Summer Internship

Project Report

Bharat Serums and Vaccines Ltd.

Bharat Serums & Vaccines Ltd.

(April 1 to May 31, 2015)

Study on prescription pattern of Parenteral Nutrition and Antifungals in Neonatal Intensive Care Unit (NICU) Setup

Submitted By

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2014-2016

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Certificate

This is to certify that **Mr. Prajakt Dahake**, student of Masters in Business Administration Pharmaceutical Management 6th Batch, IIHMR University, Jaipur has successfully completed his project titled **"Study on prescription pattern of Parenteral Nutrition and Antifungals in Neonatal Intensive Care Unit (NICU) Setup"** as a part of his Summer Internship project at Bharat Serums and Vaccines Ltd. from 1st April 2015 to 31st May 2015.

The project was field work and was carried out independently with sincere, scientific and analytical approach under my supervision and guidance.

I wish him all the success and luck in his future endeavors.

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Acknowledgement

I am highly grateful to My Mentor and Guide, Ms. Aparna Shinde, Senior Product Executive, Bharat Serums and Vaccines Ltd. for her invaluable guidance throughout my Internship.

I am privileged to be a part of an institute like IIHMR which provided me this opportunity. I express my gratitude to our Director, Dr. S.D. Gupta, IIHMR University.

I would like to extend my sincere thanks to Mr. Rakesh Dave, Vice President, Bharat Serums and Vaccines Ltd. for providing me the opportunity to learn and develop professionally.

I would like to extend my gratitude to Mr. Mukesh Parekh, Area Sales Manager, Bharat Serum and Vaccines Ltd.

I would like to extend my sincere thanks to Mr. Rahul Sharma, Assistant Professor, IIHMR Jaipur.

I would also like to express my gratitude to Mr. Hemant Kothawade and Dr. Sandeep Narula for their invaluable guidance.

I owe a debt of gratitude to all my teachers for grooming me and my classmates for their inspirational support, encouragement and motivation throughout my internship at Bharat Serums and Vaccines Ltd.

I hope that I can build upon the experience and knowledge that I have gained and make a valuable contribution towards the industry in coming future.

Prajakt Dahake

Date: July 31, 2015

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Executive summary

Many sick newborn infants cannot obtain adequate nutrition via the GI tract and therefore, require parenteral nutritional (PN) support. the GI tract may not function for days to weeks (*e.g.*, necrotizing enterocolitis, bowel anomalies), so the infant receives all nutrition parenterally.

Parenteral Nutrition is required in neonates with conditions such as Preterm, Very Low Birth Weight, Respiratory disorders and chronic conditions such as Short gut syndrome, Microvillus inclusion disease, Necrotising enterocolitis, etc.

There are two routes of infusion of PN, Peripheral and Central. the parenteral nutrition should meet the nutrition requirements of the neonates.

With the advancements of NICUs in India, the demand for PN has drastically increased. The manufacturers of these products are very less.

The neonates are also prone to several infections due to their developing immune system. Fungal infections are one of the majorly encountered infections in NICUs. The majorly encountered specie by the Neonatal Intensivists is the Candida and Fluconazole and Amphotericin B are the drugs used against this infection.

List of Key words:

Parenteral Nutrition, Neonates, Antifungal therapy, Neonatal Intensive Care Unit, Jaipur

Company profile

(bharat serum company overview, 2015)

Bharat Serums And Vaccines Limited (BSV) is one of the fastest growing biopharmaceutical companies in India and has been ranked amongst the top 10 Indian biopharmaceutical companies. The Company, founded in 1971, is based in Mumbai, India and has over 900 employees.

BSV researches, develops, manufactures, and markets injectable biological, pharmaceutical, and biotech products. Its product portfolio comprises 25 brands which include plasma derivatives, monoclonals, fertility hormones, antifungals, anaesthetics, cardiovascular drugs and equine immunoglobulins / antitoxins. BSV provides its products to retail outlets and hospitals through distributors primarily in India and also internationally. In addition to its commercial operation, the Company has an extensive research and development platform working on the development of new drug delivery systems, biotechnology / recombinant therapeutics, and biological / equine products.

BSV currently has two private equity investors, Kotak Private Equity and Orbimed.

Vision & commitment

To be an innovative, caring and trustworthy partner in bringing life to life

Mitigating the anguish and suffering of millions. Underlying fairness and transparency in dealings with all stakeholders including employees and business partners. The Group is driven by an informal culture fostering cohesion and innovation

“Innovative Caring Trustworthy”

“Enhancing qualityof life is our life purpose”

“Bringing path breakingpharma, bio & biotechnology products”

“Research drivenmanufacturing, people driven marketing”

“Seeking life as it should be”

Products categories

Gynecology, Assisted reproductive technology, Critical care emergency medicine, Neurology, Nephrology, Hematology, Urology.

Global Subsidiaries and JV's

BSV BioSciences

BSV BioScience

Zydus BSV Pharma Pvt.

A 100% subsidiary of BSV, BSV BioSciences Inc is a research and drug development company dedicated to the early stage development of recombinant molecules.. Utilizing in-house molecular biology and recombinant expression capabilities, BSV Biosciences has developed multiple cell lines for various products. Specifically, the company has developed cell lines and lab scale processes for two biosimilar products and two "first-in the world" products. These products are in various stages of clinical development and commercialization.

Group / Affiliate Companies

Advy Chemical Pvt. Ltd.
Aksigen
Kasiak Research Pvt. Ltd.
Next Line Diagnostics

Advy Chemical Pvt. Ltd. was incorporated in 1991 and has been servicing the global In Vitro Diagnostics (IVD) industry ever since. Over the years, Advy Chemical has developed into a globally recognized provider of high quality reagents and components specifically tailored to suit the needs of its customers.

Today, the company exports its immunodiagnostic reagent products to customers spread across the Americas, Europe, China and Japan. Advy has also entered the domestic market with the manufacture of lateral flow assays, in its state-of-the-art production facility.

Introduction

Many sick newborn infants cannot obtain adequate nutrition via the GI tract and therefore, require parenteral nutritional (PN) support. In some, GI function is adequate to allow some feedings. In others, the GI tract may not function for days to weeks (*e.g.*, necrotizing enterocolitis, bowel anomalies), so the infant receives all nutrition parenterally. (Chaudhari & Kadam, 2006)

Need for parenteral nutrition in neonates

Parenteral Nutrition is required in neonates with conditions such as Preterm, Very Low Birth Weight, Respiratory disorders and chronic conditions such as Short gut syndrome, Microvillus inclusion disease, Necrotising enterocolitis, etc. (Riskin, 2006)

Current available parenteral feeding options

- **Central cannula:** Peripherally inserted central catheters (PICC's) should be used preferentially to provide central venous access in neonates receiving prolonged TPN as PICC use results in improved nutrient intake and fewer insertion attempts.
- **Umbilical catheters:** In neonates, umbilical vessels can be used for TPN.UVC compared to peripheral venous catheter reduces insertion attempts with no increase in risk of infection or necrotizing enterocolitis.The risk of complication may increases if umbilical venous catheters are being left in place for more than 14 days.
- **Peripheral cannula:** As phlebitis of peripheral veins can be expected when the osmolality of the intravenous solution exceeds 600 mOsm, peripheral veins should be used for short term venous access and for providing partial nutritional supplementation. Although extravasation injury occurs in up to 10% of infants managed only with peripheral infusion of TPN, it is unclear if the risk of peripheral TPN is greater than the risk of peripheral crystalloid infusion.

  (Fusch, 2009)

Routes of infusion

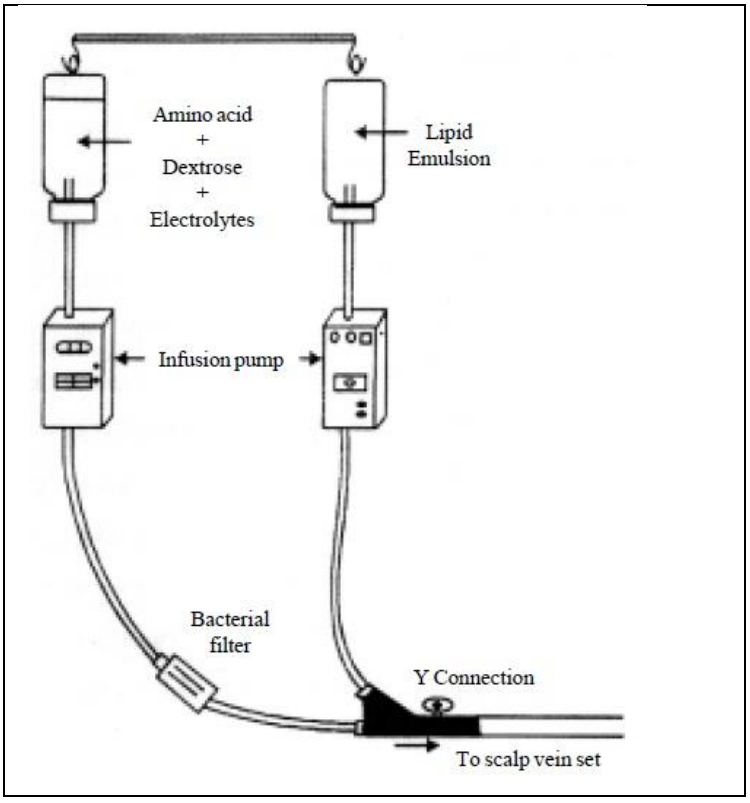
- **Peripheral** route is used for partial or supplemental PN. This route is usually used for short-term nutritional support. Peripheral PN solutions cannot exceed 12.5% dextrose (D12.5) or 3.5% amino acids due to the risk of thrombophlebitis and should not contain calcium because of the serious complications resulting from extravasation of calcium.
- **Central** PN is delivered by a venous catheter with the tip in a central location. This route is used for patients who require long-term nutritional support, usually TPN. (Ben, 2008)

Nutritional requirements of neonates

Caloric needs	90-120 kcal/kg/day
Glucose	4-6 mg/kg/min
Protein	3-4 g/kg/day
Lipid	3-4 g/kg/day
Sodium	2-5 mEq/kg
Potassium	2-4 mEq/kg
Calcium	2-4 mEq/kg
Phosphorus	1-2 mmol/kg
Magnesium	0.3-0.5 mEq/kg

(Ben, 2008)

TPN infusion assembly



Total Parenteral Nutrition is administered with Amino acid and Glucose in one chamber and Lipid emulsion IV in the other chamber. These chambers are connected to different infusion pumps which infuse the measured quantity for individual patient at specified rate. These solutions are mixed just before they enter into the venous system. (Chaudhari & Kadam, 2006)

Antifungal therapy

Neonates are prone to various infections due to their poorly developed immune system. One of the majorly encountered type of infection in NICUs is Fungal infection.

There are four major species responsible for infection in NICUs. They are Candida, Aspergillus, Mucorales and Cryptococcus.

Out of these species, Candida and Aspergillus are the most encountered species in NICU setup and the drugs used for these infecting species are Fluconazole & Amphotericin B and Voriconazole respectively. (Kaufman, 2015)

Review of Literature

Parenteral Nutrition (PN) allows us to meet a neonate's requirement for growth and development when their size or condition precludes enteral feeding. The cost of the TPN infusate with additives is around Rs. 700-800/day (Chaudhari and Kadam, 2006).

Premature very low birth weight (< 1500 g) infants comprise one of the largest groups receiving parenteral nutrition. PN should be optimized to answer their high nutritional requirements and suit their metabolic status, but should also be validated pharmaceutically.The main advantage of individually prescribed PN is that it is tailored to suit a specific patient, thereby assuring the best possible nutrition and biochemical control. Batch-produced standardized PN bags can be readily available as ward stocks in neonatal intensive care units, enabling initiation of early PN immediately after the delivery of a premature infant (Riskin et al, 2006).

Age and maturity-related changes of the metabolism and fluid and nutrient requirements must be taken into consideration along with the clinical situation during which PN is applied (Fusch et al, 2009).

Parenteral nutrition (PN) has become an integral part of clinical management of very low birth weight premature neonates. Traditionally different components of PN are prescribed individually considering requirements of an individual neonate (IPN). More recently, standardised PN formulations (SPN) for preterm neonates have been assessed and may have advantages including better provision of nutrients, less prescription and administration errors, decreased risk of infection, and cost savings (Simmer et al, 2013).

When TPN solutions are compounded centrally, significant cost savings are achieved, especially in newborns. Therefore, Hospital management should implement centralized compounding (Alonso et al, 2012). Hospital-acquired infection (HAI) is a major complication of PN (Chawla et al, 2008).

Rationale for study

Neonates comprise one of the largest groups receiving parenteral nutrition. PN should be optimized to answer their high nutritional requirements and suit their metabolic status. Due to advancement in neonatal care, a lot of neonates are saved but they require PN support for longer period in NICUs. PN allows us to meet a neonate's requirement for growth and development when their size or condition precludes enteral feeding.

Recent emergence of NICUs in India has lead for the growing market for neonatal products. The Parenteral nutrition manufacturers are very limited in India and therefore it appears to be a potential market. Since NICUs is a developing concept in India, there are only limited studies performed on PN. However, the number of patients in this segment is increasing drastically over days. Parenteral nutrition products are not available in readily administrable form. They need to be calculated and compounded for individual patient according to the need.

Fungal infections are encountered in neonates since they have developing immune system. They are prone to several infections. Also, Parenteral Nutrition is administered through Peripheral or central venous routes which could also pave a way for infections. Fungal infections are majorly encountered in neonates and prescribed quite frequently in NICUs and therefore a potential market.

Objectives of study

- To understand the market scenario for Parenteral Nutrition and antifungal molecules in NICU.
- To study the prescription pattern of Parenteral nutrition and antifungals in NICUs.
- To study the key brands of Parenteral Nutrition products prescribed in NICUs.
- To identify the gaps in existing Parenteral Nutrition products.
- To identify the highly prescribed molecules of Antifungals in NICUs.

Methodology

Study Design:

Descriptive study.

Sampling method:

Non probability convenience sampling.

Sample population studied:

Neonatal Intensivists.

Sample area:

Jaipur, Rajasthan.

Sample size:

28 Intensivists (On duty-prescribing doctors in NICUs)

Data collection:

Primary Data- The Primary data was collected through Semi-structured questionnaire by face-to-face interaction.

Secondary Data- Secondary data was collected from Review articles available over the Internet.

Tools and Techniques- A questionnaire consisting of Open and Close ended questions was used as a tool. The questionnaire used was brief so as to comply with the limited time of interaction with the Neonatal Intensivist.

Study duration- 2 months [April 1 to May 31, 2015].

Results and Findings

Q1. How many neonates require Parenteral Nutrition in your NICU?

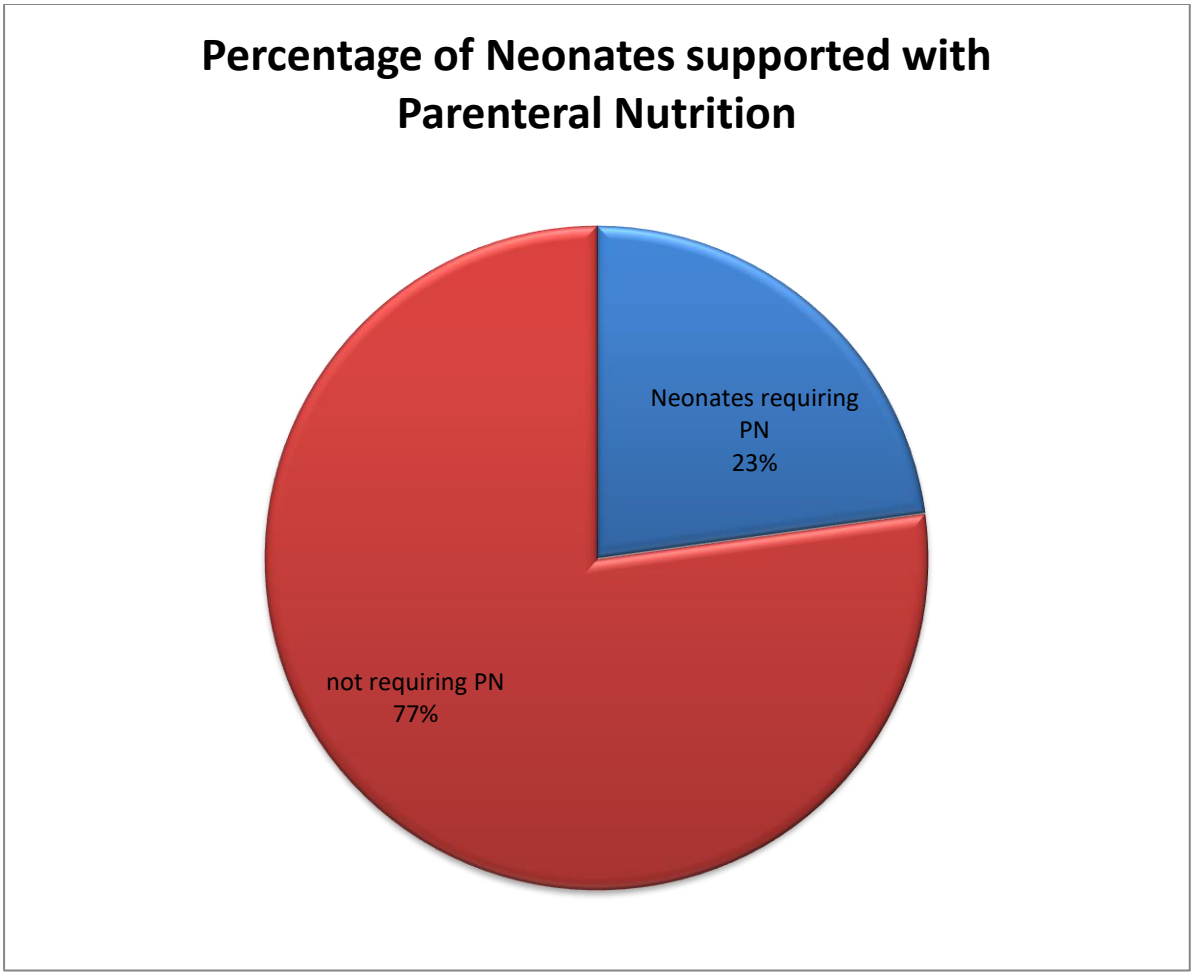


Chart 1 Percentage of Neonates supported with PN in NICUs

- The Neonatal Intensivists said that about 20-30% of neonates in their NICU were supported with Parenteral Nutrition.
- From the responses collected from Neonatal Intensivists of Jaipur, it was found that, on an average about 23% of Neonates in NICUs required Parenteral Nutrition support.

Q2. For what condition were the neonates supported with Parenteral Nutrition?

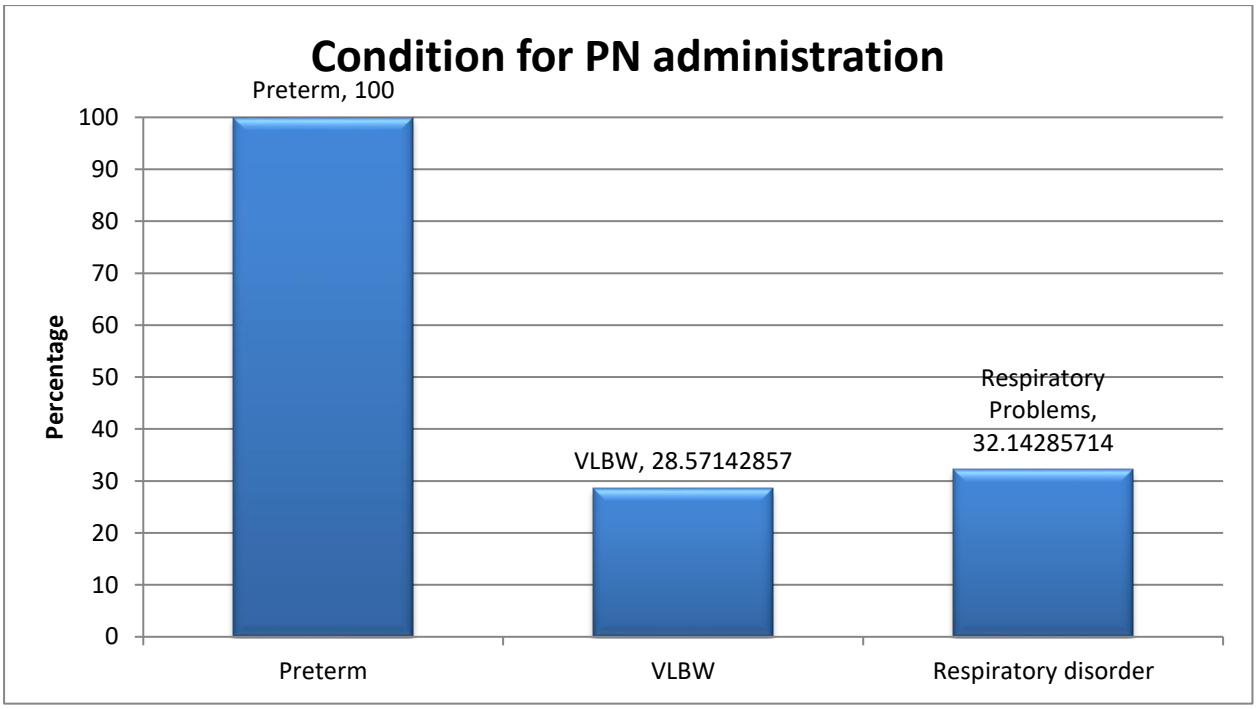


Chart 2 Percentage cases of Conditions for PN support

- 100% of the Neonatal Intensivists said that the reason for supporting the neonates with Parenteral Nutrition (PN) was because they were **Preterm babies**.
- **28.57%** of these doctors also said that **Very Low Birth Weight (VLBW)** was also one of the reason for supporting neonates with PN.
- **32.14%** of the doctors said that **Respiratory Problems** were also responsible for supporting neonates with PN.

Q3. Which type of Parenteral Nutrition do you prescribe?

- The majorly prescribed Parenteral Nutrition was **Total Parenteral Nutrition (TPN)**.
- About **570** parenteral nutrition doses were prescribed in a duration of One Month in the NICUs.

Brand Prescription:

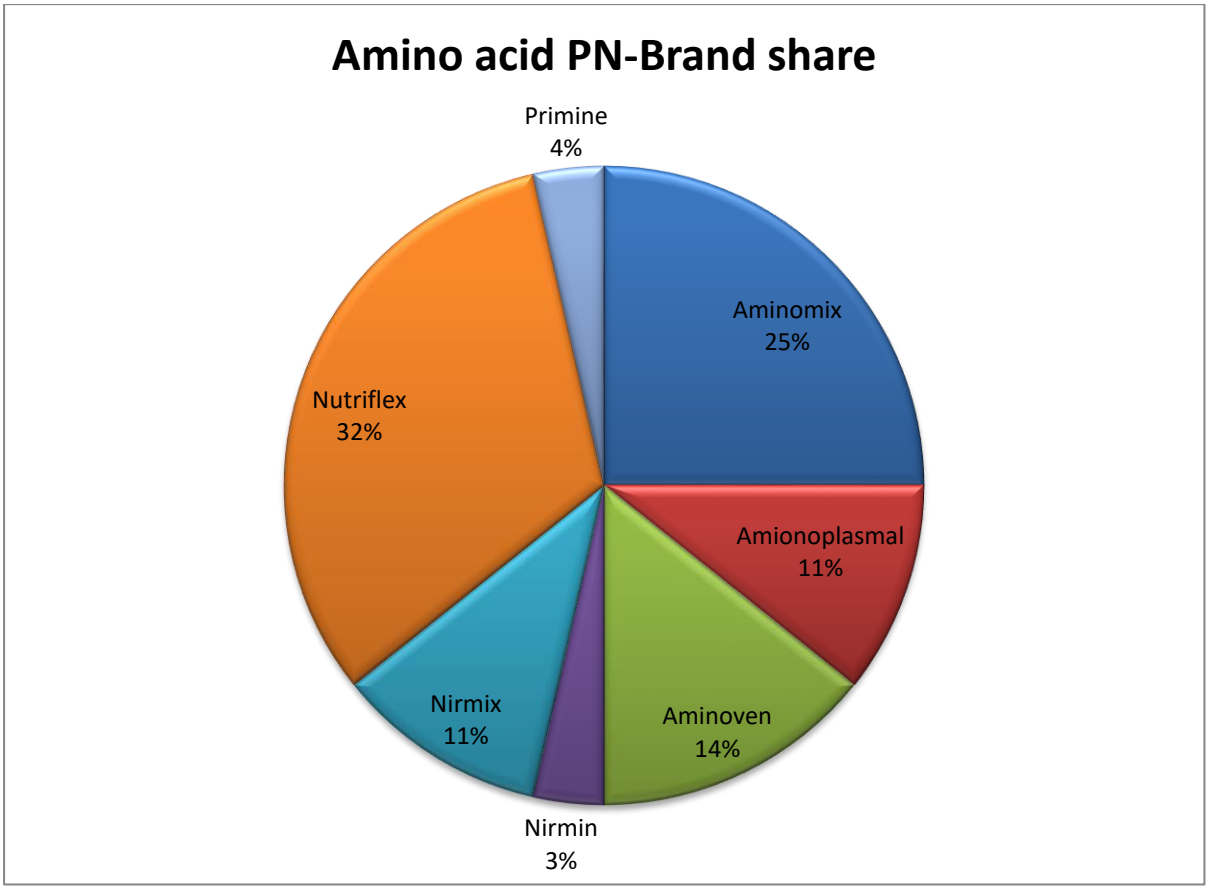


Chart 3 Percentage distribution of Amino acid brands prescribed

- Amino acid and Glucose were administered as single or in combination under the various Brands of Parenteral products.
- Different Brands of Amino acids are prescribed for the Neonates in NICUs.

Brand	Manufacturer	% Prescription
Nutriflex	B. Braun	32
Aminomix	F. Kabi	25
Aminoven	F. Kabi	14
Aminoplasmal	B. Braun	11
Nirmix	Nirlife	11
Primine	Baxter	04
nirmin	Nirlife	03

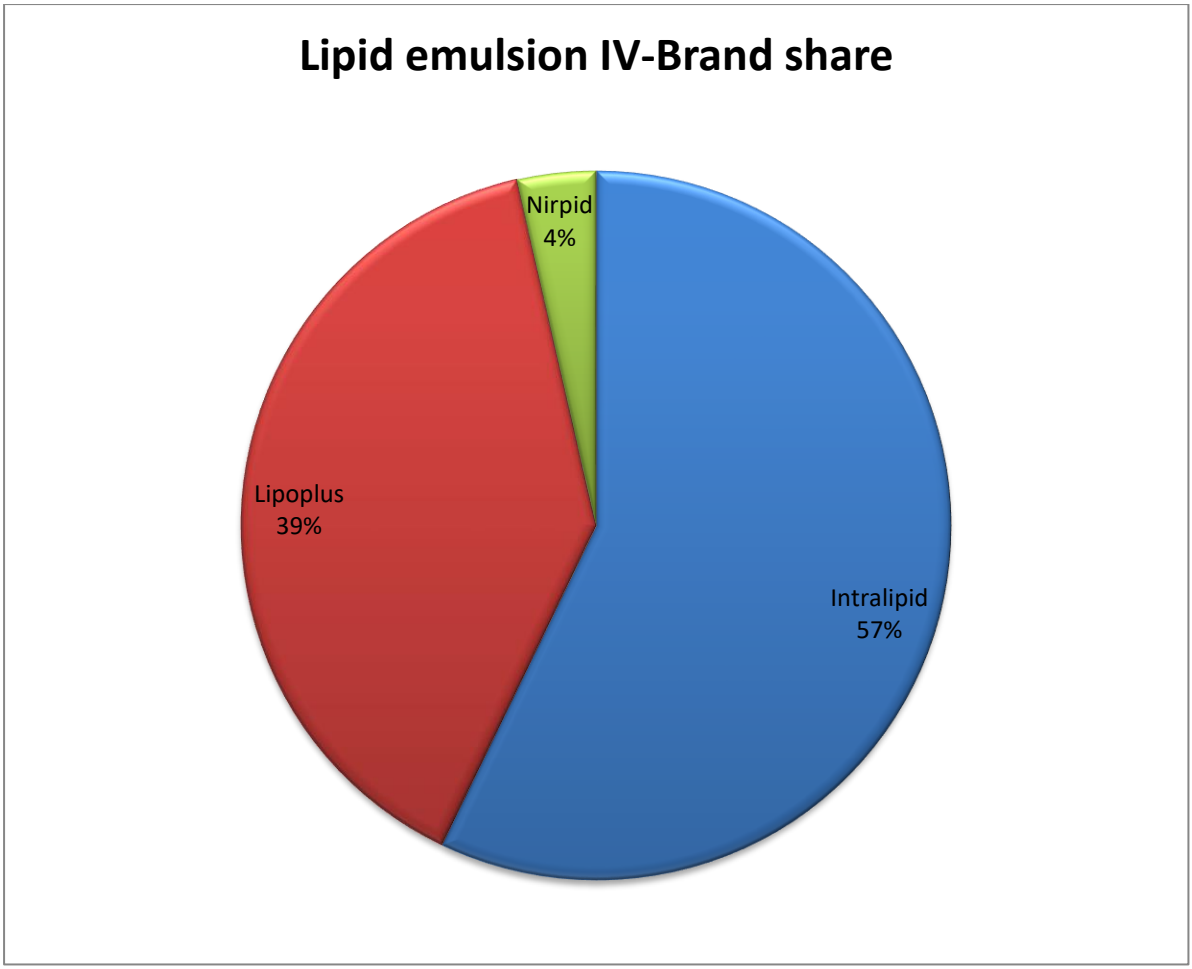


Chart 4 Percentage distribution of Lipid emulsion Brands prescribed

- Since Lipid emulsion in Three-in-one product is not optimized for Neonates, Lipid emulsion IV was administered separately according to the need of individual Neonate.
- The above chart shows the share of different brands of Lipid emulsion IV used in NICUs in Jaipur.

Brand	**Manufacturer**	**% Prescription**
Intralipid	F. Kabi	57
Lipoplus	B. Braun	39
Nirpid	Nirlife	04

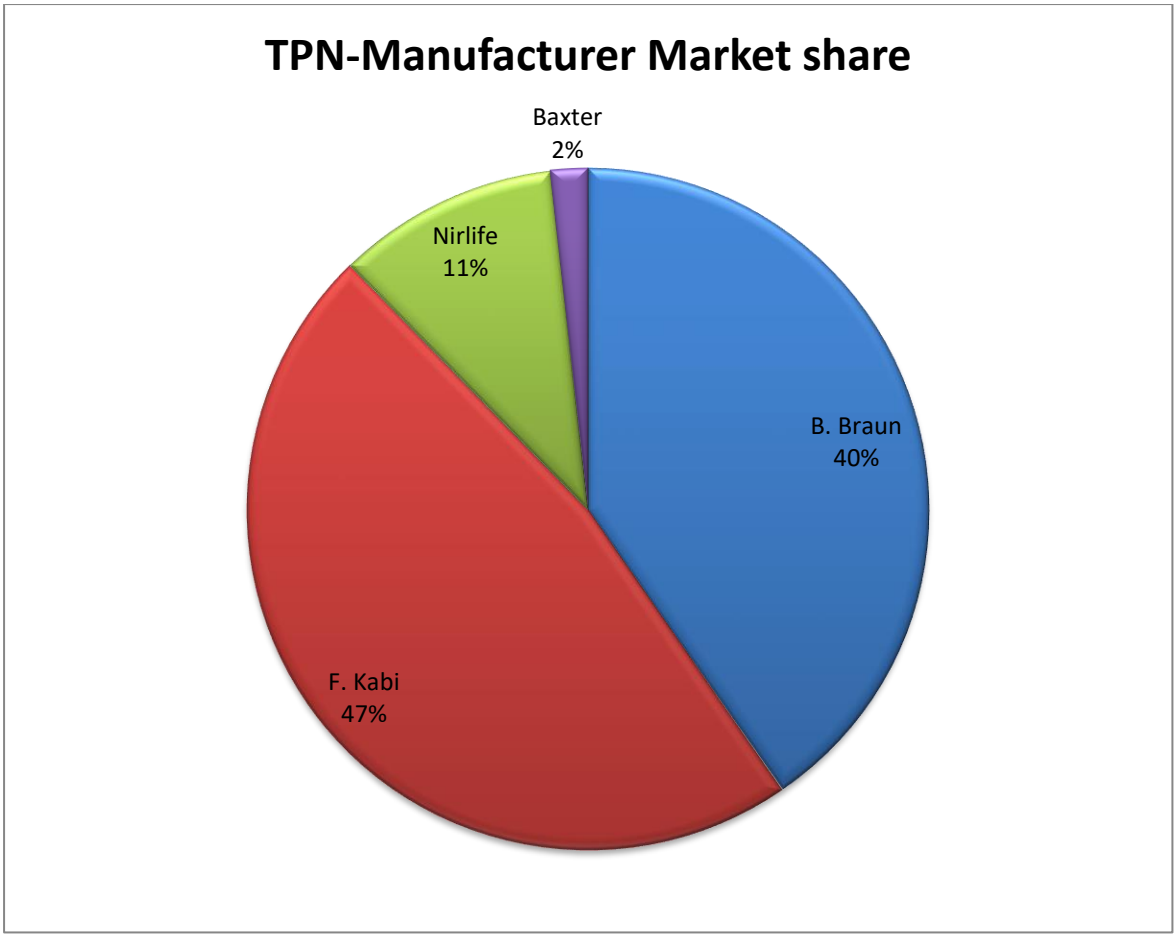


Chart 5 Market share of PN product Manufacturers from prescription preference

Manufacturer	**Amino acid Products**	**Lipid emulsion IV**	**Market share (%)**
B. Braun	Nutriflex* Aminoplasmal	Lipoplus	40
F. Kabi	Aminomix* Aminoven	Intralipid	47
Nirlife	Nirmix* Nirmin	Nirpid	11
Baxter	Primine		02

*Amino acid + Glucose

Q4. What according to you are the lacunas in Parenteral Nutrition that you prescribe?

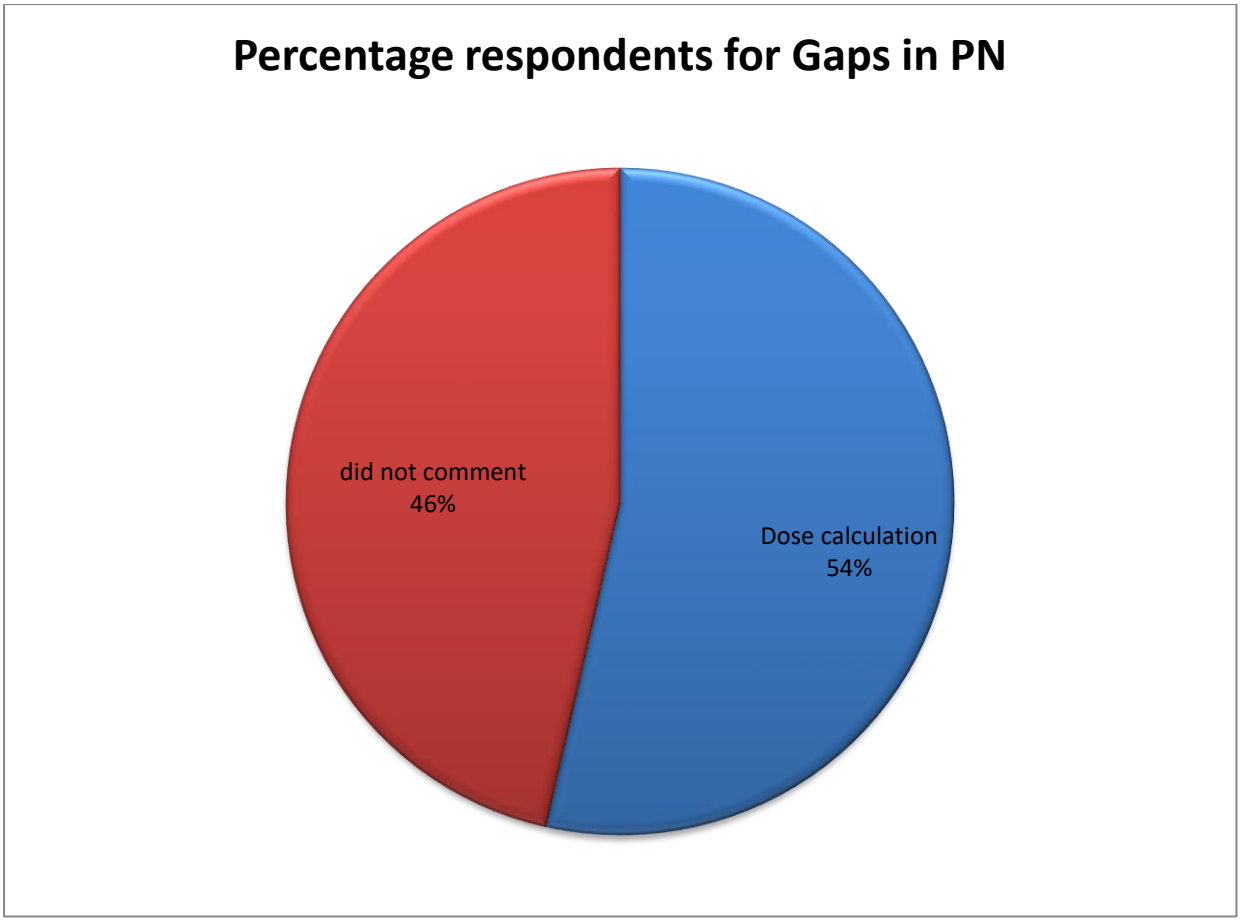


Chart 6 Percentage response for reasons of gaps in Current PN products

- The number of non-respondents for this question were 46%, however, 54% of the Neonatal Intensivists said that they had difficulty in Dose calculation while combining different components of PN such as Glucose, Amino acid and Lipids.

Antifungal Therapy

Q1. How many neonates require antifungal therapy in you NICU?

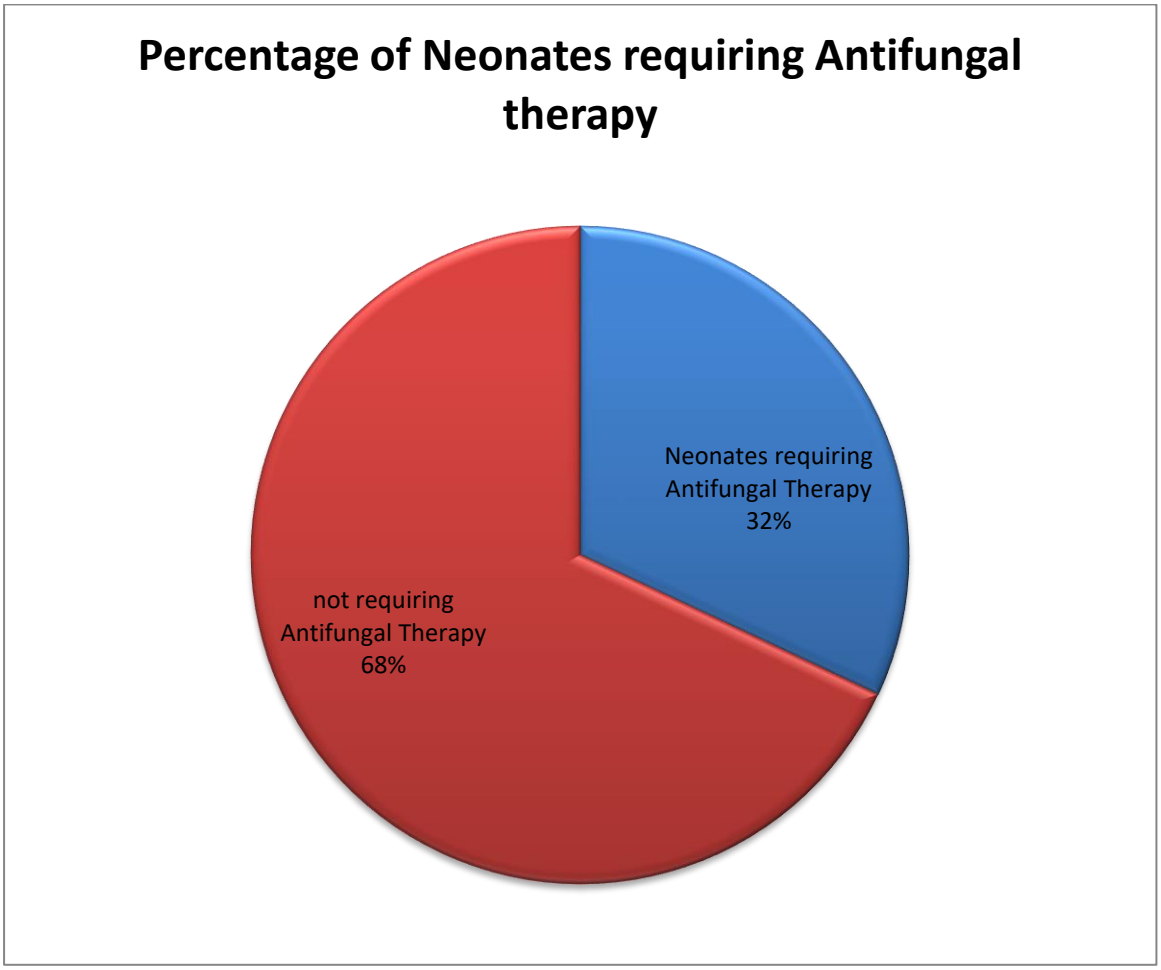


Chart 7 Percentage of Neonates requiting Antifungal therapy in NICUs

- The Neonatal Intensivists said that about 30-40% of neonates in their NICU required Antifungal therapy.
- From the responses collected from Neonatal Intensivists of Jaipur, it was found that, on an average about 32% of Neonates in NICUs required Antifungal drugs.

Q2. What are the fungal species commonly encountered in your NICU setup?

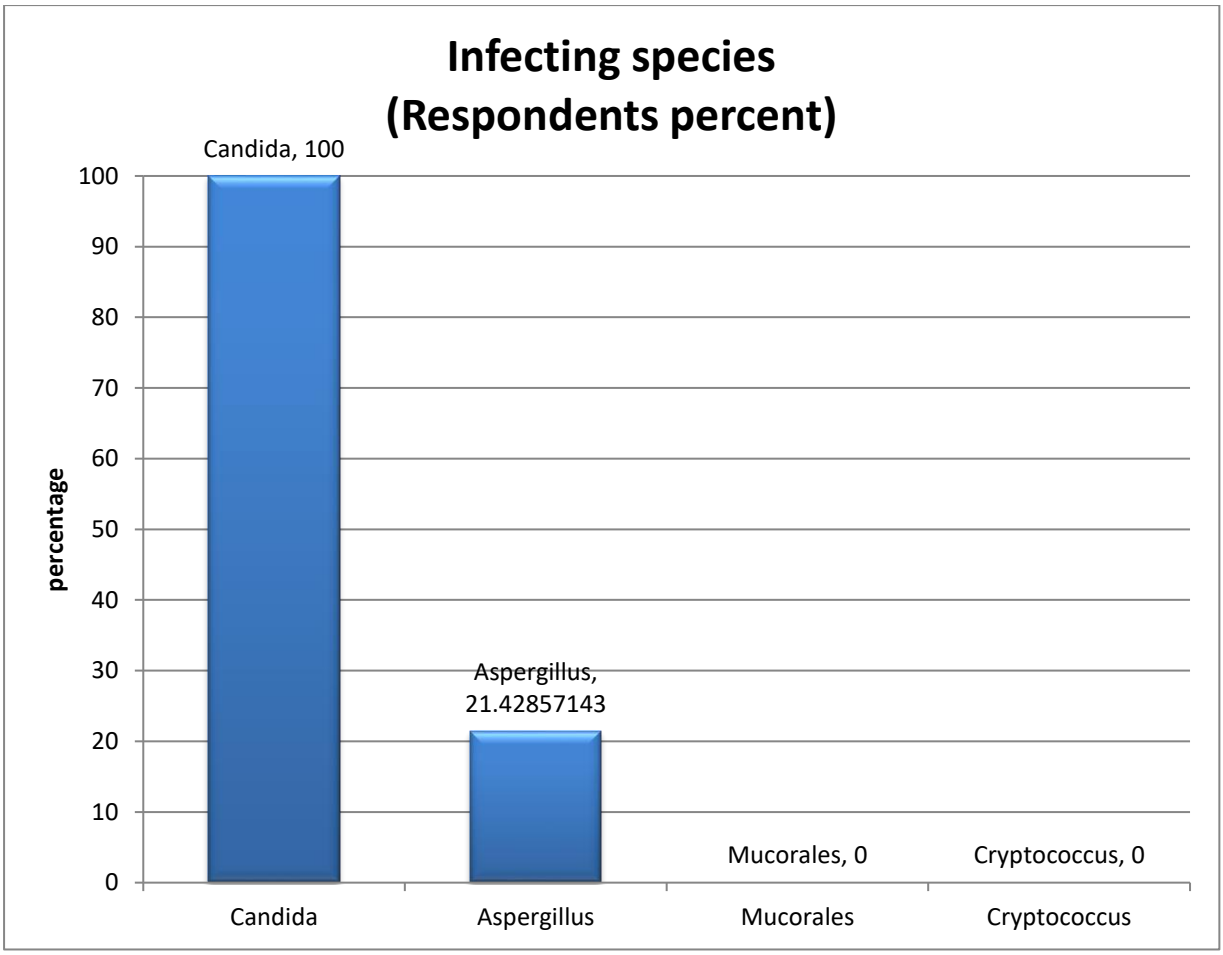


Chart 8 Percentage of infecting species in the NICUs

- 100% of the Intensivists encountered Candida infection in their NICU
- 21.43% of these intensivists also encountered Aspergillus infection along with Candida.
- However, Mucorales and Cryptococcus species were not encountered by these intensivists.

Q3. What is the treatment protocol for antifungal therapy in your NICU?

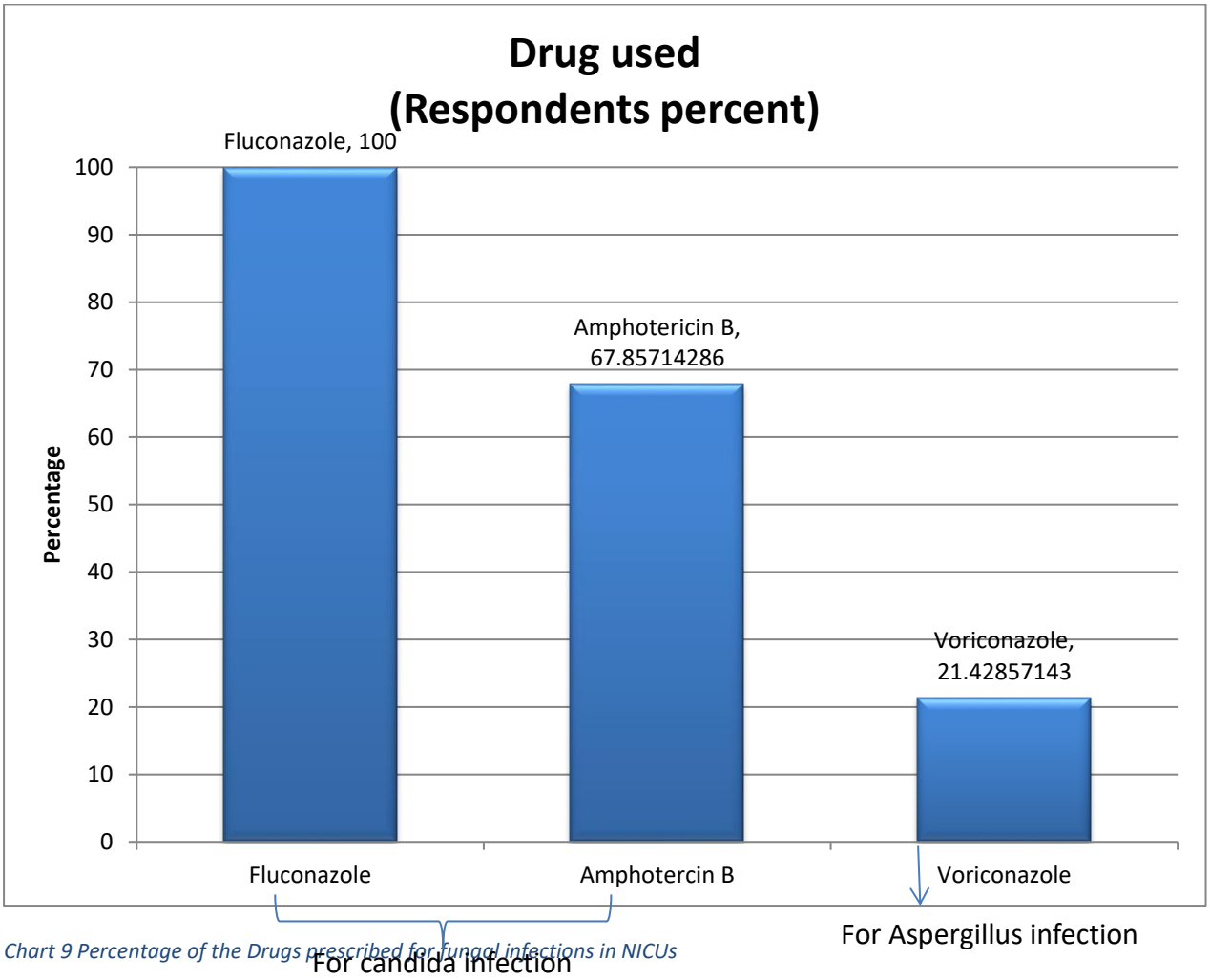


Chart 9 Percentage of the Drugs prescribed for fungal infections in NICUs

- Fluconazole was used against Candida infection by 100% intensivists.
- 67.86% of these intensivists also prescribed Amphotericin B for Candida species.
- Voriconazole was used for the treatment of Aspergillus infection.

Q4. Which type of Amphotericin B do you prescribe?

- All Neonatal Intensivists prescribed Liposomal Amphotericin B, while Lipid complex and Lipid emulsion Amphotericin B was not prescribed in their NICUs.

Discussion

The concept of NICUs has come to India quite late and is still in its blooming stage. The Market of Parenteral Nutrition is still not well addressed by Indian Pharmaceutical Industries and thus, there are very few manufacturers of these products. With rise in physiological malfunctions of the human body due to several external factors, many infants are born with disorders like Very Low Birth Weight (VLBW), prematurity ets. These neonates require Parenteral Nutrition to fulfill the demand of their growing body. Compounding of PN require proper calculation in accordance with the need of individual neonate and there are no standardized PN products available. This provides the pharmaceutical companies an opportunity to enter into a new market segment. Also, the parenteral nutrition market is in its growing phase. Some of the formulation scientists are trying to develop the Standardized Parenteral Nutrition (SPN) which would give them advantage over Individualized Parenteral Nutrition (IPN). The development of SPN will not only be advantageous in terms of cost but also in its effectiveness due to dose accuracy.

Suggestions

- Manufacturing of Parenteral nutrition product could be beneficial for the company since there are less competitors and rising demand.
- Amino acid and Glucose combination (2-chamber PN) product and a Lipid emulsion IV product could be a good addition to the product line of the company.
- Dose calculation is one of the challenges in administration of TPN. Therefore, development of standardized TPN formulation could be of greater advantage over competitors.

- Candida infection is highly encountered fungal infection in NICUs, therefore Amphotericin B should be targeted towards this section
- Fluconazole is highly prescribed Antifungal drug in NICUs over Amphotericin B, therefore addition of Fluconazole formulation to the product line could be beneficial to company.

Limitations of the study

- The study was conducted only in Jaipur city of Rajasthan.
- Due to limited interaction time with Neonatal Intensivists, the questionnaire was kept short and brief and therefore other related questions were not asked.

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Annexure

Questionnaire

1. Name of the hospital : _____
2. Name of Doctor : _____
3. Capacity of NICU : _____
4. How many neonates require Parenteral Nutrition in your NICU? _____
5. For what condition were the neonates supported with Parenteral Nutrition? _____

6. Which type of parenteral nutrition do you prescribe

Type	Please tick	Concentration prescribed	Brand prescribed
a) Amino acid			
b) Lipid emulsion			
c) Total Parenteral Nutrition			
d) Others	_____		

7. What according to you are the lacunas in Parenteral Nutrition that you prescribe?
   _____
   _____

Antifungal Therapy:

1. How many neonates require antifungal therapy in your NICU? _____
2. What are the fungal species commonly encountered in your NICU setup?
   a. Candida
   b. Aspergillus
   c. Mucorales
   d. Cryptococcus

3. What is the treatment protocol for antifungal therapy in NICU?

Type of infection	Drug used in treatment
a) Candida	
b) Aspergillus	
c) Mucorales	
d) Cryptococcus	

4. Which type of Amphotericin B do you prescribe?

Drug	Type	Please tick
Amphotericin B	a) Amphotericin B Liposomal	
	b) Amphotericin B lipid complex	
	c) Amphotericin B lipid emulsion	
Other antifungals	_____(specify)	