 1.8 mL of water for injections.

The reconstituted solution should be clear. Do not use if particles are present.
1 g vial has displacement volume of 0.8 mL.
Ceftriaxone should not be mixed in the same syringe with any drug other than 1% Lidocaine Injection BP (for IM injection only).
Max concentration for IV administration is 40mg/mL and 350 mg/mL for IM use.

METHOD OF ADMINISTRATION

Doses of 50mg/kg or over should be given by slow intravenous infusion over at least 30 minutes. IV administration in neonates is recommended to be over 60 min. [4] Doses greater than 80mg/kg body weight should be avoided because of the increased risk of biliary precipitates.
IV injection: Give doses of 1g slowly over 2-5 minutes directly into a vein preferably into a large vein [7] or via the tubing of an IV infusion. Doses of 2g or higher over at least 30 minutes. Doses of 4g may be given by administering 2 x 2g infusion vials back-to-back, by adding the total dose to an infusion bag, or by giving 2g twice a day. [7]
-In the neonate, the IV dose should be given over 60 minutes to reduce the displacement of bilirubin from albumin, thereby reducing the potential risk of bilirubin encephalopathy.
Intermittent infusion 10-40 mg/mL infused over 30 minutes. [39]
Max concentration 40 mg/mL for IV administration and 350 mg/mL for IM use. [39]
IM injection: Administered by deep IM injection. Doses greater than 1g should be divided and injected at more than one site.

DOSAGE

Renal impairement: no need to reduce the dosage provided hepatic function is not impaired. Only in cases of pretermial renal failure(CrCl <10mL/min) dosage should not exceed 2g daily. [8,24,31]
Monitor serum levels to avoid accumulation in severe renal failure. [24]
Hepatic impairment: dosing adjustment is not required if the renal function is not impaired. [8,24,31]
Dosing adjustments are required only in anephric patients with a major additional impairment of nonrenal biliary elimination (decreases in nonrenal clearance of greater than 80%).

Indication	Age	Dose
Surgical prophylaxis (dental, respiratory, or infected skin/skin structure, or musculoskeletal tissue procedures)	Neonate up to 15 days	20–50 mg/kg for 1 dose IV (infusion), dose to be administered 30–90 minutes before procedure. [8,24,39]
	Child 15 days–11 years (body-weight up to 50 kg)	50–80 mg/kg for 1 dose IV (infusion) or IM, dose to be administered 30–90 minutes before dure.[8,24,39] If a neonate (<(28 days) weighs less than 2000 g then max dose is 50mg/kg q 24 hours. [39]
	Child 9–11 years (body-weight 50 kg and above) 12-17 years	2 g for 1 dose IV (infusion or injection) or IM, dose to be administered 30–90 minutes before procedure. [8,24]
Bacterial meningitis, Bacterial endocarditis (Duration of bacterial endocarditis therapy should be 4 to 6 weeks). [8,31] Duration of bacterial meningitis therapy should be 10 to 14 days. [31]	Neonate up to 15 days	50 mg/kg once daily IV (infusion). [24,31]
	Neonate 15 days to 28 days	80–100 mg/kg once daily IV (infusion), 100 mg/kg once daily dose should be used for bacterial endocarditis. [8,24,39] If weight is less than 2000 g then max dose is 50mg/kg q 24 hours. [39]
	Child 1 month–11 years (body-weight up to 50 kg)	80–100 mg/kg once daily IV (infusion) or IM, 100 mg/kg once daily dose should be used for bacterial endocarditis; max 4 g per day. [8,24,31,39]
	Child 9–11 years (body-weight 50 kg and above) 12-17 years	2–4 g once daily IV (infusion or injection) or IM, doses at the higher end of the recommended range used in severe cases. [8,24, 31,39]
Complicated skin and soft tissue infections, Infections of bones and joints and	Neonate up to 15 days	20–50 mg/kg once daily IV (infusion), doses at the higher end of the recommended range used in severe cases. [8,24]
	Neonate 15 days to	50–100 mg/kg once daily IV

Suspected bacterial infection in neutropenic patients Continue therapy for at least 2 days after signs and symptoms of skin/subcutaneous infection have disappeared. The usual duration of therapy is 4 to 14 days.	28 days	(infusion), doses at the higher end of the recommended range used in severe cases. If weight is less than 2000 g then max dose is 50mg/kg q 24 hours.
	Child 1 month–11 years (body-weight up to 50 kg)	50–100 mg/kg once daily IV (infusion or injection) or IM, doses at the higher end of the recommended range used in severe cases; max 4 g per day.
	Child 9–11 years (body-weight 50 kg and above) 12-17 years	2 g once daily IV (infusion or injection) or IM.
Lower respiratory tract infection (CAP, HAP),Intra-abdominal infections, urinary tract infections, Suspected bacterial infection in neutropenic patients, sepsis, Lyme disease. The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of Ceftriaxone should be continued for a min 48 to 73 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.	Neonate up to 15 days	20–50 mg/kg once daily IV (infusion), doses at the higher end of the recommended range used in severe cases.
	Neonate 15 days to 28 days	50–100 mg/kg once daily IV (infusion), doses at the higher end of the recommended range used in severe cases. If weight is less than 2000 g then max dose is 50mg/kg q 24 hours.
	Child 1 month–11 years (body-weight up to 50 kg)	50–100 mg/kg once daily IV (infusion) or IM, doses at the higher end of the recommended range used in severe cases, maximum 4 g per day .
	Child 9–11 years (body-weight 50 kg and above) 12-17 years	2 g once daily IV (infusion or injection) or IM.

Gnorrhea (Uncomplicated)	Child 1 month–11 years (body-weight up to 50 kg)	25 to 50 mg/kg IV or IM as a single dose ,max dose 125 mg.
	Child 9–11 years (body-weight 50 kg and above)	250 mg for 1 dose.
	Child 12-17 years	500 mg for 1 dose.
Gonococcal conjunctivitis		25 to 50 mg/kg IV (infusion over 60 min) or IM as a single dose. Max per dose 125mg.
Prophylaxis for infants born to mothers with Gonococcal infections		25 to 50 mg/kg IV/IM as a single dose.
Gonorrhea Bacteremia or Arithritis	Newborn and children < 45 kg	25 to 50 mg/kg IV/IM once daily for 7 days; treat for 10 to 14 days for meningitis
	Children > 45 kg	1 g IV or IM once daily for 7 days.
Otitis media	Child 1 month–11 years (body-weight up to 50 kg)	50 mg/kg for 1 dose IM, dose can be given for 3 days if severely ill or previous therapy failed.
	Child 9–11 years (body-weight 50 kg and above)	1–2 g for 1 dose, dose can be given for 3 days if severely ill or previous therapy failed.

COMPATIBILITY AND STABILITY

Compatible with: D5NS, D5½NS, D5W, D10W, NS. Compatibility varies for dextrose-saline combinations. Amiodarone hydrochloride, aztreonam, heparin sodium, metronidazole, tigecycline.
At Y-site with ready-diluted medicines: Foscarnet, Linezolid, Propofol 1%.
At Y-site with: Aciclovir, Morphine, Pantoprazole, Pethidine, Remifentanil, Tacrolimus, Zidovudine.
Incompatible with: calcium-containing fluids such as compound sodium lactate (Hartmann's solution) and Ringer's solution for injection. Aminophylline, Aminoglycosides (amikacin, gentamicin, tobramycin), Calcium chloride, Calcium gluconate, Clindamycin, Fluconazole, Labetolol hydrochloride, Thiopental, Vancomycin.

Ceftriaxone should not be mixed or administered simultaneously with IV calcium treatment or calcium containing infusions because of the risk of precipitation of ceftriaxone-calcium salts. They can be administered one after another if the patient is over 28 days of age and ceftriaxone is infused into a different infusion site or flushing of infusion line is done or the infusion line is replaced between infusions.

Stability: 250 and 350 mg/mL reconstituted solutions are stable for 24 hours at room temperature and for 72 hours if refrigerated. 100 mg/mL for 48 hours at room temperature and for four days if refrigerated.
Protect from light before reconstitution.

POTENTIAL HAZARDS OF ADMINISTRATION
Hypersensitivity reactions as with all beta-lactam antibacterial agents, rash, erythema, pruritis, pain at injection site. Phlebitis, pain and inflammation at the injection site (pain after IM administration). Anaemia, jaundice, diarrhoea, nausea and vomiting. Transient elevation in BUN, serum creatinine and transaminases. Prothrombin time alteration in patients with low vitamin K stores. Risk of ceftriaxone-calcium precipitates in the urinary tract (urolithiasis, ureteral obstruction and post-renal) or gallbladder pseudolithiasis. Cautions in history of hypercalciuria; history of kidney stones; use with caution in neonates. In case of severe hypersensitivity reactions, treatment should be discontinued immediately and adequate emergency measures must be initiated (treatment with epinephrine, oxygen, IV steroids, antihistamines, pressor amines and airway management). Before beginning treatment it should be established whether the patient has a history of severe hypersensitivity reactions to ceftriaxone, to other cephalosporins or to any other type of beta-lactam agent. If a decision is made to give this medication to a patient with known penicillin hypersensitivity, the patient should be closely observed for allergenicity and immediate emergency treatment is available.
MISCELLANEOUS
Each gram of ceftriaxone contains approximately 82 mg (3.6mmol) of sodium. Contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age+ chronological age) and hyperbilirubinemic patients. Lidocaine added to IV ceftriaxone solutions is contraindicated. Monitor: CBC, prothrombin time/INR (especially if on warfarin) or in high risk patients (e.g. chronic hepatic disease and malnutrition), signs and symptomps of anaphylaxis signs and symptoms of Clostridium difficile-associated diarrhea. Monitor signs and symptoms of gallbladder disease, serum electrolytes, BUN, Crearinine, AST and ALT. Not dialyzable; administer dose post dialysis Treatment with Ceftriaxone may interfere with the following laboratory results to give false-positive tests: • Coombs' test. • Tests for galactosaemia. • Non-enzymatic methods such as copper reduction methods (Benedict's, Fehling's or Clinitest) for glucose determination in urine. For this reason, urine-glucose determination during therapy with ceftriaxone should be carried out enzymatically. • Accu-Chek devices may give falsely low blood glucose readings for patients receiving ceftriaxone therapy.
REFERENCES
1,2,4,7,8, 24,31,39

NAME OF MEDICATION	**Flucloxacillin**
STRENGH / TRADE NAME / MANUFACTURER	Flucloxacillin 250mg and 1g powder for solution for injection or infusion /Bowmed Ibisqus
CLASSIFICATION	Antibiotic-Penicillin

INDICATIONS FOR USE

Flucloxacillin is indicated for the treatment of infections due to sensitive Gram positive organisms, including β-lactamase-producing staphylococci and streptococci. Typical indications include:

- Skin and soft tissue infections
- Respiratory tract infections.
- Other infections caused by flucloxacillin-sensitive organisms: Osteomyelitis, Urinary tract infection, Enteritis, Meningitis, Endocarditis, Septicaemia.
- Prophylaxis during major surgical procedures when appropriate; for example cardiothoracic and orthopaedic surgery.

RECONSTITUTION and DILUTION

IV: 250mg vial: Average displacement value 0.2mL. Reconstitute with 4.8mL WFI to give a final concentration of 50mg/mL.

1g vial: Average displacement value is 0.6ml. Reconstitute with 19.4mL WFI to give a final concentration of 50mg/mL.

IV infusion: add reconstituted vial to infusion fluids (NS, D5W).

IM: Add 1.5mL WFI to 250mg vial.

Intrapleural: Dissolve 250mg in 5-10mL WFI.

Intra-articular: Dissolve 250-500 mg in up to 5 ml WFI or 0.5% lidocaine hydrochloride solution.

METHOD OF ADMINISTRATION

IV injection: Give 250mg and 1 g doses by slow IV injection over 3-5 minutes. Administer 2g doses over 6-8 minutes.
IV Infusion: Administer over 30-60 minutes.
IM: Administer into a large muscle such as the gluteus or the lateral aspect of the thigh. Rotate injection sites for subsequent injections.

DOSAGE

- *Treatment of infections due to beta-lactamase producing staphylococci including otitis externa, adjunct in pneumonia, impetigo and cellulitis.*

IV infusion or slow IV injection

- Neonates up to 7 days: 25mg/kg every 12 hours and in severe infections 50mg/kg.
- Neonates 7 days to 20 days: 25mg/kg every 8 hours and severe infections 50mg/kg.
- Neonates 21 to 28 days: 25mg/kg every 6 hours and in severe infections 50mg/kg.
- Child: 12.5-25 mg/Kg every 12 hours (max. per dose 1g every 6 hours). In severe infections 25-50mg/kg (max. per dose 2 g every 6 hours). IM: 12.5–25 mg/kg every 6 hours (max. per dose 500 mg every 6 hours).

- *Treatment of Endocarditis:*

- Child: 50 mg/kg every 6 hours (max. per dose 2 g every 6 hours).

- *Treatment of Cerebral abscess ,Staphylococcal meningitis ,Osteomyelitis:*

By slow IV injection, or by IV infusion

- Neonates up to 7 days: 50–100 mg/kg every 12 hours.
- Neonates 7 days to 20 days: 50–100 mg/kg every 8 hours.
- Neonates 21 to 28 days: 50–100 mg/kg every 6 hours.
- Child: 50 mg/kg every 6 hours (max. per dose 2 g every 6 hours).

- *Treatment of Staphylococcal lung infection in cystic fibrosis:*

- Child: 50 mg/kg every 6 hours (max. per dose 2 g every 6 hours).

COMPATIBILITIES AND STABILITY

Compatible with NS, D5W, sodium chloride 0.18% with glucose 4%.
Incompatible with blood products, proteinaceous fluids and lipid emulsions.
If used in combination with an aminoglycoside (e.g. amikacin, gentamicin, tobramycin), preferably administer at a different site. If this is not possible then flush the line with a compatible solution between drugs.
If flucloxacillin is prescribed concurrently with an aminoglycoside, the two antibiotics should not be mixed in the syringe, intravenous fluid container or giving set as precipitation may occur
Reconstituted solution is stable for 24 hours under refrigeration.

POTENTIAL HAZARDS OF ADMINISTRATION
Sensitivity reactions including urticaria, maculo-papular rashes, pruritus, fever, joint pains and angioedema. Phlebitis and thrombophlebitis may occur. Some patients with spirochaete infections such as syphilis or leptospirosis may experience a Jarisch-Herxheimer reaction. Hepatitis and cholestatic jaundice (especially with prolonged treatment and in patients with pre-existing hepatic dysfunction). Flucloxacillin is contraindicated in patients with a previous history of flucloxacillin-associated jaundice/hepatic dysfunction.
MISCELLANEOUS
Each vial contains approximately 0.57 mmol (13mg) sodium. Caution in hepatic impairment. Not to be used in patients with a history of hepatic dysfunction associated with flucloxacillin. careful enquiry should be made about hypersensitivity reactions to beta-lactam antibacterials Flucloxacillin may be administered in combination with other antibiotics including ampicillin to produce a wider spectrum of antibacterial activity. Flucloxacillin 250 mg may also be inhaled by nebuliser.
REFERENCES
4,7,13,23,24,48,49,50

NAME OF MEDICATION	PARACETAMOL
STRENGTH / TRADE NAME / MANUFACTURER	10 mg/mL (1 g in 100 mL) solution for infusion/ Paracetamol/ Actavis 10 mg/mL (1 g in 100 mL) solution for infusion / Paracetamol/ Combino Pharm 10 mg/mL (1 g in 100 mL) solution for infusion / Paracetamol/ Fresenius Kabi
CLASSIFICATION	**Antipyretic, Analgesic**

INDICATIONS FOR USE

Short-term treatment of pyrexia or moderate pain (especially following surgery) when administration via other routes is not possible or appropriate or when the IV route is justified by
an urgent need to treat pain or hyperthermia.

RECONSTITUTION and DILUTION

Ensure that the dose is measured accurately. The dose of paracetamol in the final volume to be administered must correspond to the prescribed total dose.
Take care to ensure the dose is measured and administered accurately.
The volume of paracetamol to be administered must correspond to the prescribed total dose.
ATTENTION : Each 1 mL of undiluted solution contains 10mg of paracetamol.
Ensure that the paracetamol dose in the final volume to be administered, is within the dosage range according to the patient's weight.

- **IV infusion:**
  - Child >10 kg : No further dilution required.
  - Neonate and child ≤10 kg : Dilute to a final conc. of not less than 1 mg/mL: Withdraw the prescribed dose of paracetamol solution from the vial into a syringe and dilute with max. 9 times it volume with NS or D5W e.g if dose to be administered is 50 mg (5 mL) dilute this volume with max. 45 mL of NS or D5W.

METHOD OF ADMINISTRATION

The vial should not be hung as infusion for patients ≤ 10 kg due to small volumes to be administered.

- **IV infusion:** administer over 15 min
  - **Doses <1 g**: In order to avoid inadvertent administration of the whole vial;
    - Neonate and child ≤10 kg : Withdraw the prescribed dose from the vial and place in a syringe for IV infusion. Administer via syringe pump after appropriate dilution.
    - Child > 10 kg and < 50 kg : Remove excess volume from the vial before administration

DOSAGE

Caution - confusion between **mg and mL** which could result in accidental overdose and death. **Doses should be prescribed as mg** not mL to prevent prescribing errors. When writing prescriptions include both the total dose in mg and the total dose in volume.

- Neonate (excluding preterm neonate) and child <10 kg: 10 mg/kg every 4 to 6 hours; max daily dose 30 mg/kg. Use a 5 mL or 10 mL syringe to measure the dose as appropriate for the weight of the child and the desired volume. Max. volume per dose is 7.5 mL.
- Child 10 -50 kg: 15 mg/kg every 4 to 6 hours; max daily dose 60 mg/kg.
- Child > 50 kg: 1 g every 4 to 6 hours; max daily dose 4 g (3 g in case of additional risk factors for hepatotoxicity e.g chronic malnutrition, hepatocellular insufficiency).

Max. of 4 doses every 24 hours.

Renal impairment – Dose adjustments required when CrCL< 30 mL /min

Max daily dose is taking into consideration that patient is not receiving other paracetamol containing products.

COMPATIBILITIES AND STABILITY

- **Compatible infusion solutions:** NS, D5W.
- To be used immediately after opening. Discard any unused solution.
- Diluted solution to be administered within 1 hour of dilution.

POTENTIAL HAZARDS OF ADMINISTRATION

Local: pain and burning sensation at injection site. Rarely - Anaphylaxis, hypersensitivity reactions.

Skin reactions; Tachycardia, Hypotension increase in liver enzymes, rash, thrombocytopenia, leucopenia, neutropenia.

MISCELLANEOUS

- **Monitor:** infusion reaction, pain, body temperature – regularly; LFT, U&E – periodically.
- Check when paracetamol or paracetamol containing products were last administered and cumulative dose over previous 24 hours.
- Avoid in patients with hypersensitivity or patients with severe hepatic impairment.
- Sodium content < 1 mmoL per vial.
- Contraindicated in patients with severe hepatic impairment or severe active liver disease.
- Caution in patients with severe hypovolemia (due to dehydration or blood loss), chronic malnutrition or severe renal impairment.

REFERENCES

3, 6,7, 9, 11, 12, 13, 19, 31 , 36, 37, SPC Combino Pharma

Appendix 10- Drug Monographs Released Forms

NAME OF MEDICATION	**Aciclovir**
STRENGH / TRADE NAME / MANUFACTURER	250 mg powder for solution for infusion /Aciclovir /Wockhardt 250 mg powder for solution for injection /Aciclovir /Mylan 25 mg/ml Concentrate for solution for infusion /Aciclovir /Claris Lifesciences
CLASSIFICATION	Antiviral agent

INDICATIONS FOR USE

Treatment of *Herpes simplex* and *Herpes encephalitis*
Treatment of *Varicella zoster* and *Herpes zoster*, including treatment in encephalitis

RECONSTITUTION and DILUTION

Reconstitute 250 mg vial with 10 mL WFI or NS – resultant concentration: 25 mg/mL.
Further dilute up to 50 mL using NS – final concentration: 5 mg/mL.

METHOD OF ADMINISTRATION

Slow IV infusion over 1 hour.
Preferably administer via a central venous access device. If unavailable use a large peripheral vein.

DOSAGE

Treatment of *Herpes simplex, Varicella zoster and Herpes zoster*:

- Neonate up to 2 months:
  - *(i)* *Herpes simplex:* 20 mg/kg every 8 hours for 14 days (for at least 21 days if CNS involvement—confirm cerebrospinal fluid negative for herpes simplex virus before stopping treatment).
  - *(ii)* *Varicella zoster and Herpes zoster:* 10–20 mg/kg every 8 hours for at least 7 days.
- Child 3 months – 11 years: 250 mg/m^2 every 8 hours usually for 5 days.
- Child 12-17 years: 5 mg/kg every 8 hours usually for 5 days.

Treatment of *Herpes simplex, Varicella zoster & Herpes zoster* in immunocompromised patients or in *Herpes simplex encephalitis*:

- Child 3 months - 11 years: 500 mg/m^2 every 8 hours usually for 5 days (given for at least 21 days in simplex encephalitis)*
- Child 12-17 years: 10 mg/kg every 8 hours usually for 5 days (given for at least 14 days in simplex encephalitis and for at least 21 days if also immunocompromised)*

*Confirm cerebrospinal fluid negative for herpes simplex virus before stopping treatment).

Herpes Zoster and *Varicella zoster* treatment in encephalitis: ➢ Neonate up to 2 months: 10–20 mg/kg every 8 hours** ➢ Child 3 months–11 years: 500 mg/m^2 every 8 hours** ➢ Child 12–17 years: 10 mg/kg every 8 hours** **Treatment given for 10–14 days in encephalitis, possibly longer if also immunocompromised. Dose adjustment required in renal impairment. Doses for overweight children are calculated using the ideal weight for height.
COMPATIBILITIES AND STABILITY
• **Compatible** with: ½ NS, NS, Hartmann's. **Flush** with: NS • Do not store above 25°C. Keep vials in the outer carton to protect from light. Not to be refrigerated. • Use immediately upon reconstitution. Discard solution if it becomes cloudy or crystals appear before or during the infusion. • Avoid mixing with other IV medications in the same tubing or same infusion.
POTENTIAL HAZARDS OF ADMINISTRATION
• Extravasation which may cause phlebitis and inflammation at injection site. • Risk of transient renal dysfunction and crystalluria is minimized by slow infusion rates and adequate patient hydration. • Risk of neurological reactions increased (tremor, ataxia, convulsions) ; Elevation of hepatic transaminases; Neutropenia. • Resistant viral strains may emerge during long-term therapy.
MISCELLANEOUS
Monitor: FBC, U&Es, LFTs, urinalysis and IV site for phlebitis. (renal function - nephrotoxicity) **Sodium content:** 1.1 mmol/ 250mg powder for injection. Cross-sensitivity between aciclovir and valaciclovir.
REFERENCES
1, 2, 3, 4,5, 6, 7, 8, 9, 10

NAME OF MEDICATION	AMOXICILLIN
STRENGH / TRADE NAME / MANUFACTURER	250 mg powder for solution for injection or infusion/ Amoxicillin /Bowmed Ibisqus 500 mg powder for solution for injection / Amoxicillin Sodium/ Wockhardt
CLASSIFICATION	Broad Spectrum Antibiotic-Aminopenicillin

INDICATIONS FOR USE

- Treatment of susceptible infections which include: Infections of ENT, Genitourinary tract, Biliary-tract, Lower respiratory tract (including pneumonia), Skin, Severe dental abscess with spreading cellulitis, Oral infections, Bone and Joints including prosthetic joint infections, Gastroenteritis, Typhoid and paratyphoid fever, Lyme disease, Bacterial meningitis.
- Treatment and prophylaxis of endocarditis.

RECONSTITUTION and DILUTION

Slow IV injection: For the 250 mg vial -reconstitute with 5mL WFI (Final conc. 48 mg/mL); For the 500 mg vial - reconstitute with 10 mL WFI (Final conc. 48 mg/mL) Concentrations of 100 mg/mL for neonates have been used. Shake vigorously before injection and administer within 30 min of reconstitution.
IV infusion: dilute up to 10 mL for the 250 mg vial and up to 20 mL for the 500 mg vial with a compatible infusion fluid. Final concentration after dilution: 25 mg/mL.

METHOD OF ADMINISTRATION

Slow IV injection: (for doses ≤ 30mg/kg)**:** over 3-4 minutes in vein or drip tube.
IV infusion: (for doses > 30mg/kg): over 30 minutes. Preferably administer via a central venous access, if unavailable use a large peripheral vein. **Wockhardt brand is not to be administered in neonates and infants under 1 year.**

DOSAGE

Treatment of susceptible infections (including urinary tract infections, otitis media, sinusitis, uncomplicated CAP, salmonellosis and oral infections. – IV injection or infusion

- Neonate up to 7 days: 30 mg/kg every 12 hours, increased if necessary to 60 mg/kg every 12 hours, increased dose used in severe infection, community-acquired pneumonia or salmonellosis.
- Neonate 7 to 28 days :30 mg/kg every 8 hours, increased if necessary to 60 mg/kg every 8 hours, increased dose used in severe infection, CAP or salmonellosis.
- Child: 20–30 mg/kg every 8 hours (max. per dose 500 mg), increased if necessary to 40–60 mg/kg every 8 hours (max. per dose 1 g every 8 hours), increased dose used in severe infection.

Dose to be adjusted according to indication, severity and site of infection
Dose adjustment necessary in renal impairment.

COMPATIBILITIESAND STABILITY
• **Compatible** with: NS, **Flush** with NS. • **Incompatible** with: Hartmann's, KCL. • Amoxicillin should not be mixed with blood products, other proteinaceous fluids such us protein hydrolysates or with intravenous lipid emulsions. • Use immediately upon reconstitution. Vials are single use. • During reconstitution a transient pink colour may occur (Bowmed); reconstituted solutions are usually colourless or pale straw in colour. Do NOT administer if reconstituted solution is pink. • Do not mix with aminoglycosides in same syringe, intravenous fluid container or giving set. Administer at different site or flush line thoroughly between drugs. Don't mix Wockhardt brand with Ciprofloxacin.
POTENTIAL HAZARDS OF ADMINISTRATION
• Anaphylaxis; angioedema; diarrhoea; fever; hypersensitivity reactions; joint pains; rashes; serum sickness-like reaction; urticaria; superinfection (especially if prolonged treatment). • Convulsion especially in patients with impaired renal function or in those who receive high doses. • Risk of crystalluria with high dosesand reports of precipitation in bladder catheters. • Amoxicillin-induced flare of DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) has been reported.
MISCELLANEOUS
- **Monitor:** U&Es, LFTs and FBC periodically, INR or PT if patient is on anticoagulant. -Not to be used if patient experienced previous beta-lactam allergy. - Sodium content: 0.825mmol/ 250mg vial; 1.3mmol/ 500mg vial. -Discontinue treatment if skin rash appears. -Maintain adequate fluid intake and urinary output. -Amoxicillin can be removed by haemodialysis.
REFERENCES
1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 14, 15, 16, 36

NAME OF MEDICATION	**Amphotericin B Liposomal (Ambisome®)**
STRENGH / TRADE NAME / MANUFACTURER	50 mg (50, 000 units) per vial amphotericin encapsulated in liposomes, powder for solution for infusion/ Ambisome®/ Gilead Sciences International Ltd
CLASSIFICATION	Polyene antifungal

INDICATIONS FOR USE

Treatment of severe systemic or deep mycoses
Empirical treatment of presumed fungal infections in febrile neutropenic patients, unresponsive to broad spectrum antibiotics
Treatment of visceral leishmaniasis in immunocompetent and immunocompromised (off-license) patients

RECONSTITUTION and DILUTION

Reconstitute with 12 mL WFI. Instil the reconstituted solution through a 5 micron filter into a syringe containing 37.5 mL of D5W or D10W. Final concentration of solution is 1 mg/mL.
Solution can be made more dilute or more concentrated depending on clinical circumstances. The final solution should have a concentration between 0.2 mg/mL and 2 mg/mL.

METHOD OF ADMINISTRATION

Check that the prescription specifies AmBisome® and that the product you are using is AmBisome®.
Calculate the required volume according to the prescribed dose.
IV infusion:

- Doses up to and including 5 mg/kg/day: over 60 minutes
- Doses over 5 mg/kg/day or if non-anaphylactic infusion-related reactions occur with doses < 5 mg/kg/day: over 2 hours

Flush the cannula with dextrose before and after administration.

DOSAGE

A test dose of 100 micrograms/kg (max. 1 mg per dose) to be given over 10 minutes is advisable **except in neonates** before the first dose of each treatment course. Observe the patient carefully for the next 30 minutes.

- Continue the infusion if no severe allergic or anaphylactic/anaphylactoid reactions.
- Stop the infusion immediately if severe allergic reaction occurs at any point during administration. Do not give further amphotericin-based preparations to the patient.

Treatment of severe systemic or deep mycosis & empirical treatment of presumed fungal infections in febrile neutropenic patients.

- Neonates (Off-label): 1 mg/kg once daily, increased if necessary to 3 mg/kg once daily; max 5 mg/kg per day.
- Child: Test dose as above, then: 3 mg/kg once daily; max 5 mg/kg per day.

Treatment of Visceral leishmaniasis in child > 1 month:

- Immunocompetent patients: Test dose as above, then: 3 mg/kg IV once daily on days 1 to 5, and on days 14 and 21.
- Immunocompromised patients: Test dose as above, then: 4 mg/kg IV once daily on days 1 to 5, and on days 10, 17, 24, 31, 38.

COMPATIBILITIES AND STABILITY

- **Compatible:** D5W; **Incompatible** with: NS; may not be mixed with other medicinal products or electrolytes.
- Use immediately upon reconstitution and dilution.
- Do not store above 25°C. Keep the container in the outer carton to protect from light.

POTENTIAL HAZARDS OF ADMINISTRATION

- Anaphylactoid reactions; Acute infusion reactions (fever/ chills/ rigors; less frequently: back pain, chest tightness or pain, dyspnoea, bronchospasm, flushing, tachycardia and hypotension) may occur 1-3 hours after initiating infusion.
- Anaemia, thrombocytopenia, hypokalemia, hypomagnesaemia & abnormal liver function (discontinue), nephrotoxicity.
- Acute pulmonary toxicity reported in patients during and shortly after simultaneous leukocyte transfusions.

MISCELLANEOUS
• Monitor: FBC, LFT- Weekly, U&Es (particularly Mg2+ and K+)-daily then twice weekly, signs of infusion related reactions, • Lipid-based and conventional formulations are not interchangeable and have different dosing recommendations. • Facilities for cardiopulmonary resuscitation should be available during administration due to the possibility of anaphylactic reactions. • Each vial contains 900 mg of sucrose. This should be taken into account when treating diabetic patients.
REFERENCES
1, 2, 3, 4, 6, 8, 9, 10, 12, 15, 16

NAME OF MEDICATION	**BENZYLpenicillin sodium**
STRENGH / TRADE NAME / MANUFACTURER	600 mg (equivalent to 1 Million Unit) powder for solution for injection/ Penicillin G /Cooper 600 mg (equivalent to 1 Million Unit) powder for solution for injection/ Benzylpenicillin sodium/ Genus Pharmaceuticals
CLASSIFICATION	Antibiotic, Penicillin

INDICATIONS FOR USE

Treatment of infections due to susceptible non beta-lactamase producing organisms.

RECONSTITUTION and DILUTION

- **IM injection:** 600 mg dissolved in 1.6-2 mL WFI. If using part of a vial add 1.6 mL WFI or NS to the vial (Final conc. 300 mg/mL)
- **IV bolus**: 600 mg dissolved in 4 mL WFI or NS. If using part of a vial add 3.6 mL WFI or NS to the vial (Final conc. 150 mg/mL)
- **IV Infusion**: 600 mg dissolved in 4 mL WFI or NS. Dilute up to 10ml to administer. The maximum concentration that can be used for peripheral administration: 60 mg/mL. The solution can be added to 50 mL NS or D5W bag.
- In patients with renal and/or heart failure consider reconstituting with WFI and diluting with 5% Dextrose.

METHOD OF ADMINISTRATION

IM injection: maximum concentration ≤ 100,000 units/mL can be administered through this route.
Slow IV injection: (recommended for doses < 50 mg/kg): the maximum rate of administration is 300mg/minute.
IV infusion: (recommended for doses > 50 mg/kg): infuse over 15-30 minutes. Longer administration time is particularly important when using doses of 50 mg/kg (or greater) to avoid CNS toxicity.

DOSAGE

Treatment of throat infections, otitis media, cellulitis and pneumonia: By IM injection, slow IV injection, or by IV infusion. IV route recommended in children and neonates

- Neonate up to 7 days: 25 mg/kg every 12 hours; increased if necessary to 25 mg/kg every 8 hours
- Neonate 7 – 28 days: 25 mg/kg every 8 hours; increased if necessary to 50 mg/kg every 8 hours in severe infection
- Child: 25 mg/kg every 6 hours; increased if necessary to 50 mg/kg every 4–6 hours (max. per dose 2.4 g every 4 hours) in severe infection, intravenous route recommended in infants.

Treatment of Endocarditis (in combination with other antibacterial if necessary): slow IV injection or infusion
25 mg/kg every 4 hours; increased if necessary to 50 mg/kg every 4 hours (max. per dose 2.4 g every 4 hours).
Treatment of meningococcal disease:

- Neonate up to 7 days: 50 mg/kg every 12 hours
- Neonate 7-28 days: 50 mg/kg every 8 hours
- Child: 50 mg/kg every 4-6 hours (max. per dose: 2.4 g every 6 hours)

Dose adjustment necessary in renal impairment; further adjustments in patients with both renal and hepatic impairment

COMPATIBILITIES AND STABILITY

- Reconstituted product should be used immediately.
- Compatibilities: NS, D5W (but less stable); Flush: NS
- Inactivated by acids, alkalis, oxidising agents and glucose solutions containing bicarbonates.
- Not to be mixed with other medications or administered in the same set

POTENTIAL HAZARDS OF ADMINISTRATION

- Hypersensitivity (rashes); anaphylactic reactions. Leukopenia and thrombocytopenia in treatment with high doses.
- The Jarisch-Hersheimer reaction (fever, chills, myalgia, headache, tachycardia, hyperventilation, mild hypotension) may occur after initiation of therapy in patients with syphilis or other spirochetal infections (ie, Lyme disease).
- Neurotoxic reactions (convulsions), renal tubular damage, occurred after large doses or in renal impairment.
- Congestive heart failure (due to high sodium intake) and fatal electrolyte abnormalities occurred after large doses.

MISCELLANEOUS
• Monitor: Periodic U&Es, FBC – if treatment exceeds 5 days, LFTs, cardiac function tests during prolonged/high-dose therapy; observe for signs and symptoms of anaphylaxis during first dose and changes in bowel frequency • 1 vial of benzylpenicillin contains 1.68 mmol of sodium. • Penicillins may interfere with: Urinary glucose test, coomb's tests, tests for urinary or serum proteins, tests which use bacteria e.g. Guthrie test.
REFERENCES
1, 2, 4, 8, 9, 12, 14, 15, 17, 18, 19, 20

NAME OF MEDICATION	**cefOTAXime**
STRENGH / TRADE NAME / MANUFACTURER	1 g Powder for solution for injection or infusion /Cefotaxime/ Wockhardt
CLASSIFICATION	**Third Generation Cephalosporin**

INDICATIONS FOR USE

Treatment of infection due to susceptible Gram–positive and Gram-negative bacteria
Surgical prophylaxis

RECONSTITUTION and DILUTION

- **IV and IM injection:** Add 4 mL WFI. If using part of vial add 4.4 mL (Final conc. 200 mg/mL).
- **IV infusion:** Add 4 mL WFI. Dissolve in 40-100 mL NS or D5W.

METHOD OF ADMINISTRATION

Slow IV injection: over 3-5 minutes. Max conc. for IV is 200 mg/mL
Intermittent IV infusion: over 20-60 minutes.
Preferably administer via a central venous access device or a large peripheral vein and monitor closely.
IM injection: Doses above 1 g should be distributed between two sites of injection; if pain occurs 1% Lidocaine can be used for reconstitution**.**

DOSAGE

Dose depends on the severity of infection. Usual dose ranges as follows:
Neonate up to 7 days: 25 mg/kg every 12 hours.
Neonate 7 days to 20 days: 25 mg/kg every 8 hours.
Neonate 21 days to 28 days: 25 mg/kg every 6–8 hours.
Child 1 month of age and older: 50 mg/kg every 8–12 hours.

Dose may be doubled for neonates with severe infection or meningitis.
Dose adjustment required if eGFR is less than 5mL/minute/1.73m^2.
Maximum dose: 12 g per day.

COMPATIBILITIES AND STABILITY
• **Compatible:** WFI, NS, D5W, D5NS, D5$^{1}/_{2}$NS, Hartmann's solution. • **Incompatible:** alkaline solutions or solutions with a pH greater than 7.5 (e.g. sodium bicarbonate). • Do not mix with aminoglycosides in same syringe or perfusion fluid. Administer at different site but if not possible, flush line thoroughly between administrations. Do not mix with other medicinal products. Contact pharmacy. • Use immediately upon reconstitution. A straw-coloured solution is formed when reconstituted. Variations in the intensity of colour of freshly prepared solutions may occur; this does not indicate change in potency or safety.
POTENTIAL HAZARDS OF ADMINISTRATION
• Pain/inflammation at injection site, phlebitis, thrombophlebitis • Anaphylactic reactions, angioedema, bronchospasm, rash, urticaria, fever, encephalopathy, seizures. • Arrhythmias (following rapid administration through a central venous access device) • Transient elevation in BUN, serum creatinine and transaminases. • Leukopenia, Eosinophilia and thrombocytopenia • Granulocytopenia and more rarely agranulocytosis may develop during prolonged treatment (>10 days).
MISCELLANEOUS
• **Monitor:** FBC, U&Es, LFTs. • Avoid using cephalosporins in patients with a history of anaphylactic reactions to penicillin and use with caution in patients with delayed-type reaction (rash, fever) to penicillins. • Lab tests interference: False positive Coomb's test; false-positive urinary glucose results (if tested for reducing substances). • **Sodium content:** 2.09 mmol (48 mg) /1 g
REFERENCES
2, 3, 4, 7, 8, 9, 12, 14, 15, 16

NAME OF MEDICATION	cefTAZidime
STRENGH / TRADE NAME /MANUFACTURER	1 g Powder for solution for injection/ Ceftazidime pentahydrate / Wockhardt 1 g Powder for solution for injection/ Ceftazidime / Villerton 1 g Powder for solution for injection/ Ceftazidime / Fresenius Kabi
CLASSIFICATION	Cephalosporin Antibiotic

INDICATIONS FOR USE

Treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria, especially infections due to *Pseudomonas* spp; Surgical infection prophylaxis. Regulated by DPA protocol MP 35.

RECONSTITUTION and DILUTION

IV injection:

- If using a whole vial - add 10 mL NS**.**
- If using part of a vial: For Wockhardt & Fresenius Kabi brands – add 9.1 mL NS. Final concentration: 100 mg/mL
  For Villerton brand – add 9.5 mL NS. Final concentration: 100 mg/mL

IV infusion: Reconstitute as above. Dilute up to at least 25 mL NS or D5W. Maximum concentration of 40 mg/mL.

IM injection: add 3 mL lidocaine 1%. Final concentration: 260 mg/mL for Wockhardt & Fresenius Kabi; 286 mg/mL for Villerton

1. Insert syringe needle through the vial closure and inject diluents.
2. Remove the syringe and shake to dissolve. Carbon dioxide is released and a clear solution will be obtained in about 1 to 2 minutes.
3. Invert the vial and with syringe fully depressed insert the needle through the vial closure and withdraw the required dose in the syringe. The withdrawn solution may contain small bubbles of carbon dioxide; they may be disregarded.

METHOD OF ADMINISTRATION

IV injection administer over 3–5 minutes.
IV infusions infuse over 20–30 minutes. Maximum conc. 40 mg/mL.
Deep IM injection: Considered only when IV route is not possible or less appropriate.

DOSAGE

Susceptible infections due to sensitive Gram-positive and Gram-negative bacteria (IV injection or IV infusion)

- Neonate up to 7 days: 25 mg/kg every 24 hours, in severe infections or meningitis use 50 mg/kg every 24 hours.
- Neonate 7 days to 20 days: 25 mg/kg every 12 hours, in severe infections or meningitis use 50 mg/kg every 12 hours.
- Neonate 21 days to 28 days: 25 mg/kg every 8 hours, in severe infections or meningitis use 50 mg/kg every 8 hours.
- Child: 25 mg/kg every 8 hours; maximum 6 g per day, in severe infections or meningitis use 50 mg/kg every 8 hours (maximum: 6 grams/day).

Pseudomonal lung infection in cystic fibrosis (IV injection, IV infusion or deep IM injection):

- Child 50 mg/kg every 8 hours; maximum 9 g per day.

Febrile neutropenia by IV infusion or IV injection:

- Child 50 mg/kg every 8 hours; maximum 6 g per day.

Dose adjustments necessary in renal impairment.

COMPATIBILITIES AND STABILITY

Compatible with: NS, Ringer's solution, Lidocaine hydrochloride 1%.
Incompatible: sodium bicarbonate.
If used in combination with aminoglycosides, administer at different sites. If not possible, flush line thoroughly.
Not be added to blood products, protein hydrolysates or amino acids.
Solutions range from light yellow to amber depending on concentration, diluents and storage conditions used.
Use immediately after reconstitution. Discard any unused portion.
Ceftazidime Fresenius Kabi needs to be protected from light.

POTENTIAL HAZARDS OF ADMINISTRATION

- Anaphylaxis including bronchospasm and hypotension, angioedema, headache, dizziness, itch, rash, phlebitis, thrombophlebitis.
- Transient increases in serum creatinine & BUN; disturbances in liver enzymes; increase in INR.
- Transient leukopenia, neutropenia, thrombocytopenia; neurotoxicity (especially with high doses and in renal impairment).

MISCELLANEOUS

- **Monitor:** U&Es, LFTs, FBC, prothrombin time in high risk patients.
- Sodium content: 2.26 mmol/1g vial
- Cross-sensitivity with other beta-lactam antibiotics.
- False positive Coomb's test; false-positive urinary glucose results (if tested for reducing substances).

REFERENCES

2, 3, 4, 6, 8, 9, 12, 14, 15, 16, 18, 20, 21

NAME OF MEDICATION	**cefTRIAXone**
STRENGH / TRADE NAME (MANUFACTURER)	500 mg powder for solution for injection / ceftriaxone sodium / Sagent Pharmaceuticals 1 g powder for solution for injection / ceftriaxone sodium / Wockhardt UK Ltd 1 g powder for solution for injection / Sirtap® / So.Se. Pharm 2 g powder for solution for infusion / ceftriaxone sodium / Villerton 2 g powder for solution for infusion/ Travilan® /Anfarm Hellas S.A.
CLASSIFICATION	Antibiotic-Cephalosporin

INDICATIONS FOR USE

Treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria.
Regulated by DPA protocol MP 40.

RECONSTITUTION and DILUTION

IV injection: Reconstitute each 1 g and 2 g vial with 10 mL WFI; and each 500 mg vial in 5 mL of WFI.
IV infusion: reconstitute 2 g vial up to 40 mL using NS or D5W or D10W (Final conc. 50 mg/mL).
reconstitute 1 g vial up to 40 mL using NS or D5W or D10W (Final conc. 25 mg/mL).
reconstitute 500 mg vial up to 20 mL using NS or D5W or D10W (Final conc. 25 mg/mL).
IM injection: 1 g vial should be dissolved in 3.5 mL of 1% Lidocaine injection BP. (Not applicable for SIRTAP® 1 g/10 mL solution)
500 mg vial should be reconstituted in 1.8 mL of WFI to provide 250 mg/mL or with 1 mL to provide 350 mg/mL.
Gives a Pale yellow to amber clear solution, variation in intensity of the colour of freshly prepared solutions is acceptable for the brands **Wockhardt, Sirtap, Sagent**.

METHOD OF ADMINISTRATION

- **Slow IV injection-** for doses of up to 50 mg/kg: over 5 minutes, preferably into a large vein.
- **IV infusion** (preferred route) – for doses of 50 mg/kg or greater **-** over 30 minutes (60 minutes in neonates).
- **IM injection** doses over 1 g must be divided between more than one site. Maximum IM dose is 2 g, doses greater than 2 g must be given via IV route.
-

DOSAGE

Dose depends on severity, site and type of infection. **Usual dose range:**

- Neonates up to 15 days of age: 20 to 50 mg/kg once daily
- Neonates 15 days up to children of 11 years and weighing less than 50 kg: 50 to 80 mg/kg once daily. Dose may be increased to 100 mg/kg daily (maximum 4 g daily) in bacterial endocarditis, complicated skin and soft tissue infections, infections of the bone and joints, suspected bacterial infections in neutropenic patients and in syphilis. Dose used in meningitis is of 80-100 mg/kg daily.

Children of 12 years and over OR with body weight more than 50 kg: 1 to 2 g daily, increased to 4 g daily in severe infections, meningitis, and endocarditis.

Dose adjustments necessary in patients with CrCl less than 10 mL/min/1.73m^2 OR with concomitant hepatic and renal impairment.

- **Doses greater than 80 mg/kg increase risk of biliary precipitate.**

COMPATIBILITIES AND STABILITY

- **Compatible with:** NS, D5W, D10W.
- **Incompatible with:** calcium-containing infusion fluids such as compound sodium lactate, Ringer's solution and IV nutrition.
- Ceftriaxone should not be mixed or administered simultaneously with IV calcium containing preparations because of the risk of precipitation of ceftriaxone-calcium salts. They can be administered one after another ONLY if the patient is over 28 days of age AND ceftriaxone is infused through different infusion lines at different sites OR flushing of infusion line is done thoroughly.

POTENTIAL HAZARDS OF ADMINISTRATION

- Anaphylactic reactions; bronchospasm, allergic dermatitis, hypersensitivity reactions; rash, erythema, pruritis, phlebitis and pain at injection site. Leukopenia, neutropenia, thrombocytopenia and granulocytopenia.
- Transient elevation in BUN, serum creatinine, transaminases and INR.
- Primary cholelithiasis, nephrolitiasis, haemolytic anaemia; seizures with high doses and in renal impairment.

MISCELLANEOUS

- **Monitor:** FBC, prothrombin time, U&Es, LFTs. **Sodium content:** 3.6 mmol per gram
- Cross-sensitivity with other beta-lactam antibiotics.
- Use with caution in neonates - Contraindicated in premature neonates who are less than 41 weeks of postmenstrual age (gestational age+ chronological age)., contraindicated in neonates with hyperbilirubinaemia, jaundice or other conditions in which bilirubin binding is impaired. Reported to displace bilirubin from albumin binding sites
- False positive Coomb's test; false-positive urinary glucose results (if tested for reducing substances).

REFERENCES

1, 2, 3, 4, 7, 8, 9, 12, 13, 15, 16, 18, 20, 21, 22

NAME OF MEDICATION	ceFUROXime
STRENGH / TRADE NAME / MANUFACTURER	250 mg powder for solution for injection / cefuroxime / Villerton or Bowmed 750 mg powder for solution for injection or infusion /Axetine® / Medochemie
CLASSIFICATION	Cephalosporin Antibiotic

INDICATIONS FOR USE

Treatment of infections caused by staphylococci, group B streptococci, H. Influenza (type A and B), E. Coli, Enterobacter, Salmonella, and Klebsiella.

- Treatment of susceptible infections of the lower respiratory tract, urinary tract, skin and soft tissue, bone and joints, otitis media, sepsis and gonorrhoea.
- Surgical infection prophylaxis.

RECONSTITUTION and DILUTION

IV injection: add 2 mL WFI to 250 mg vial. Dilute up to 5 mL using NS or D5W (final concentration 50 mg/mL).
add 6 mL WFI to 750 mg vial. Dilute up to 15 mL using NS or D5W (final concentration 50 mg/mL).
IV infusion: Reconstituted solution to be added to 50 or 100 mL of compatible infusion solution e.g. NS or D5W. Max conc. is 30 mg/mL.
IM injection: add 1 mL WFI to 250 mg vial. Shake gently to produce an opaque suspension (For Villerton brand).
add 3 mL WFI to 750 mg vial.

METHOD OF ADMINISTRATION

- **IV injection:** over 3-5 min.
- **IV infusion:** over 15-30 minutes with a concentration between 1-30 mg/mL.
- **IM injection:** into a deep large muscle.

DOSAGE

Usual dose range:

- Children and infants: 30-240 mg/kg/day given in 3-4 divided doses
- Neonates: 30-100 mg/kg/day given as 2-3 divided doses.
- Doses will vary according to indication and severity of infection.
- Dose adjustment required in renal impairment.

COMPATIBILITIES AND STABILITY

Compatible with: NS, D5W, Hartmann's, Ringer's solution; **Flush** with: NS or D5W.
Incompatible with: sodium bicarbonate
Store in the original packaging to protect from light. Use immediately upon reconstitution and dilution.
Do not mix in syringe with aminoglycoside antibiotics. If administering concurrently, give at different sites.
For **Axetine** brand: solution can turn darker when standing but change of intensity in colour doesn't affect safety or effectiveness. Freshly prepared solution for IV administration is yellowish, while suspension for IM administration is almost white.
For **Villerton** brand: reconstituted solution can vary from light yellow to amber.

POTENTIAL HAZARDS OF ADMINISTRATION

- Cross-sensitivity may occur in penicillin-allergic patients (up to 10% of patients); severe reactions including anaphylaxis.
- Thrombophlebitis following IV injection and pain and/or inflammation following IM injection.
- Seizures reported especially in patients with renal impairment, when the dosage was not decreased.
- Neutropenia, eosinophilia, leukopenia.
- Liver enzyme elevations, cholestatic jaundice and transient hepatitis reported rarely.
- May increase INR, especially in nutritionally-deficient patients, prolonged treatment, hepatic or renal disease.

MISCELLANEOUS

- **Monitor**: U&Es, LFTs, FBC, prothrombin time in patients at risk; observe for signs and symptoms of anaphylaxis during the first dose.
- Sodium content: 0.55 mmol/250 mg vial; 1.8 mmol/750 mg vial.
- May interfere with: Coombs' test; non-enzymatic methods for glucose determination in urine (eg. Benedict's, Fehling's or Clinitest). For this reason, urine-glucose determination during therapy with cefuroxime should be carried out enzymatically.

REFERENCES

1, 2, 4, 7, 8, 9, 10, 12, 14, 15, 18, 20, 21, 23, 24, 25

NAME OF MEDICATION	CLARITHROmycin
STRENGH / TRADE NAME / MANUFACTURER)	500 mg powder for solution for infusion / clarithromycin/ Bowmed Ibisqus Ltd. 500 mg powder for solution for infusion / Maxilin®/ AnFarm Hellas S.A.
CLASSIFICATION	Macrolide Antibiotic

INDICATIONS FOR USE

Treatment whenever parenteral therapy is required for infections by susceptible organisms in the following conditions:

- Lower respiratory tract infections for example acute and chronic bronchitis and pneumonia
- Upper respiratory tract infections for example sinusitis and pharyngitis
- Skin and soft tissue infections

Off-license IV infusion is not licensed for use in children under 12 years.

RECONSTITUTION and DILUTION

Using a whole vial: Reconstitute with 10 mL WFI and shake the vial to dissolve the contents (final conc. 50 mg/mL). Dilute up to 250 mL D5W or NS. This provides a 2 mg/mL solution.
Using part of vial: If a dose is less than 500 mg dilute each 1 mL of the reconstituted solution with 25 mL of NS or D5W (final conc. 2mg/mL)
DO NOT reconstitute with NS.

METHOD OF ADMINISTRATION

IV infusion over 60 minutes. Administer via a large peripheral vein. Max. conc. 2 mg/mL.
Fluid restriction: **(Off-license):** concentrations of up to 5 mg in 1 mL can be given via a central venous access device.

DOSAGE

Treatment of respiratory tract infections, skin and soft tissue infections, otitis media:

- 1 month-11 years (Off-license): 7.5 mg/kg every 12 hours (max. per dose 500 mg every 12 hours) maximum duration 5 days, switch to oral route when appropriate, to be administered into a large proximal vein.
- 12 years-17 years: 500 mg every 12 hours maximum duration 5 days, switch to oral route when appropriate, to be administered into a large proximal vein.

Dose adjustments necessary in renal impairment

COMPATIBILITIES AND STABILITY

- **Compatible with:** NS, D5W, Hartmann's and Ringer's solution. **Flush** with NS.
- Use immediately. Vials are single use; discard any unused portion.
- Solution should be clear and colourless.
- Not to be administered if the solution becomes more intensely coloured

POTENTIAL HAZARDS OF ADMINISTRATION

- QT prolongation and infrequent cases of arrhythmias, including torsades de pointes
- Elevated LFTs and hepatitis (hepatocellular and/or cholestatic with or without jaundice) reported; usually reversible after discontinuation.
- Severe acute reactions reported, including anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis , drug rash with eosinophilia and systemic symptoms (DRESS), Henoch-Schönlein purpura (IgA vasculitis), and acute generalized exanthematous pustulosis; discontinue therapy and initiate treatment immediately for severe acute hypersensitivity reactions.
- Diarrhoea, ranging in severity and including *C. difficle* diarrhoea and pseudomembranous colitis.
- May aggravate myasthenia gravis.
- Injection site inflammation, tenderness, phlebitis and pain. Extravasations if administered too rapidly.

MISCELLANEOUS

- **Monitor:** FBC, U&Es, LFTs; injection site at regular intervals.
- Avoid in severe hepatic failure if renal impairment also present.
- Use with caution in electrolyte abnormalities as this may potentiate QT interval prolongation.
- Should not be used with HMG Co-A reductase inhibitors (statins).
- Concomitant use with oral hypoglycaemic agents and/or insulin can result in significant hypoglycaemia.
- Increased risk of haemorrhage and significant elevations in INR and PT when used with warfarin. Monitor frequently.
- Possibility of cross resistance between clarithromycin and lincomycin and clindamycin.

REFERENCES

1, 2, 3, 4, 6, 7, 8, 10, 12, 14, 16, 18, 19, 26

NAME OF MEDICATION	**Co-Amoxiclav**
STRENGH / TRADE NAME / MANUFACTURER	500 mg/100 mg powder for solution for injection or infusion / Co-Amoxiclav / Bowmed Ibisqius Ltd 1000 mg/200 mg powder for solution for injection or infusion / Co-Amoxiclav / Bowmed Ibisqius Ltd 1000 mg/200 mg powder for solution for injection or infusion / Augmentin ® / GlaxoSmithKline Ltd
CLASSIFICATION	**Beta-Lactam Penicillin Antibiotic**

INDICATIONS FOR USE

Infections due to beta-lactamase producing strains (where amoxicillin alone not appropriate), including infections of respiratory tract, bone and joint, genito-urinary tract, abdomen, cellulitis, dental infections, animal bites and surgical prophylaxis.

RECONSTITUTION and DILUTION

Slow IV injection:

- Dissolve 600 mg (500 mg/100 mg) vial in 10mL WFI; dilute up to 15 mL using NS (resultant concentration: 40 mg/mL)
- Dissolve 1.2 g (1000 mg/200 mg) vial in 20mL WFI; dilute up to 30 mL using NS (resultant concentration: 40 mg/mL)

IV infusion:

- Doses up to 500/100 mg: add dose to 50 mL of infusion fluid.
- Doses higher than 500/100 mg up to 1000 mg/200 mg vial: add dose to 100 mL of infusion fluid.

To be administered within 20 min of reconstitution. To be added to infusion fluid without delay after reconstitution.

METHOD OF ADMINISTRATION

- **Slow IV injection:** over 3 to 4 minutes directly into a vein or via a drip tube.
- **IV infusion:** over 30 to 40 minutes.

Children aged **less than 3 months** should be administered Co-amoxiclav by infusion only.

DOSAGE

Treatment of Infections where amoxicillin alone not effective, including respiratory tract infections, bone and joint infections, genito-urinary and abdominal infections, cellulitis and animal bites.

- Neonate up to 2 months: 25 mg/5 mg per kg every 12 hours.
- Child 3 months to 17 years: 25 mg/ 5 mg per kg every 8 hours; max. per dose 1000 mg/ 200 mg every 8 hours.

Dose to be adjusted in renal impairment.

COMPATIBILITIES AND STABILITY
• **Compatible with:** NS, WFI. **Flush** with NS. • **Incompatible with:** D5W. • Do not mix with aminoglycosides in same syringe, intravenous fluid container or giving set. Administer at a different site or flush line thoroughly between drugs. • Vials are single use; any unused portion should be discarded. • Reconstituted solutions are normally colourless or a pale straw colour. A transient pink colouration may develop during reconstitution, which solution should be discarded.
POTENTIAL HAZARDS OF ADMINISTRATION
• **Not to be used if patient experienced previous beta-lactam allergy.** • Anaphylaxis/ hypersensitivity reactions. Thrombophlebitis at the site of injection. • Severe hepatic events (Increased transaminases, hepatitis and cholestatic jaundice), usually in patients with serious underlying disease or taking concomitant hepatotoxic drugs. • Accumulation of electrolytes with high doses or renal failure. • Convulsions may occur with impaired renal function or high doses. • Abnormal prolongation of prothrombin time in patients receiving anticoagulants. • Antibiotic associated colitis, diarrhoea developed post antibiotic. • Superinfection especially if treatment is prolonged.
MISCELLANEOUS
• Monitor: FBC, LFTs and U&Es periodically with prolonged therapy. • Check patency of bladder catheter with large doses. • Maintain adequate fluid intake and observe frequent urine output. • Sodium content: 1.4 mmol per 600 mg vial; 2.7 mmol per 1.2 g vial. • Potassium content: 0.5 mmol per 600 mg vial; 1 mmol per 1.2 g vial. • May interfere with urinary glucose tests (Benedict's solution, Clinitest), might yield false positive Coomb's test.
REFERENCES
1, 2, 3, 4, 6, 7, 8, 10, 12, 13, 15, 16, 19, 20

NAME OF MEDICATION	FlucLOXacillin
STRENGH / TRADE NAME / MANUFACTURER	250 mg & 1 g powder for solution for injection or infusion / Bowmed Ibisqus Ltd. 250 mg powder for solution for injection or infusion / Wockhardt
CLASSIFICATION	Antibiotic-Penicillin

INDICATIONS FOR USE

Treatment of susceptible infections caused by gram-positive organisms, including Beta-lactamase-producing Staphylococci and Streptococci.
Prophylactic agent during major surgical procedures when appropriate.

RECONSTITUTION and DILUTION

IV injection: 250 mg vial: Reconstitute with 4.8 mL WFI to give a final concentration of 50 mg/mL.

1 g vial: Reconstitute with 19.4 mL WFI to give a final concentration of 50 mg/mL.

IV infusion: add reconstituted solution to a convenient volume of NS or D5W (usually 100 mL). Max conc. for infusion 20 mg/mL

IM injection: Add 1.5 mL WFI to 250 mg vial.

METHOD OF ADMINISTRATION

Slow IV injection: over 3-5 minutes.
IV Infusion: Administer over 30-60 minutes. Maximum conc. 20 mg/mL.
IM injection

Dosage

Infections due to beta-lactamase-producing staphylococci including otitis externa; adjunct in pneumonia, impetigo and cellulitis:

- Neonate up to 7 days: IV – 25 mg/kg every 12 hours
- Neonate 7 days up to 20 days: IV – 25 mg/kg every 8 hours
- Neonate 21 days up to 28 days: IV – 25 mg/kg every 6 hours
- Child: IV/IM - 12.5–25 mg/kg every 6 hours (max. per dose 1 g every 6 hours)

Dose per kg may be doubled in severe infections.

For osteomyelitis, cerebral abscess, and staphylococcal meningitis:

- Neonate up to 7 days: IV - 50–100 mg/kg every 12 hours
- Neonate 7 days up to 20 days: IV - 50–100 mg/kg every 8 hours
- Neonate 21 days up to 28 days: IV - 50–100 mg/kg every 6 hours
- Child: 50 mg/kg every 6 hours (max. per dose 2 g every 6 hours)

Endocarditis (in combination with other antibacterial if necessary):

- Children from 1 month of age: IV - 50 mg/kg every 6 hours (max. per dose 2 g every 6 hours).

Staphylococcal lung infection in cystic fibrosis:

- Child: IV - 50 mg/kg every 6 hours (max. per dose 2 g every 6 hours).

Dose adjustments necessary when creatinine clearance is less than 10 mL/minute.

COMPATIBILITIES AND STABILITY
• **Compatible with:** NS, D5W. • Use immediately upon reconstitution and dilution, discard any unused portion. • Solution should be clear , colourless, pale yellow and particles free. • If used in combination with an aminoglycoside, preferably administer at a different site. If this is not possible then flush the line with a compatible solution between drugs. Not to be combined with other drugs in solution for parenteral administration. • Should not be mixed with blood products, proteinaceous fluids (e.g. protein hydrolysates) or IV lipid emulsions.
POTENTIAL HAZARDS OF ADMINISTRATION
• Anaphylaxis, angioedema, rash and phlebitis, Stevens-Johnson syndrome, toxic epidermal necrolysis. • Hepatitis and cholestatic jaundice (especially with prolonged treatment and in patients with pre-existing hepatic dysfunction). • Seizure activity (especially with high doses and in patients with pre-existing neurological disorders). • Accumulation of electrolytes with high doses or in renal impairment. • Risk of kernicterus in jaundiced neonates with high doses.
MISCELLANEOUS
Monitor: U&Es, LFTs, FBC. **Sodium content:** 0.57 mmol/ 250 mg Wockhardt & Bowmed Ibisqus vial; 2.26 mmol/ 1g Bowmed Ibisqus vial. Contra-indicated in history of previous beta-lactam hypersensitivity.
REFERENCES
2, 3, 4, 5, 7, 8, 9, 10, 12, 14, 28

NAME OF MEDICATION	**GENTAMICIN**
STRENGH / TRADE NAME / MANUFACTURER	40mg/ mL Solution for injection 2mL/ Gentamicin /Sopharma 80mg/2mL Solution for injection or infusion 2mL / Gentamed®/ Medochemie limited
CLASSIFICATION	**Aminoglycoside Antibiotic**

INDICATIONS FOR USE

Treatment of infections caused by susceptible Gram-negative bacilli and Gram-positive *Staphylococcus*

RECONSTITUTION and DILUTION

IV injection: Ready diluted. May be further diluted with NS or D5W to aid slow administration.
IV infusion: Dilute 2 ml (80 mg) up to 40 mL using NS or D5W. Concentration: 2 mg/mL.

METHOD OF ADMINISTRATION

Slow IV injection (not recommended) : over 3-5 min
Intermittent IV infusion (preferred): over 20 minutes. Preferably administer via central venous access device, if unavailable administer via large peripheral vein.
IM injection

DOSAGE

1. Septicaemia, CNS infections and meningitis, biliary-tract infection, acute pyelonephritis, endocarditis, pneumonia in hospital patients and adjunct in listerial meningitis:
   i. Child – IV infusion: Initially 7 mg/kg given in a once daily regimen (not suitable for endocarditis or meningitis), subsequent doses adjusted according to serum-gentamicin concentration- **SPC Gentamed**
   ii. Child 1 month – 11 years – slow IV/ IM injection: 2.5 mg/kg every 8 hours, to be given in a multiple daily dose regimen- **SPC Sopharma**
   iii. Child 12-17 years – slow IV/IM injection: 2 mg/kg every 8 hours, to be given in a multiple daily dose regimen- **SPC Sopharma**
2. Neonatal sepsis - slow IV injection/ IV infusion:
   i. Neonate up to 7 days: 5 mg/kg every 36 hours, to be given in an extended interval dose regimen **(Unlicensed)**
   ii. Neonate 7 – 28 days: 5 mg/kg every 24 hours, to be given in an extended interval dose regimen- **SPC Gentamed**
3. Pseudomonal lung infection in cystic fibrosis - slow IV injection/ IV infusion:
   i. Child 3 mg/kg every 8 hours, to be given in a multiple daily dose regimen **(Unlicensed)**

Dose adjustments necessary in renal impairment and extremes of body weight.

COMPATIBILITIES AND STABILITY
Compatible with: NS, D5W. Use immediately upon opening/ dilution. If used in combination with a penicillin or cephalosporin, preferably administer at a different site. If this is not possible then flush the line thoroughly with a compatible solution between drugs.
POTENTIAL HAZARDS OF ADMINISTRATION
Ototoxicity (irreversible, cumulative). Nephrotoxicity (reversible if discontinued at first sign of azotemia). Neurotoxicity. Electrolyte disturbances on prolonged therapy.
MISCELLANEOUS
Monitor: Gentamicin serum concentrations, U&Es, fluid balance, auditory and vestibular function, LFTs, FBC, urinalysis, urine output , signs and symptoms of phlebitis and extravasation. Serum conc. to be taken at least twice weekly(every 3rd day) : Trough level to be taken one hour before next dose and it should not exceed 2 mg/L when administering gentamicin twice daily and not to exceed 1 mg/L when administering it once daily or in endocarditis treatment. Peak level to be taken one hour after administering dose and it should not exceed 10 mg/mL. Ensure good hydration status. If possible, dehydration should be corrected before starting therapy. Caution in patients with neuromuscular disorders since they may aggravate muscle weakness. Use with caution in patients with hypocalcemia, hypokalemia, or hypomagnesemia. Larger doses or shorter dosing intervals of aminoglycosides are sometimes required in patients with cystic fibrosis, major thermal burns or dermal loss, ascites, or in patients with febrile granulocytopenia. **Laboratory interference**: Serum concentrations may be falsely elevated when blood samples are collected through central venous Silastic catheters.
REFERENCES
2, 4, 6, 7, 8, 9, 10, 12, 14, 18, 19, 20, 27, 28, 29, 30, 31, 32

Monitoring Appendix

Monitoring of serum Gentamicin is not required in patients with negative blood culture after 48 hours of receiving Gentamicin and who has no increase in inflammatory markers e.g C-reactive protein (CRP) at 18 and 24 hours post Gentamicin treatment and are assessed to be clinically well to discontinue treatment.

Serum Gentamicin is required to be monitored in patients who will continue with treatment.

Monitoring is done by withdrawing trough levels 0 to 60 minutes prior next dose. Sample has to be taken from the same central line it was infused through (use a different port if it has more than one lumen) if a different infusion was being infused continuously between the Gentamicin doses.
The first trough level should be taken post first dose and prior to second dose and then it has to be taken at least twice weekly (every 3rd day). Frequency of the monitoring depends on the patient's condition and presence of risk factors.

- Patients with normal renal function: trough levels for the first time has to be taken before 2nd dose. If the level is < 1.5 mg/L then trough level need to be withdrawn every 3rd dose.
- Patients with normal renal function but with any of the risk factors listed below: the trough level has be to taken every alternate dose
- Patients with renal impairment and risk factors: tough level needs to be taken prior to each dose

Risk factors:

1- Clinical factors: Dehydration , diarrhoea or persistent vomiting , renal impairment (reduced urine output < 1 mL/kg/ hour) , poor cardiac output, sepsis requiring inotropes , asphyxiated neonates
2- Concomitant medications: Amphotericin, ACE inhibitors, Cephalosporins e.g Cefotaxime, Furosemide, NSAIDs (Ibuprofen or Indomethacin), Vancomycin.

Trough level values must not exceed 2 mg/L in multiple daily dosing and must not exceed 1 mg/L in once daily dosing and in endocarditis treatment. Dose interval adjustment is required in case trough levels are high. Peak concentration must be taken 1 hour post dose and should be in the range 5-10 mg/mL. A peak concentration higher than 10 mg/mL requires dose adjustment.

Dosing intervals adjustment depending on trough level value

Trough levels taken before 2nd or 3rd dose in once daily dosing regimen in neonates < 1 month	Action
< 1.5 mg/L	Repeat monitoring every 3rd dose if there are no risk factors
1.5 – 1.9 mg/L	Repeat trough gentamicin level prior next dose and then daily before subsequent doses if levels remain within this range
> 2 mg/L	Withhold dose. If on 24 hourly dosing interval increase interval to 36 hourly; if on 36 hourly dosing interval increase interval to 48 hourly. Random trough gentamicin level must be < 2mg/L before subsequent dose can be given

Trough levels taken before the 4th dose in Neonates and in all Infants (≥ 1 month old)	Action
< 1 mg/ mL	Repeat monitoring every 3rd dose if there are no risk factors
> 1 mg/ mL	Withhold dose. If on 24 hourly dosing interval increase interval to 36 hourly; if on 36 hourly dosing interval increase interval to 48 hourly. Random trough gentamicin level must be < 1mg/L before subsequent dose can be given

NAME OF MEDICATION	**hydrocortisone**
STRENGH / TRADE NAME / MANUFACTURER	100 mg powder for solution for injection and Infusion/ Hydrocortisone Medo/ Medochemie
CLASSIFICATION	**Corticosteriod; Anti-inflammatory agent**

INDICATIONS FOR USE

- Conditions when rapid and intense corticosteroid activity is required.
- Conditions which require corticosteroid treatment when the oral route is temporarily unavailable or inappropriate.

RECONSTITUTION and DILUTION

- **IV injection:** reconstitute with 2 mL WFI.
- **IV infusion:** reconstitute with 2 mL WFI. Add to 100mL with NS, D5W, and D5NS. Maximum concentration: 1mg/ml.
- **IM injection:** reconstitute with 2 mL WFI.

METHOD OF ADMINISTRATION

- **IV injection:** over 3-5 min. Take the required volume which contains the prescribed dose and top up as necessary with NS to facilitate administration
- **IV infusion:** over 20-30 min. Maximum concentration is 1 mg/mL.
- **IM injection:** avoid giving in deltoid muscle because of high incidence of tissue atrophy.

DOSAGE

Acute adrenocortical insufficiency (Addisonian crisis)

- Neonate: slow IV injection. Initially 10 mg then 100 mg/m^2 daily as a continuous infusion or in divided doses every 6-8 hours.
- Child 1 month -11 years: slow IV injection/IV infusion. Initially 2-4 mg/kg, then 2-4 mg/kg every 6 hours.
- Child 12-17 years: 100 mg every 6-8 hours by slow IV injection or IV infusion.

Inflammatory bowel disease-induction of remission

- Child 2-17 years: 2.5 mg/kg every 6 hours (max. per dose 100mg) by IV injection OR 10 mg/kg daily; max 400 mg/day by continuous IV infusion.

Acute hypersensitivity reactions, Angioedema (by IM/IV injection)

- Child 1-5 months: initially 25 mg 3 times a day.
- Child 6 months – 5 years: initially 50mg 3 times a day.
- Child 6-11 years: initially 100 mg 3 times a day.
- Child 12-17 years: initially 200 mg 3 times a day.

Hypotension resistant to inotropic treatment and volume replacement (Unlicensed)

- Neonate: IV injection initially 2.5 mg/kg then 2.5 mg/kg after 4 hours if required, followed by 2.5 mg/kg every 6 hours for 48 hours or until blood pressure recovers, dose to then be reduced gradually over at least 48 hours.
- Child: IV injection 1mg/kg every 6 hours (max. per dose 100 mg).

Severe acute asthma, life-threatening asthma

- Child 1 month-1 year: IV injection 4 mg/kg every 6 hours (max. per dose 100 mg), alternatively 25 mg every 6 hours.
- Child 2-4 years: IV injection 4 mg/kg every 6 hours (max. per dose 100 mg), alternatively 50 mg every 6 hours.
- Child 5-17 years: IV injection 4 mg/kg every 6 hours (max. per dose 100 mg), alternatively 100 mg every 6 hours.

Dose adjustment may be necessary in liver cirrhosis and hypothyroidism.

COMPATIBILITIES AND STABILITY

- **Compatible with:** D5W, NS, D5NS
- Reconstituted solution to be used immediately. Should be inspected visually for particle formation or discoloration prior to administration. Protect reconstituted solution from light.

POTENTIAL HAZARDS OF ADMINISTRATION

- Anaphylaxis and other hypersensitivity reactions reported; acute myopathy (with high doses). Pheochromocytoma crisis.
- **Short-term use***:* ↑BP, Na and water retention, ↓K, ↓Ca, ↑blood glucose, peptic ulceration and perforation, psychiatric reactions (depression, euphoria, and mood disorder) behavioural disturbances, ↑susceptibility to infection, muscle weakness, tendon rupture, insomnia, ↑intracranial pressure, ↓seizure threshold, impaired healing and injection site reaction.

MISCELLANEOUS

- Monitor: BP, weight, serum glucose frequently during acute illness, signs of infection, U&Es, If on long term treatment - growth status, bone mineral density, intraocular pressure.
- Acute adrenal insufficiency may occur with abrupt withdrawal after long term therapy or with stress; taper off slowly.
- Avoid live vaccinations in those with immunosuppressive doses.
- Patients may require higher doses when subject to stress (ie, trauma, surgery, severe infection).
- Sodium content: 0.39 mmol per vial.

REFERENCES

4, 6, 8, 9, 14, 15, 18, 27, 33

NAME OF MEDICATION	**metroNIDAZOLE**
STRENGH / TRADE NAME / MANUFACTURER	5 mg/mL solution for Infusion/ Metronidazole /B. Braun Melsungen AG 500 mg/100 mL solution for Infusion/ Metronidazole Kabi/Fresenius Kabi
CLASSIFICATION	**Amebicide; Antibiotic, Anaerobic; Antiprotozoal**

INDICATIONS FOR USE

Treatment and prophylaxis of infections due to susceptible microorganisms (mainly anaerobic bacteria) and protozoa.

RECONSTITUTION and DILUTION

Ready diluted.

METHOD OF ADMINISTRATION

- **Slow IV infusion** over 30-60 min.
- Do not use aluminium containing equipment that would come in contact with the drug (e.g. needles, cannulae).

DOSAGE

Infections caused by anaerobes:

- 0 to 8 weeks: 15 mg/kg in a single daily dose or divided into 7.5 mg/kg every 12 hours.
- 8 weeks up to 12 years old: 20-30 mg/kg/day as a single dose or divided into 7.5 mg/kg every 8 hours for 7 days. The daily dose can be increased up to 40 mg/kg, depending on the severity of the infection.
- Children over 12 years: 500 mg every 8 hours.

Prophylaxis against postoperative infections caused by anaerobic bacteria:

- Neonates with a gestational age <40 weeks: 10 mg/kg body weight in a single dose before the operation.
- Children under 12 years old: 20-30 mg/kg in a single dose given 1-2 hours before the surgery.
- Children over 12 years old: 500 mg immediately before, during or after the operation followed by same dose every 8 hours.
- Dose adjustment in patients with impaired liver function.

COMPATIBILITIES AND STABILITY

- **Flush:** NS, D5W.
- No additives to be added into the injection.
- Protect from exposure to light during storage.
- Use immediately. Discard any unused portion.

POTENTIAL HAZARDS OF ADMINISTRATION
• Anaphylaxis, erythema, urticaria, angiodema, pruritus, thrombophlebitis. • Peripheral neuropathy characterized by numbness of an extremity, convulsive seizures with large cumulative doses, headaches, and dizziness. • GI symptoms: Nausea, vomiting, diarrhoea, furred tongue, metallic taste in the mouth.
MISCELLANEOUS
• **Monitor**: serum conc. if treatment exceeds 10 days, or after few days in neonates with gestational age < 40 days. LFTs, FBC periodically. Symptoms of peripheral or central neuropathy (paraesthesia, ataxia, dizziness and convulsive crisis). • Sodium content: 13.13 mmol/100 mL for Fresenius Kabi; 14 mmol/100 mL for B. Braun. • Caution in hepatic impairment and hepatic encephalopathy. • May decrease levels of enzymatic assay of ALT, AST, Lactate dehydrogenase, triglycerides and glucose. • Causes darkness in urine colour. • May ↑side effects of coumarin anticoagulants (warfarin), monitor INR, monitor phenytoin level, monitor busulfan level. • Due to interactions between metronidazole and alcohol, prescribers should be cautious when prescribing liquid preparations that contain alcohol concurrently with metronidazole. • Avoid alcoholic beverages or products containing propylene glycol during oral or injectable therapy and for at least 3 days after therapy.
REFERENCES
2, 4, 5, 6, 8, 9, 12, 18, 20, 21

NAME OF MEDICATION	ONDANSETRON
STRENGH / TRADE NAME / MANUFACTURER	4 mg/ 2 mL solution for injection/ Ondansetron / Accord 4 mg/ 2 mL solution for injection/ Ondansetron / Hamlen 8 mg/ 4 mL solution for injection/ Ondansetron / Accord
CLASSIFICATION	

INDICATIONS FOR USE

Management of chemotherapy and radiotherapy -induced nausea and vomiting in children aged ≥6 months.
Prevention and treatment of post-operative nausea and vomiting in children aged ≥ 1 month.
Not licensed for use in radiotherapy-induced nausea and vomiting.

RECONSTITUTION and DILUTION

IV injection: Give undiluted.
IV infusion: Dilute each 1 mL (2 mg) up to 5 mL using NS or D5W. Final concentration: 0.4 mg/mL
Required concentration can be in the range of 0.32-0.64 mg/mL diluted with D5W or NS.

METHOD OF ADMINISTRATION

Slow IV injection in post-operative nausea and vomiting**:** over at least 30 seconds, preferably over 2 to 5 minutes.
Intermittent IV infusion in chemotherapy/radiotherapy-induced nausea and vomiting**:** over at least 15 minutes.
Preferably administer via a central venous access device; if unavailable administer via a large peripheral vein.

DOSAGE

Prevention and treatment of chemotherapy- and radiotherapy-induced nausea and vomiting:
Initial dose in children aged ≥ 6 months and adolescents: 5mg/m^2; Maximum dose: 8mg. Give orally after initial IV dose; Can be repeated every 8-12 hours during chemotherapy and for at least 24 hours after chemotherapy. Maximum: 32mg per day.
Prevention and treatment of postoperative nausea and vomiting: in children aged from 1 month, 100 micrograms/kg (maximum 4 mg) may be given as a single dose by slow intravenous injection before, during, or after the induction of anaesthesia.)
Dose adjustment necessary in moderate or severe hepatic impairment.

COMPATIBILITIES AND STABILITY

Compatible with: NS, D5W.
Incompatible with: sodium bicarbonate.
After first opening or dilution, use immediately.
Protect unopened ampoules from light.

POTENTIAL HAZARDS OF ADMINISTRATION

Anaphylactic reactions.
Local injection site reactions; extravasation.
Extrapyramidal reactions, dizziness and transient visual disturbances (e.g. blurred vision) during rapid IV administration (resolves within few minutes up to 48 hours). Increasing infusion time can prevent or resolve dizziness.
Blood pressure changes and QT interval prolongation. Elevation in LFTs.

MISCELLANEOUS

- **Monitor:** baseline ECG (if applicable); U&Es (particularly potassium and magnesium); ECG changes in patients with hypokalemia , hypomagnesemia, CHF, arrhythmias or patients receiving medications leading to QT prolongation.
- Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration.
- Contraindicated in congenital long QT syndrome, and contraindicated in concomitant use with apomorphine.
- **Sodium content:** A maximum daily dose of 32mg ondasteron contains; 2.3mmol of sodium (Hameln); 2.5mmol of sodium (Accord).

REFERENCES

2, 3, 4, 5, 6, 7, 8, 9, 15, 18, 20

NAME OF MEDICATION	**piperacillin/tazobactam**
STRENGH / TRADE NAME / MANUFACTURER	2 g/0.25 g Powder for Solution for Infusion/ Piperacillin/Tazobactam / Wockhardt 4 g/0.5 g Powder for Solution for Infusion / Piperacillin/Tazobactam / Wockhardt 4 g/0.5 g Powder for Solution for Infusion / Piperacillin/Tazobactam / Stragen
CLASSIFICATION	**Antibiotic - Penicillin**
INDICATIONS FOR USE	
Licensed for children over 2 years old only in : • Complicated intra-abdominal infections & neutropenic children with fever. **Licensed in adolescents of 12 to 17 years old only in:** • Severe pneumonia; Complicated urinary tract infections, intra-abdominal infections, skin and soft tissue infections; • Management of neutropenic patients with fever. **Regulated by DPA protocol MP 162**	
RECONSTITUTION and DILUTION	
Reconstitute each 2 g/ 0.25 g vial with 10 mL and each 4 g/ 0.5 g vial with 20 mL of WFI or NS. The reconstituted solution should be further diluted to at least 50 mL with NS or D5W.	
METHOD OF ADMINISTRATION	
IV infusion over 30 min.	

DOSAGE

Dose and frequency depend on severity and localisation of the infection and expected pathogens.

Hospital-acquired pneumonia, septicaemia and complicated infections involving urinary-tract, skin and soft tissues:

- Neonate up to 1 month: 80 mg Piperacillin/10 mg Tazobactam per kg body weight every 8 hours. **(Unlicensed use).**
- Child 1 month-11 years: 80 mg Piperacillin/10 mg Tazobactam per kg body weight every 6-8 hours (max. per dose 4 g/0.5 g every 6 hours). **(Unlicensed till the age of 12 years).**
- Child 12-17 years: 4 g/ 0.5 g every 8 hours increased if necessary to 4 g/ 0.5 g every 6 hours, increased frequency may be used for severe infections

Complicated intra-abdominal infections:

- Child 2-11 years: 100 mg Piperacillin/12.5 mg Tazobactam per kg body weight every 8 hours (max. per dose 4 g/ 0.5 g).
- Child 12-17 years: 4 g/ 0.5 g every 8 hours; increased if necessary to 4 g/ 0.5 g every 6 hours, increased frequency may be used for severe infections.

Infections in neutropenic patients:

- Child: 80 mg Piperacillin /10 mg Tazobactam per kg body weight every 6 hours (max. per dose 4 g/ 0.5 g).

- **Dose adjustment necessary in renal impairment.**

COMPATIBILITIES AND STABILITY

- **Compatible with:** WFI, NS, D5W.
- **Incompatible with**: Hartmann's solution.
- Do not infuse with any other medicines or infusion fluids.
- To be administered only if solution is clear and free from particles. Use immediately upon reconstitution and dilution.

POTENTIAL HAZARDS OF ADMINISTRATION

- Penicillin anaphylaxis/ hypersensitivity reactions; thrombophlebitis; serious skin reactions (Stevens-Johnson syndrome).
- Pseudomembranous colitis manifested during or after treatment.
- Prothrombin time, platelet aggregation, and clotting time abnormalities particularly in patients with renal impairment. Discontinue if thrombocytopenia or bleeding occurs.

CNS toxicity (including convulsions and encephalopathy) especially with high doses and impaired renal function.

MISCELLANEOUS
• **Monitor:** U&Es, FBC, LFTs, prothrombin time (PT), partial thromboplastin time (PTT), signs of anaphylaxis. • **Sodium content:** 4.72 mmol per 2 g/0.25 g vial/Wockhadt; 9.44 mmol per 4 g/0.5 g vial/Wockhardt; 9.4 mmol per 4 g/0.5 g vial/Stragen. • Hypokalaemia may occur in patients with low potassium reserves or those receiving concomitant medicinal products that may lower potassium levels. False positive Coomb's test; false-positive urinary glucose results (if tested for reducing substances).
REFERENCES
2, 3, 4, 5, 8, 10, 14, 16 , 20, 21

NAME OF MEDICATION	POTASSIUM CHLORIDE
STRENGTH / TRADE NAME / MANUFACTURER	Sterile Potassium Chloride 20% w/v Concentrate for Solution for Infusion (2.6 mmol/mL)/ Martindale Pharmaceuticals
CLASSIFICATION	Electrolyte Supplement

INDICATIONS FOR USE

Treatment or prevention of hypokalemia when oral replacement is inadequate.

RECONSTITUTION and DILUTION

Dilute by adding to an appropriate volume of a suitable infusion fluid to achieve a concentration of 20-40 mmol/L.
Mix well before use, invert bag 10 times to ensure thorough mixing.

METHOD OF ADMINISTRATION

IV infusion via a peripheral line: usual maximum potassium concentration 40mmol/L
Give at a maximum rate of 0.2mmol/kg/hour (but no more than 20mmol/hour) using an infusion pump
IV infusion via a central venous access device: Continuous ECG monitoring is required for rates exceeding 0.2 mmol/kg/hour. Usual maximum rate is 0.5mmol/kg/hour (but no more than 20mmol/hour).

Take potassium content of any concurrent parenteral nutrition into account.

DOSAGE

1-2 mmol/kg/day dose dependent on deficit or daily maintenance requirements.
Maximum dose: 3 mmol/kg/day

COMPATIBILITIES AND STABILITY

Compatible with: NS (preferred), D5W, NSD5W, Hartmann's.

POTENTIAL HAZARDS OF ADMINISTRATION (6, 14)

- Extravasation; ensure proper catheter or needle position prior to and during infusion.
- Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use with caution or avoid use in patients with predisposing conditions for hyperkalemia (e.g., chronic or severe renal impairment, extensive burns or tissue injury, heart failure, acute dehydration, systemic acidosis, adrenal insufficiency, or the administration of potassium-sparing diuretics). Monitor serum potassium closely.
- Hypersensitivity/infusion reactions, including anaphylaxis and chills.

MISCELLANEOUS
• **Monitor:** serum $K^{+,}$ $Cl^{-,}$ Mg^{2+}, glucose, continuous ECG if rate exceeds 0.2 mmol/kg/hour, urine flow. Initial potassium replacement therapy should not involve glucose infusions as glucose may cause a further decrease in the plasma-potassium conc. Smaller doses must be used in the prevention of hypokalaemia, to reduce the risk of hyperkalaemia.
REFERENCES
4, 6, 7, 8, 9, 12, 18, 20, 21, 35, 36

Appendix:

Potassium requirement:

1. Calculate total dose required per day i.e. 2mmol/kg x weight of baby in Kg = A mmol
2. Calculate total fluid requirement of the baby per day in mLs/kg, mLs/kg multiplied by weight = B mLs
3. Therefore you require A mmol of potassium in B mLs over 24 hours
4. To calculate how much potassium you require to add to the 500 mL bag :
   $\frac{500 \times A}{B}$ = C mmol to be added to the 500 mL bag
5. Potassium is available as 26.8 mmol / 10 mL To calculate the number of mLs to be added = number of mmol needed x 0.37 mL
6. Rate of infusion should be calculated as 0.2 mmol/kg/hour – (BNF) over at least 2-3 hours (BNF, PID, Medusa) but max of 20 mmol/hour (SPC, Medusa).

- Each 0.37 mL of 20% w/v Potassium chloride has 1 mmol of potassium

East Chire -NHS Trust. Intravenous Potassium Policy, version 4 Lead Pharmacist Surgical Specialities. 10/11/2015. Available from: http://www.eastcheshire.nhs.uk/About-The-Trust/policies/P/Potassium%20-%20Intravenous%20Policy%20ECT2422.pdf

Maintenance fluid calculation:

- For infants 3.5 to 10 kg the daily fluid requirement is 100 mL/kg.
- For children 11-20 kg the daily fluid requirement is 1000 mL + 50 mL/kg for every kg over 10.
- For children > 20 kg the daily fluid requirement is 1500 mL + 20 mL/kg for every kg over 20, up to a maximum of 2400 mL daily.

NAME OF MEDICATION	**raNITIdine**
STRENGTH / TRADE NAME / MANUFACTURER	25 mg/mL in 2 mL solution for injection/infusion [Pep-Rani® (Medinfar)]; [Ptinolin® (Help S.A)]
CLASSIFICATION	**Histamine H_2 - Receptor Antagonist**

INDICATIONS FOR USE

Short term treatment of active duodenal or benign gastric ulcer, post-operative ulcer, reflux oesophagitis.
Treatment of pathologic gastric hypersecretory conditions such as Zollinger-Ellison syndrome.
Prophylaxis of stress ulceration .

RECONSTITUTION and DILUTION

Slow IV injection: dilute up to 10 mL **(**max. conc. 2.5 mg/mL (i.e. dilute each 1 mL neat drug (25 mg) up to 10 mL NS)
Intermittent IV infusion: dilute to a conc. not greater than 0.5 mg/mL by adding dose to a 50-100 mL NS
Continuous IV infusion: dilute to a conc. of 0.5 mg/mL or less by adding dose to a 100 mL NS

METHOD OF ADMINISTRATION

Slow IV Injection: over at least 5 minutes; Rate should not exceed 10 mg/minute.
Intermittent IV infusion: over 15 to 20 minutes.
Continuous IV infusion: rate of 0.03-0.06 mg/kg/hour for neonates and 0.125 – 0.25 mg for older.

DOSAGE

Injection not licensed for use in children under 6 months.

- *Prophylaxis of stress ulceration: Slow IV injection*

Neonate: 0.5-1 mg/kg every 6-8 hours.
Child 1 month- 11 years: 1 mg/kg every 6-8 hours (max. per dose 50 mg), may be given as intermittent infusion at a rate of 25mg/hour.
Child 12-17 years: 50 mg every 8 hours.
For dosing of continuous IV infusion contact pharmacy.

- *Reflux oesophagitis and other conditions where gastric acid reduction is beneficial: Slow IV injection*

Neonate: 0.5-1 mg/kg every 6-8 hours.
Child: 1mg/kg every 6-8 hours (max. per dose 50 mg) may be given as intermittent infusion at a rate of 25 mg/hour.
For dosing of continuous IV infusion contact pharmacy.
Adjust dose in patients with renal impairment

COMPATIBILITIES AND STABILITY
• **Compatible** with: NS, D5W, Hartmann's solution; **Flush** with: NS. • Use immediately; discard any unused portion. • Solution is a clear, colourless to light yellow solution. If stored correctly, slight darkening does not affect potency. • Do not infuse with any other medicines or infusions. Flush the line before and after giving IV injection.
POTENTIAL HAZARDS OF ADMINISTRATION
• Pain at the injection-site; burning and itching. • Bradycardia and cardiac arrhythmias. Do not exceed recommended administration rates. • Hypersensitivity reactions such as hypotension, bronchospasm, dyspnoea, anaphylaxis, urticaria, chest pain, fever and angioneurotic oedema.
MISCELLANEOUS
• **Monitor:** U&Es, LFTs, FBC; signs of infection throughout treatment. • **Use PEP-RANI with caution in children, since safety and efficacy in paediatric population has not been established.** • Elevation in ALT levels has occurred with higher doses for more than 5 days; monitor ALT at beginning and at day 5. • **Laboratory interference:** May result in a false-positive urine protein test; testing with sulfosalicylic acid recommended.
REFERENCES
2, 4, 5, 6, 8, 9, 12, 15, 18

NAME OF MEDICATION	**Teicoplanin**
STRENGTH / TRADE NAME / MANUFACTURER	200 mg powder for solution for injection or infusion or oral solution/ Targocid®/ Sanofi 200 mg powder for solution for injection/infusion or oral solution/ Teicoplanin/ DEMO S.A.
CLASSIFICATION	**Glycopeptide antibiotic**

INDICATIONS FOR USE

Treatment of infections caused by susceptible gram-positive bacteria; bacteremia, complicated skin and soft tissue infections, complicated urinary tract infections, community and hospital acquired pneumonia, joint and bone infections , endocarditis, peritonitis associated with CAPD, Clostridium difficile-associated diarrhea, surgical prophylaxis.
Regulated by DPA Protocol MP 280

RECONSTITUTION and DILUTION

IV injection: Slowly inject the entire amount of the supplied solvent into the powder vial. Gently roll the vial with the reconstituted solution between the hands until the powder is completely dissolved. If the solution becomes foamy leave it to stand for approximately 15 minutes. Only clear and yellowish solutions should be used.
IV infusion: reconstitute as above then withdraw the required dose and add it to a suitable volume of compatible infusion fluid.

METHOD OF ADMINISTRATION

Slow IV Injection: over 3-5 minutes. Not to be used in neonates.
IV Infusion: over 30 minutes.
Reconstituted solution may be also given IM or orally.
*Should **not** be given by mouth for systemic infections because it is not absorbed significantly. For Clostridium difficile infection-associated diarrhoea and colitis, the oral route is to be used.*

DOSAGE

- *Neonates and infants up to age of 2 months:*

Loading dose of 16mg/kg by IV infusion on the first day, then after 24 hours give 8mg/kg once daily maintenance dose.

- *Children (2 months to 12 years):*

Loading dose of 10 mg/kg administered by IV infusion every 12 hours for 3 doses, then 6-10 mg/kg once daily maintenance dose.

- *Children 12 years and older :*

Usual dose – Loading dose of 400mg or 6mg/kg IV or IM every 12 hours for 3 doses then followed by maintenance doses IV/IM of 6mg/kg once a day.
Severe infections- Loading dose of 800mg or 12 mg/kg IV every 12 hours for 3 to 5 doses, followed by maintenance doses IV/IM of 12 mg/kg once daily.

Dose adjustment necessary in impaired renal function.

COMPATIBILITIES AND STABILITY

Compatible with NS, D5W, Hartmann's, Ringer solution, D5NS. Flush with NS or D5W.
Don't mix directly with aminoglycosides.
Don't infuse with other medicines and infusion fluids.
If administered in combination therapy with other antibiotics, the preparation must be administered separately.
Once reconstituted use immediately.

POTENTIAL HAZARDS OF ADMINISTRATION

- Injection site irritation, nausea, vomiting, headache, dizziness, fever and rigors, hypersensitivity, anaphylaxis and rarely (but even at the first dose) "red man syndrome". Stopping or slowing the infusion may result in cessation of 'red man syndrome' reactions.
- Thrombocytopenia, ototoxicity and nephrotoxicity.
- Stevens-Johnson syndrome, Toxic Epidermal Necrolysis; discontinue treatment if symptoms or signs present.

Cross hypersensitivity reactions with vancomycin may occur, including fatal anaphylactic shock.

-

MISCELLANEOUS

- **Monitor**: U&Es & auditory function tests (especially during prolonged treatment, renal impairment and concomitant nephrotoxic or neurotoxic drugs), FBC, LFTs.
- Manufacturer advises monitoring for adverse reactions when doses of 12 mg/kg twice daily are administered.

REFERENCES

2, 4, 6, 7, 8, 12, 20, 21, 24

Appendix 11-Face validity results

Question		P1	P2	P3	P4	P5	P6	P7	Average	Average
Q1	Clarity	4	4	4	4	4	4	4	4	4
	Ability to answer	4	4	4	4	4	4	4	4	
	Layout, style	4	4	4	4	4	4	4	4	
Q2	Clarity	4	4	4	4	4	4	4	4	4
	Ability to answer	4	4	4	4	4	4	4	4	
	Layout, style	4	4	4	4	4	4	4	4	
Q3	Clarity	4	4	4	4	4	4	4	4	4
	Ability to answer	4	4	4	4	4	4	4	4	
	Layout, style	4	4	4	4	4	4	4	4	
Q4	Clarity	4	4	4	4	4	4	4	4	4
	Ability to answer	4	4	4	4	4	4	4	4	
	Layout, style	4	4	4	4	4	4	4	4	
Q5	Clarity	4	4	4	4	4	4	4	4	3.95
	Ability to answer	4	4	4	4	4	4	4	4	
	Layout, style	4	4	4	3	4	4	4	3.86	
Q6	Clarity	4	4	4	4	4	4	4	4	4
	Ability to answer	4	4	4	4	4	4	4	4	
	Layout, style	4	4	4	4	4	4	4	4	
Q7	Clarity	4	4	4	3	4	4	4	3.86	4
	Ability to answer	4	4	4	3	4	4	4	3.86	
	Layout, style	4	4	4	3	4	4	4	3.86	
Q8	Clarity	4	4	4	4	4	4	4	4	4
	Ability to answer	4	4	4	4	4	4	4	4	
	Layout, style	4	4	4	1	4	4	4	3.6	
Q9	Clarity	4	4	4	4	4	4	4	4	4
	Ability to answer	4	4	4	4	4	4	4	4	
	Layout, style	4	4	4	4	4	4	4	4	
Q10	Clarity	4	4	4	4	4	4	4	4	4
	Ability to answer	4	4	4	3	4	4	4	3.9	
	Layout, style	4	4	4	3	4	4	4	3.9	

Question		P1	P2	P3	P4	P5	P6	P7	Average	Average
Q11	Clarity	4	4	4	4	4	4	4	4	4
	Ability to answer	4	4	4	3	4	4	4	3.86	
	Layout, style	4	4	4	3	4	4	4	3.86	
Q12	Clarity	4	4	4	4	4	4	4	4	3.95
	Ability to answer	4	4	4	4	4	4	4	4	
	Layout, style	4	4	4	4	4	4	4	4	
Q13	Clarity	4	4	4	4	4	4	4	4	4
	Ability to answer	4	4	4	4	4	4	4	4	
	Layout, style	3	3	4	3	3	4	4	3.43	
Q14	Clarity	4	4	4	4	4	4	4	4	3.86
	Ability to answer	4	4	4	4	4	4	4	4	
	Layout, style	4	4	4	4	4	4	4	4	
Q15	Clarity	4	4	4	4	4	4	4	4	3.86
	Ability to answer	4	4	4	4	4	4	4	4	
	Layout, style	4	4	4	4	4	4	4	4	
Q16	Clarity	4	4	4	4	4	4	4	4	4
	Ability to answer	4	4	4	4	4	4	4	4	
	Layout, style	4	4	4	4	4	4	4	4	
Q17	Clarity	4	4	4	4	4	4	4	4	3.90
	Ability to answer	4	4	4	4	4	4	4	4	
	Layout, style	4	4	4	4	4	4	4	4	