



University of Nairobi

Use of Caffeine Citrate for Apnea of Prematurity



THE AGA KHAN UNIVERSITY



Hillman Medical Education Fund
Kenya



KEMRI | Wellcome Trust

Objectives

1. Define apnea and Apnea of Prematurity.
2. Discuss the pathophysiology of AoP.
3. Outline the treatment and prevention of AoP
4. Discuss mechanism of action of caffeine and its adverse effects.
5. Define how to monitor patient at risk and on treatment for AoP

Introduction

Definitions



Apnea:

- Cessation of breathing in a premature infant for 20 s or longer
- Shorter pause accompanied by **bradycardia (<100 bpm), cyanosis or pallor**



Periodic breathing:

- Pattern of regular breathing alternating with pauses in respiration of at least 3 seconds, persisting through at least three cycles of breathing.
- Less than 20 sec
- Not associated with bradycardia nor hypoxemia**

Types of Apnea

Central apnoea: 40%

- ✓ Caused by decreased CNS stimuli to respiratory muscles.
- ✓ Respiratory effort and airflow cease simultaneously.
- ✓ Absence of chest wall movement and airflow.

Mixed apnoea: 50%

- ✓ Has a mixed aetiology.
- ✓ Central apnoea is either preceded (usually) or followed by obstructed respiratory effort.

Obstructive apnoea: 10%

- ✓ Caused by pharyngeal instability, neck flexion or nasal obstruction.
- ✓ Absence of airflow in presence of inspiratory efforts.
- ✓ There is presence of chest wall movement but no airflow.

Causes of apnea

- Hypoglycemia
- Hypothermia
- Anemia
- Sepsis

Apnea of prematurity (AOP)

- Diagnosis of exclusion.
- Other causes of apnea must be ruled out

Risk factors for apnea

1. Prematurity - AoP

2. Secondary causes

- A. Central nervous causes** (seizures, intracranial hemorrhage, hypothermia, depressant drugs)
- B. Pulmonary causes** (pneumonia especially due to RSV, laryngeal reflex, vocal cord paralysis, pneumothorax, tracheal occlusion by neck flexion)
- C. Sepsis**
- D. Metabolic causes** (hypoglycemia, hypocalcemia, hyponatremia, and hypernatremia)
- E. Anemia.**

Apnea of Prematurity

Epidemiology of apnea of prematurity



AOP is inversely related to gestational age and birth weight.

10% >34 weeks GA

20%-85% 30 weeks – 34 weeks

90% <1000 grams

Newborns born <34 weeks GA are at risk for Apnea of Prematurity!

Long J-Y, Guo H-L, He X, Hu Y-H, Xia Y, Cheng R, Ding X-S, Chen F and Xu J (2021) Caffeine for the Pharmacological Treatment of Apnea of Prematurity in the NICU: Dose Selection Conundrum, Therapeutic Drug Monitoring and Genetic Factors. *Front Pharmacol.* 12:681842. doi: 10.3389/fphar.2021.681842

Neonatal breathing - Chemosensitivity



Central chemoreceptors:
-Located in the in the brain

Central chemosensitivity to high CO₂ is diminished in preterm infants, and this relative “insensitivity” is directly proportional to the level of prematurity.

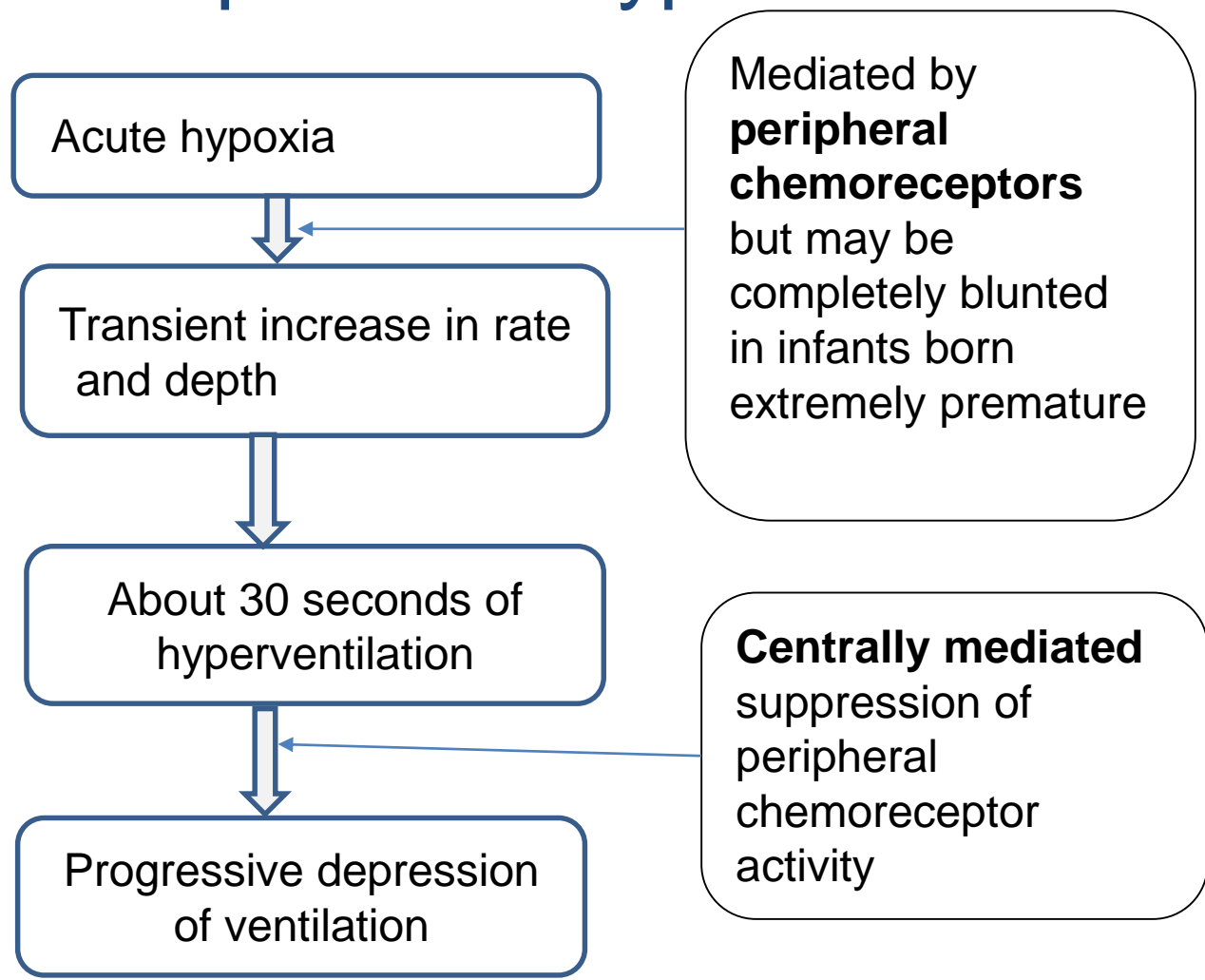
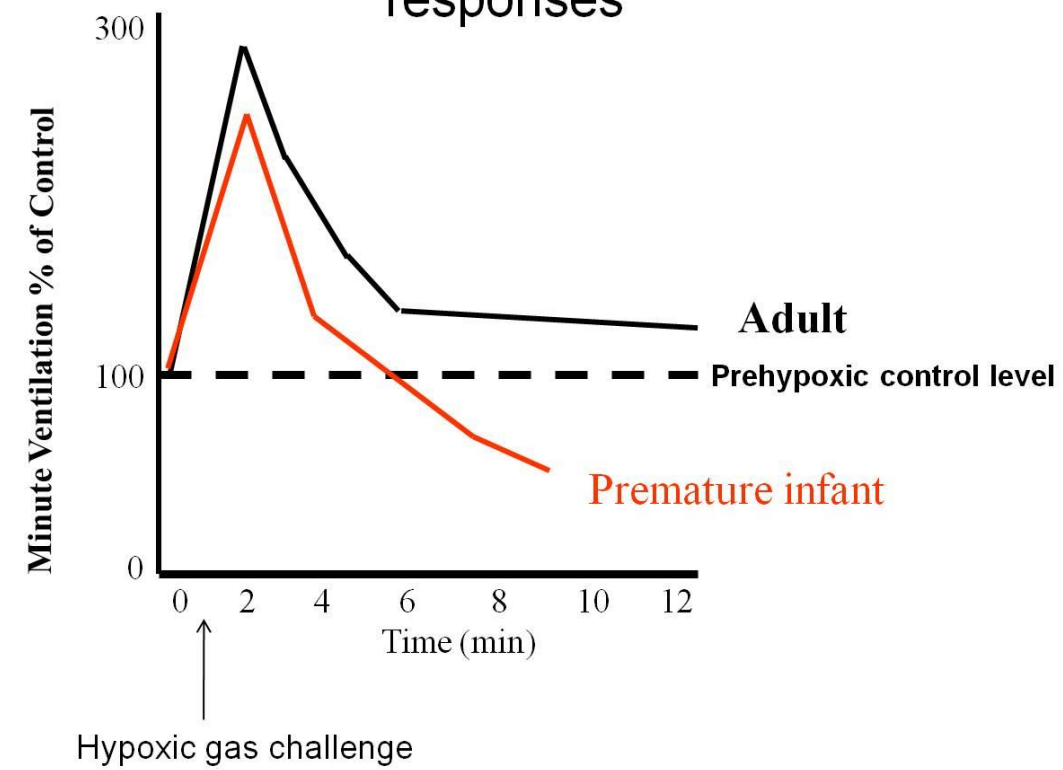
High CO₂ and acidosis in extracellular fluid

Activation results in increased respiratory rate and depth

Erickson G, Dobson NR, Hunt CE. Immature control of breathing and apnea of prematurity: the known and unknown. *J Perinatol.* 2021;41(9):2111-2123. doi:10.1038/s41372-021-01010-z

Neonatal breathing – Biphasic response to hypoxia

Effect of maturation on hypoxic ventilatory responses



Erickson G, Dobson NR, Hunt CE. Immature control of breathing and apnea of prematurity: the known and unknown. *J Perinatol.* 2021;41(9):2111-2123. doi:10.1038/s41372-021-01010-z

Prevention and Treatment of Apnea of Prematurity for preterms born at < 34 weeks gestation age

Supportive care important in care of premature neonates

– Get the basics right!

1. Stabilization – Newborn resuscitation where required.
2. Keep warm to maintain body temp 36.5-37.5⁰C
3. Initiate CPAP/oxygen as per hospital policy.
4. Feed within the first ONE hour of birth thus establish IV access and/or Nasal or Oral gastric tube as indicated.
5. Adequate history and systemic examination should be done.

-Assess gestation:

1. By dates from LNMP (Accuracy not assured)
2. Obstetric ultrasound (?taken before 15 weeks gestation)
3. Ballard score – done on day of birth. (Unreliable >4 days old)

Treatment strategies



Exclude and treat for other causes of apnea eg hypothermia, hypoglycemia.



Pharmacological therapy – Methylxanthines



Non-pharmacological therapies:

- Nasal CPAP
- Heated humidified high flow nasal cannula (HHFNC)
- Nasal intermittent positive pressure ventilation (NIPPV)

Methylxanthines

Examples

1. Caffeine citrate
2. Aminophylline

Action

- ✓ They activate the respiratory centers and increase CO_2 sensitivity
- ✓ Induce bronchodilation
- ✓ Enhance diaphragmatic function

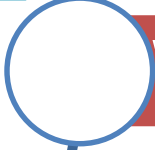
Above result in improved respiratory response to hypoxia and increased CO_2

Caffeine citrate

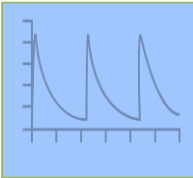
Why is caffeine citrate preferred?



Fewer side effects



Wider therapeutic index



Longer elimination half-life that allows once-daily dosing

-Caffeine is as effective as aminophylline BUT is **safer** and **easier** to administer and has better therapeutic properties.

It is therefore preferred for the treatment of apnea of prematurity.

Long J-Y, Guo H-L, He X, Hu Y-H, Xia Y, Cheng R, Ding X-S, Chen F and Xu J (2021) Caffeine for the Pharmacological Treatment of Apnea of Prematurity in the NICU: Dose Selection Conundrum, therapeutic Drug Monitoring and Genetic Factors. *Front. Pharmacol.* 12:681842. doi: 10.3389/fphar.2021.681842

Pharmacokinetics of caffeine citrate

- **Distribution of caffeine in the body:**
 - Hydrophobic and distributed evenly in all body fluids without tissue accumulation.
 - It is highly lipid-soluble and crosses all biological membranes, including the blood-brain-barrier.
- **Metabolism and excretion:**
 - Metabolism of caffeine occurs primarily in the liver.
 - In neonates, approximately 85% of caffeine is excreted unchanged in the urine compared to <2% in adults.

Caution to be taken for newborns with renal or hepatic disease

Pharmacokinetics of caffeine citrate

- **Half life:**
 - Serum half-life of caffeine in preterm infants is prolonged more than **ten times** that of adults because of immature hepatic metabolism and renal excretion
 - Mean half life is 100 hours in preterms.

-Once a day dose is adequate

-Upon stopping the medication continue monitoring of adverse effects up to 7 days.

-There is no requirement for dose tapering on cessation of treatment.

Route of administration for caffeine citrate

- Pharmacokinetics of caffeine is largely **independent** of the route of administration.
- **Oral caffeine:**

This oral route preferred unless there are contraindications of enteral feeds. Caffeine is compatible with breastmilk(EBM). 10%D, N/S, KCl

- **IV caffeine citrate:**
 - Prophylactic loading dose is given slowly over 30minutes. This achieves effect not very different from oral dosing.

Timing of caffeine citrate therapy

Rescue versus prophylactic caffeine citrate treatment?

Prophylactic caffeine recommended as it is associated with:

1. Decreased duration of oxygen therapy
2. Decreased duration of invasive and noninvasive ventilation
3. Decreased incidences of mild to moderate Bronchopulmonary Dysplasia.
4. Less need for Patent Ductus Arteriosus (PDA) treatment
5. Reduced severity of retinopathy of prematurity (ROP)
6. Improved survival rates without neurodevelopmental disability at 18–21 months age.
7. Decreased hospital length of stay in preterm infants.

Long J-Y, Guo H-L, He X, Hu Y-H, Xia Y, Cheng R, Ding X-S, Chen F and Xu J (2021) Caffeine for the Pharmacological Treatment of Apnea of Prematurity in the NICU: Dose Selection Conundrum, therapeutic Drug Monitoring and Genetic Factors. *Front. Pharmacol.* 12:681842. doi: 10.3389/fphar.2021.681842

Elmowafi M, Mohsen N, Nour I, Nasef N. Prophylactic versus therapeutic caffeine for apnea of prematurity: a randomized controlled trial [published online ahead of print, 2021 Mar 26]. *J Matern Fetal Neonatal Med.* 2021;1-9. doi:10.1080/14767058.2021.1904873

Dose of Caffeine Citrate – Loading dose

Stable newborn:

- Oral Caffeine citrate **20mg/kg** as a loading dose via Nasal or Oral gastric tube within first 4hrs of birth (or first contact for <10 days old)

Unstable newborn: (convulsions, unconscious, severe chest wall in drawing or absent bowel sounds)

- Oral Caffeine citrate **20mg/kg** as a loading dose via Nasal or Oral gastric tube given with the first or second trophic feed

OR

- IV Caffeine citrate **20mg/kg** as a loading dose over 30min.

What is trophic feeds?

- Small volume, hypo-caloric feeding for gut priming or minimal enteral feeding to acclimate the immature gut of enteral fasting preterm neonates.
- **Expressed breast milk. NEVER FORMULA**
- 1–2 mL/kg/dose or 10-15ml/kg/day
- Early trophic feeds are given within 24 hours of birth.
- Benefits:
 - More energy intake, improved feeding tolerance, greater and faster weight gain and head growth, less sepsis, significantly fewer days of parenteral nutrition and oxygen supplementation, and consequently earlier discharge.

Kebede DA, Tafere Y, Eshete T, Abebaw E, Adimasu M, Endalew B (2022) The time to initiate trophic feeding and its predictors among preterm neonate admitted to neonatal intensive care unit, Multicenter study, Northwest Ethiopia. PLoS ONE 17(8): e0272571. <https://doi.org/10.1371/journal.pone.0272571>

Loading dose of caffeine citrate – worked example.

- **1.4kg stable neonate:**
 - 20mg/kg oral caffeine citrate
 - We give 28mg
 - 20mg/ml = 1.4 ml.
- **1.4kg unstable neonate:**
 - 20mg/kg caffeine = 28mg
 - 20mg/ml = 1.4ml
 - 10mg/ml = 2.8ml
 - Oral or slow IV
 - Need to top up volume for syringe pump!

A preterm baby 1.4kg would get $80\text{ml} \times 1.4\text{kg} = 112\text{ml}/24\text{hrs}$
 $= 4.6\text{mls every hr}$
Approx 1.5ml given in 20 minutes

- Effect of this volume as a bolus???
- Hemodynamic effect of rapid bolus caffeine citrate???

Dose of caffeine citrate – maintenance dose

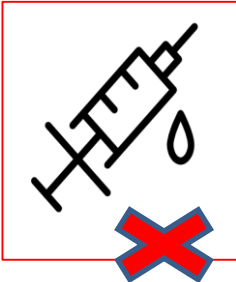
- **Oral Caffeine 5mg/kg** via NGT/oral tube starting from 24th hour after the loading dose and then every 24hours.

- If apnea is recorded on treatment:
 - Increase Caffeine maintenance dose to **10mg/kg** via **Nasal or Oral gastric tube.**

Higher doses of Caffeine Citrate?

1. Loading dose 40mg/kg and maintenance 20mg/kg:
 - ✓ Better therapeutic effect but significant increase in **tachycardia episodes**.
 - ✓ No data on the long term effects.
 2. Loading dose 80mg/kg:
 - ✓ Increased incidence cerebellar hemorrhage
 - ✓ Increased seizure incidence
- Therapeutic drug levels 8 – 20mg/L
 - **Toxic levels** >50mg/L
 - Routine drug monitoring at standard doses **not** recommended as caffeine citrate has a wide therapeutic index.

Monitoring patient on treatment



-No need for routine therapeutic drug monitoring on standard doses of caffeine citrate.



- CONTINUOUS MONITORING** of SpO₂, HR, RR
- Monitoring of vital signs – watch out for tachycardia
- CHANGE** oximeter probe site **every 4 hours** to prevent skin injury
- Stop continuous monitoring if no episodes of apnoea for 5 - 7 days without caffeine.



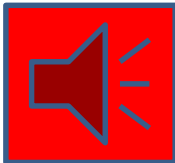
-Observe clinical response

- Practitioners **are required to recognize an alarm within 30seconds** and **respond within 1minute** of the alarm sounding.
- Baby is growing so need to adjust dose regularly – every week.

Stopping caffeine citrate



- ✓ Stop caffeine when newborn is **34 weeks post-menstrual age**
- ✓ **MUST** be apnea free for 48hrs before discontinuing caffeine
- Continue continuous monitoring the newborn for 5-7 days after stopping caffeine.



If apnea recurs after stopping caffeine restart the caffeine citrate – similar dose to the previous dose!

Because of the slow elimination of caffeine in this patient population, there is no requirement for dose tapering on cessation of treatment.

Non-respiratory effects of caffeine citrate

- Receptors through which caffeine acts are present throughout the body.

- **Cardiac muscle:**

- Increase heart rate and strength of contraction of heart muscle.
- Predisposition to arrhythmias and tachycardia

Avoid in symptomatic heart disease

Monitor heart rate and withhold if HR > 180bpm

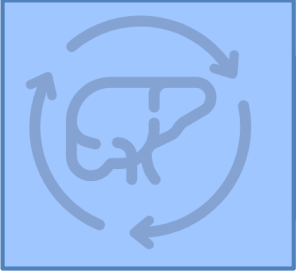
- **CNS:**

- Reduced seizure threshold

Avoid in patients with kernicterus

Use with caution in patients with seizures

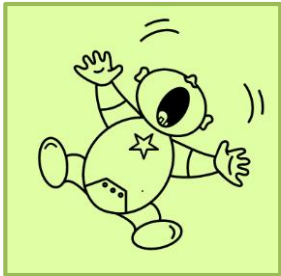
Side effects of caffeine citrate



Increased metabolic rate - may lead to transient slowing of physical growth in the first 3 weeks after starting caffeine



Tachycardia
Consider withholding dose **if HR >180bpm at rest**



Irritability

All hospitals should have a system for pharmacovigilance in place to register and report any suspected adverse effects!

Long term safety after use of caffeine for apnea of prematurity to the immature brain.



- Improved abilities at age 11 years:
 - Neurobehavioural abilities eg catching a ball, tying laces, solving puzzles.



- Not adversely affected:
 - General intelligence
 - Attention
 - Behavior

Administering caffeine citrate.

- Caffeine is compatible with breastmilk, dextrose solution, KCL, normal saline and PPN
- Caffeine citrate vials are single patient vial; for individual patient needs.
 - **Discard unused drug** – There is high risk of contamination as it has no antimicrobial preservative. Aseptic procedures should be used during the preparation of the loading dose especially IV.
- Caffeine citrate does not require any dilution.

Point of caution on drug interaction with caffeine citrate.

- Caution when used with:
 - **Adenosine** - possible decreased therapeutic effect of adenosine.
 - **Cimetidine** - monitor for caffeine toxicity as cimetidine decreases caffeine clearance.
 - **Clonazepam** - reduced sedative and anxiolytic effects of clonazepam.

Contraindication for use of caffeine citrate

- **Contraindications:**
 - Kernicterus
 - Symptomatic cardiac disease especially arrhythmias
- **Caution while using caffeine citrate in:**
 - Renal disease
 - Hepatic disease
 - Seizures

WHO recommendations for care of the preterm or low-birth-weight infant - 2022

1. Caffeine is recommended for the treatment of apnoea in preterm infants.
2. Caffeine is recommended for the extubation of preterm infants born before 34 weeks' gestation.
3. Caffeine may be considered for the prevention of apnoea in preterm infants born before 34 weeks' gestation.

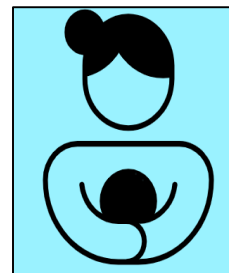


Availability and cost are barriers for the use of caffeine citrate formulations in LMICs

Other therapies for AoP



Tactile stimulation



Kangaroo Mother Care

Blood transfusion.

- Associated with improved oxygen carrying capacity
- Conflicting evidence
- Additional investigation of neurodevelopmental and other long term outcomes needed to decide on liberal versus restrictive transfusion thresholds

Cramer SJE, Dekker J, Dankelman J, Pauws SC, Hooper SB, Te Pas AB. Effect of Tactile Stimulation on Termination and Prevention of Apnea of Prematurity: A Systematic Review. Front Pediatr. 2018;6:45. Published 2018 Mar 2. doi:10.3389/fped.2018.00045

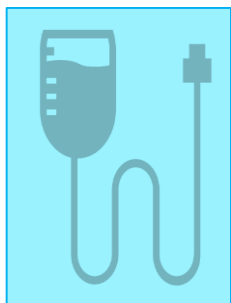
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Other therapies for AoP



Gastric acid suppression.

- Controversial
- Not sufficient evidence to support a temporal, much less a causal relationship between GER and AoP
- Harmful effects include increased sepsis, NEC and death
- Not indicated** for the treatment of AOP



Doxapram.

- Nonspecific CNS stimulant
- Requires continuous IV infusion
- Side effects: Hypertension, Tachycardia, Jitteriness, Vomiting, and Low seizure threshold

Cramer SJE, Dekker J, Dankelman J, Pauws SC, Hooper SB, Te Pas AB. Effect of Tactile Stimulation on Termination and Prevention of Apnea of Prematurity: A Systematic Review. *Front Pediatr.* 2018;6:45. Published 2018 Mar 2. doi:10.3389/fped.2018.00045

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Planning discharge

- Improvement in occurrence of apnea occurs with increasing age.
- Resolution of apnea happens around 34–36 weeks postmenstrual age.
- Infants born at younger gestations may have persisting symptoms to 40–44 weeks postmenstrual age.
- Infants need to be symptom-free for a period of time prior to discharge
 - CAP suggested 5 days
- There is no data to support use of home electronic surveillance for apnea monitoring.

Questions?

Summary

- Apnea of prematurity is inversely related to gestational age and birth weight.
- All preterm infants at risk of AoP should be initiated on prophylactic caffeine citrate and continuously monitored for occurrence of apnea and adverse effects of caffeine
- Caffeine citrate is the preferred pharmacological agent for prevention and treatment of apnea of prematurity.
- Oral caffeine is preferred for loading and maintenance dose.
- Other standard preterm care strategies are key in caring for preterms with/ at risk of AoP.



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with the use of Equipment.**

(Incorporating the new WHO recommendations
for the care of preterms)



6th-10th
February, 2023



University of Nairobi,
Kenyatta National
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Cost of the training:

Ksh 35,000 - East Africans

Ksh 30,000 - Students

500\$ - Foreigners

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