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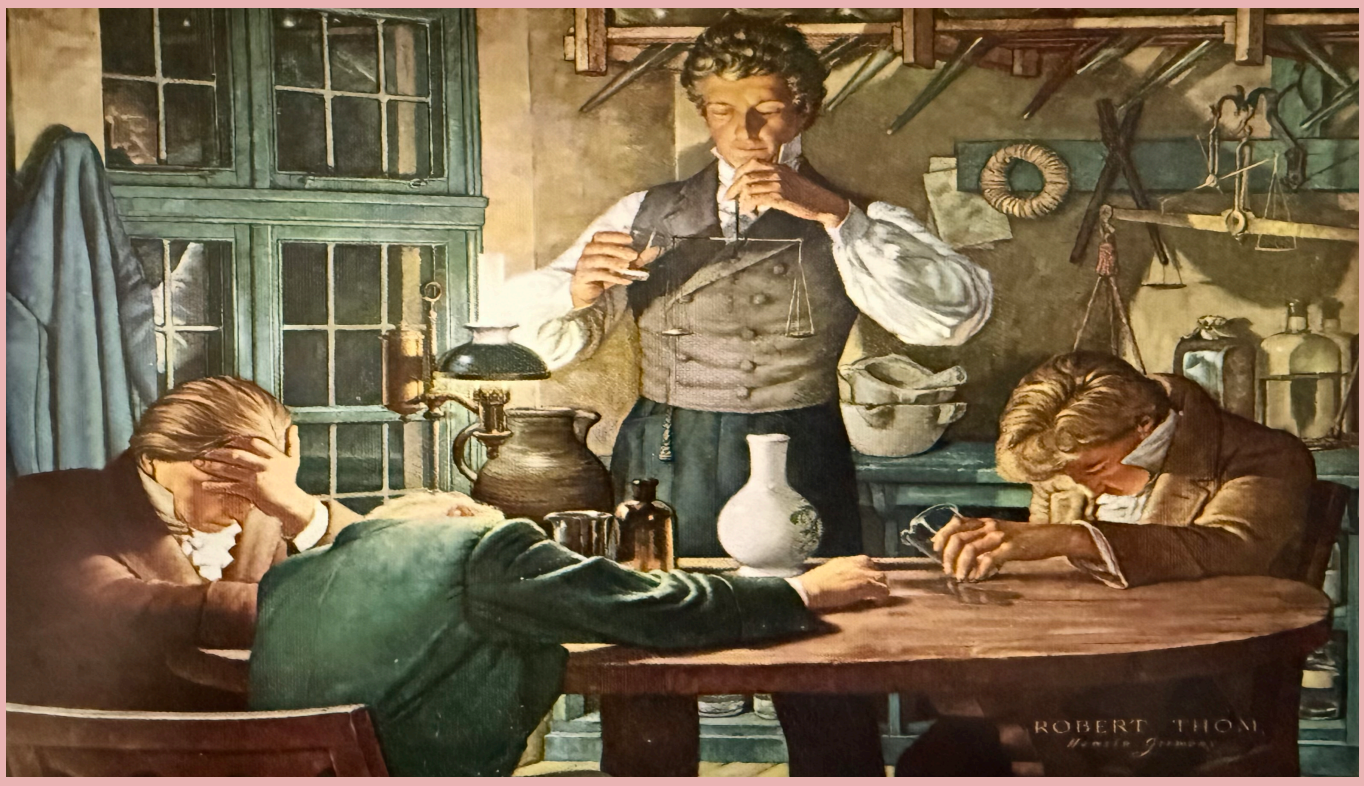

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Cover Picture

Serturner, First Alkaloid Chemist (About 1816)

Friedrich Wilhelm Serturner, young German apothecary, discovered plant alkaloids, and isolated morphine from opium. Extensive experiments, including physiologic tests of morphine on himself and three friends, took place in his apothecary shop.

The Sri Lanka Prescriber

Oxygen Therapy

A continuous oxygen supply is essential for all aerobic organisms to sustain cellular metabolism. In aerobic metabolism, glucose and other substrates are oxidized to carbon dioxide, and oxygen is reduced to water. Oxygen can be considered the most widely used drug in acute hospital care settings. Failure of oxygen delivery to the cells leads rapidly to cellular dysfunction and can lead to cell death and organ dysfunction.

Physiology of Oxygen Delivery

There is approximately 21% oxygen in the atmospheric air. Following are the steps of oxygen delivery into tissues;

1. Ventilation – convection of oxygen from the atmosphere into the body (alveoli in the lungs)
2. Oxygen uptake – diffusion of oxygen into the blood through the alveolar-capillary membrane
3. Reversible bonding of oxygen with haemoglobin
4. Transport of oxygen into tissue (cardiac output)
5. Diffusion into the cells and organelles

Oxygen is transported in blood in two forms. The majority is bound to haemoglobin circulating in the blood. The extent of saturation of haemoglobin with oxygen is expressed as oxygen saturation. A negligible amount of oxygen is transported as dissolved oxygen due to the poor solubility of oxygen in the water. Various factors affect the affinity of haemoglobin for oxygen (e.g., pH, temperature).

$DO_2 = COP \times [(1.34^* \times Hb \times SPO_2) + 0.003 \times PaO_2]$

DO_2 - Oxygen delivery

COP – Cardiac Output

SPO_2 – Oxygen saturation

Hb – Haemoglobin concentration in blood

PaO_2 – Arterial partial pressure of oxygen

1.34* - the amount of oxygen (ml at 1-atmosphere pressure) bound per gram of haemoglobin (Hufner`s constant)

Indications of oxygen therapy

Hypoxaemia, is defined as inadequate oxygen delivery to tissues. Any disturbance in the oxygen delivery pathway described above can lead to hypoxia. There are four types of hypoxia.

Table 1: Types of hypoxia, their pathophysiology and examples

Type of Hypoxia	Pathophysiology	Examples
Hypoxic hypoxia	Reduced supply of oxygen to the body leading to a low arterial oxygen tension	1. Low environmental oxygen (e.g.- high altitude) 2. Airway obstruction 3. Ventilatory failure due to central pathology (e.g.- drug overdose, head injury) 4. Ventilatory failure due to peripheral pathology (e.g.- neuromuscular disease) 5. Pulmonary shunts (e.g.- pneumonia, pneumothorax, pulmonary oedema, asthma)
Anaemic hypoxia	The arterial oxygen tension is	Massive haemorrhgae, Severe anaemia,

	normal, but the circulating haemoglobin is reduced or functionally impaired	Methaemoglobinaemia
Stagnant hypoxia	Failure of transport of sufficient haemoglobin due to inadequate circulation	Left ventricular failure, Pulmonary embolism, Hypovolaemia, Hypothermia
Histotoxic hypoxia	Impairment of cellular metabolism of oxygen despite adequate delivery	Cyanide poisoning, Arsenic poisoning

Any of the disturbances of oxygen delivery mentioned above is an indication for oxygen therapy. What should be considered is that supplemental oxygen is given to improve oxygenation. Still, it does not treat the underlying causes of hypoxaemia which must be diagnosed and treated as a matter of urgency. Early recognition and treatment of oxygen delivery failure is important for preserving organ function.

Oxygen Therapy Apparatus and Devices

In a hypoxic, spontaneously breathing patient, oxygen delivery to the alveoli is usually achieved by increasing the inspired fraction of oxygen (FiO_2). Most commonly, this involves the application of many oxygen therapy devices that deliver oxygen to the mouth/ nose, or both. In a hypoxic patient, it is common to find a significant increase in inspiratory flow rates and an absence of the respiratory pause. A greater proportion of inhaled gas is entrained with atmospheric air due to increased inspiratory flow rates, resulting in the actual inspired fraction of oxygen being significantly less than that to be delivered.

Table 2: Factors that influence the inspired fraction of oxygen delivered to a patient by oxygen therapy devices

Patient Factors	Device factors
Inspiratory flow rates Presence of a respiratory pause Tidal volume	Oxygen flow rate Volume of the mask Air vent size Tightness of the fit

Methods of delivering oxygen to conscious, spontaneously breathing patients with no instrumentation to their airway can be categorized as follows;

1. Variable performance devices
2. Fixed performance devices
3. High-flow systems
4. Others

Oxygen supply can be from pressurized cylinders, hospital supply from cylinder banks, a vacuum-insulated evaporator, or an oxygen concentrator.

Variable performance devices

These systems are so-called because they deliver variable-inspired oxygen concentration which depends on the patient factors outlined above.

1. Nasal cannulae/Nasal prongs

These deliver a constant flow of oxygen to the nasopharynx and oropharynx, which acts as an oxygen reservoir. As the oxygen flow rate increases, the FiO_2 increases but varies with the changes in the patient's minute ventilation. When minute ventilation increases and exceeds the oxygen flow rate, the excess ventilation is drawn from room air, and the FiO_2 begins to decline. Nasal prongs are

easy to use and well tolerated by most patients with mild hypoxia. The major disadvantage is the inability to achieve a high concentration of FiO_2 in patients who have high-minute ventilation. They can cause drying of nasal mucosa when used at higher flow rates.

2. Simple oxygen mask/ Hudson mask

This is the most commonly used type of oxygen therapy device. The device fits loosely on the face, which allows room air to be inhaled if needed (in high-minute ventilation). It has 100 to 200 ml reservoir. A minimum of 4 L/min is needed to clear exhale CO_2 from the mask (to avoid rebreathing). A maximum of 15 L/min oxygen flow rate can be delivered. A maximum FiO_2 of 0.6-0.7 can be achieved, which will be lower in the presence of respiratory distress. This device also causes drying of the respiratory mucosa when used at higher flow rates.

Fixed performance devices

The delivery of oxygen with these devices is independent of the patient factors mentioned above (Table 2).

- Venturi-type masks

Oxygen concentration is determined by the Venturi principle (based on Bernoulli theory): oxygen passing through a small orifice entrains air to a predictable dilution. The FiO_2 is adjusted by changing the Venturi `valve` and setting the appropriate oxygen flow rate. The maximum FiO_2 of only 0.6 can be achieved with an oxygen flow rate of 15L/min with an appropriate Venturi device.

- Mask with reservoir bag with non-rebreathing valve

The addition of a reservoir bag to a standard face mask increases the capacity of the oxygen reservoir by 600 to 1000 ml (depending on the size of the bag). If the reservoir bag is kept inflated, the patient will inhale only the gas contained in the bag. During expiration, oxygen accumulates in the reservoir bag, and the device has a one-way valve that prevents any exhaled gas from returning to the reservoir bag. Nonrebreather devices permit inhalation of higher concentrations of oxygen, nearly 0.9, provided the oxygen flow rate is 15 L/ min.

- High-flow nasal oxygen (HFNO)

High-flow nasal oxygen therapy is used to deliver oxygen to patients at higher flow rates than traditional supplemental oxygen delivery systems, such as standard nasal cannulas or simple face masks. This system can deliver oxygen at flow rates typically ranging from 20 to 60 L/min. This high flow helps maintain a stable supply of oxygen while flushing the upper airway, reducing the work of breathing. A critical advantage of HFNO is the ability to humidify and warm the oxygen being delivered. This feature enhances comfort for patients, especially those receiving prolonged therapy, and helps prevent airway irritation caused by dry, cold gases. The device allows for precise control of FiO_2, with concentrations that can be set between 0.21 (room air) up to nearly 1.0. HFNO employs soft, comfortable nasal prongs that are less intrusive compared to face masks. This enhances patient compliance and comfort.

- Positive-pressure devices

Non-invasive positive pressure ventilation (NIPPV) delivers oxygen with some element of positive pressure exerted during inspiration (PS – pressure support) and expiration (PEEP – positive end-expiratory pressure) to avoid collapsing of alveoli. It does not require instrumentation of the airway and is delivered either by a tight-fitting face mask or as a helmet. The NIPPV modes are CPAP (continuous positive airway pressure) or BIPAP (bilevel positive airway pressure). The FiO_2, PS, and PEEP can be adjusted according to patients` needs.

Adverse Effects of Oxygen Therapy

The need for oxygen to prevent tissue hypoxia and cerebral dysfunction is clear. Most experts emphasize the importance of keeping the SPO_2 above 90% for the majority of acutely ill patients. Aiming for an SPO_2 of 100% (hyperoxaemia) has

been shown to worsen the outcomes in vulnerable patients (e.g., patients with chronic obstructive pulmonary disease), and there is potential harm to other patients.

Potential adverse physiological effects and clinical risks of supplemental oxygen therapy and hyperoxaemia

Physiological risks

1. Worsened Ventilation/ Perfusion (V/Q) mismatch
2. Absorption atelectasis
3. Coronary and cerebral vasoconstriction
4. Reduced cardiac output
5. Damage from oxygen free radicals
6. Increased systemic vascular resistance

Clinical risks

1. Hypercapnic respiratory failure caused by high-concentration oxygen therapy in vulnerable populations such as:
    - Chronic Obstructive Pulmonary Disease
    - Severe kyphoscoliosis or severe ankylosing spondylitis
    - Cystic fibrosis
    - Musculoskeletal disorders with respiratory muscle weakness, especially if on home ventilation
2. Delay in recognition of clinical deterioration
3. Potentially worse outcomes in mild-moderate stroke
4. Specific risk in patients with previous bleomycin lung damage or with paraquat poisoning or acid aspiration
5. Association with increased risk of death in survivors of cardiac arrest and among patients in intensive care units

Targeted Oxygen Therapy

Due to the adverse effects mentioned above it is recommended that oxygen should be prescribed using a target saturation range. A prescription for oxygen should always be provided, except in sudden illness when it must be started immediately and documented retrospectively. This will ensure that every patient will receive appropriate oxygen therapy if it should be required.

Acute hypoxaemia is considered dangerous to healthy individuals below PaO_2 of about 45 mmHg or SPO_2 of about 80% due to impaired mentation and risk of tissue hypoxia. Patients with acute illness or chronic organ disease or ischaemia are likely to be at risk above this level and critical care guidelines recommend aiming to achieve SPO_2 >90%. For this reason, the present guidelines recommend a target $SPO_2 \geq 94\%$ for most hypoxaemic patients to ensure that the actual oxygen level remains above 90% most of the time with a 4% margin of safety to allow for variability in oxygen saturation levels, their recording and oximeter error. Oxygen saturation target of 88 – 92% is recommended for patients who are vulnerable to develop hypercapnic respiratory failure including those with COPD.

Good Practice Points Related to Prescribing and Administering Oxygen Therapy to Patients

- Oxygen should be prescribed on the drug chart or electronic prescribing system using a target saturation range.
- Oxygen should be prescribed to a target saturation range rather than prescribing a fixed concentration of oxygen or FiO_2.
- In most emergency situations, oxygen is given to patients immediately without a formal prescription. The lack of a prescription should never preclude oxygen being given in such situations. However, a subsequent written record must be made on oxygen prescription once the patient is stabilized.
- Pulse oximetry must be available in all locations where emergency oxygen is being used to monitor SPO_2.

- Clinicians should assess the clinical status of the patient prior to prescribing oxygen and the patient`s condition including SPO_2 should be monitored frequently during oxygen use.
- The administrating health care professional should note the SPO_2 before starting oxygen therapy whenever possible but never discontinue or delay oxygen therapy for seriously ill patients.
- Oxygen therapy should be started using an appropriate delivery system and flow rates. The target oxygen saturation should be documented.
- Staff should check the oxygen supply and connections on a regular basis.

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Prescribing in neonates and use of medicines in common neonatal problems

The World Health Organization defines a neonate as a child born up to 28 days of age [1]. While most babies are born after reaching full maturity of their organ systems after 37 weeks of gestation, around 7-10% of babies are born before 37 weeks with immature organ systems [2]. In Sri Lanka, preterm birth occurs nearly 8 per every 100 births and is the largest contributor to neonatal mortality [3].

Babies as small as 500g and born as early as 23-24 weeks gestation, are usually the sickest neonates who are admitted to the neonatal intensive care unit. Immature organ systems leading to surfactant deficiency, sepsis, congenital pneumonia, necrotizing enterocolitis, ventilator acquired pneumonia, apnoea of prematurity, gastroesophageal reflux, patent ductus arteriosus, hypontraemia, osteopenia of prematurity, anemia of prematurity, retinopathy of prematurity, pulmonary haemorrhage, intraventricular haemorrhage and bronchopulmonary dysplasia, result in the most immature babies receiving the largest number of medications.

Prescribing in neonates has many challenges including differences in pharmacokinetics due to immaturity and different phases of growth, increased frequency of drug errors commonly due to complex dose calculation dealing with minute doses that change with gestation and age, unnecessary prescription of drugs for normal phenomena, off label use of drugs as well as the rational use of antibiotics.

Neonates have different pharmacokinetics

Differences in drug absorption

Gastro-oesophageal reflux, high gastric pH (6-8) and slower gastric emptying leads to variable absorption of drugs given via the enteral route. Intramuscular route is usually avoided due to reduced muscle mass and reduced muscle blood flow leading to slower and unpredictable absorption. Unpredictable absorption due frequency of rectal contractions and absence of small dose suppositories specific to neonates, leads to avoidance of the rectal route [2].

Hence all serious neonatal conditions like sepsis, congenital pneumonia, symptomatic hypoglycemia etc., are treated with intravenous medications to ensure bioavailability. The intramuscular route is mostly confined to the administration of vitamin K for babies with a birth weight >1500g. Rectal route should be avoided. Enteral route is mostly used to administer vitamin and mineral supplements in addition to paracetamol [5].

- Intravenous route is indicated for drug administration in all sick newborns
- Intramuscular route is avoided due to small muscle mass
- Rectal route is avoided due to unpredictable rectal contractions

Differences in drug distribution

Differences in body composition of the neonate (75-85% water content) increases the volume of distribution of water-soluble drugs and decreases the volume of distribution of fat-soluble drugs [4]. Plasma concentration of aminoglycosides like gentamicin (first line antibiotic for invasive neonatal infection) may appear lower than expected due to its high level of water solubility [2].

Albumin is the main protein involved with drug binding. Lower concentration of albumin, in addition to the presence of high amounts of fetal albumin, which has a reduced binding capacity leads to a higher concentration of free drug in the plasma, increasing the risk of toxicity. Therefore, highly protein bound drugs like phenobarbitone, phenytoin and frusemide are prescribed in lower doses in neonates to achieve the same therapeutic effect [2].

- Higher volume of distribution for water soluble drugs

- Lower volume of distribution for fat soluble drugs
- Increased risk of toxicity for protein bound drugs

Differences in drug metabolism and excretion

Developmental variations of hepatic enzyme activity, decreased glucuronidation, decreased hepatic blood flow, decreased glomerular filtration rate and ongoing nephrogenesis due to immaturity, affect the hepatic metabolism and renal excretion of many drugs in neonates [2].

Dosage frequency changes according to the gestation, aminoglycosides are administered every 36- 48 hours to preterm babies, compared to every 24 hours for term babies [2].

Dosage frequency also changes according to the age, where benzyl penicillin is administered every 12 hours during the first 7 days postnatal age, every 8 hours between 7-21 days of age and every 6 hours after 21 days of age [2].

- Drug doses change according to day of life and gestation due to developmental changes in the liver and the kidney

Medication errors are common in neonates.

Medication errors that could cause potential harm has been found to be 8 times more likely in the neonatal intensive care unit (NICU).

Prescribing errors

The commonest (75%) errors were seen in the prescribing phase, where almost 50% of were due to incorrect dosing. The commonest cause for incorrect dosing was found to be the incorrect placement of decimal points or units of measurement that was associated with lack of experience in the clinicians, high clinician work load and lack of neonate specific drug protocols in the NICU [6].

Administration errors

Administration errors were the second most common type of error accounting for 30-63% of errors. Incorrect administration time was the commonest, followed by incorrect preparation and dilution of medication and administering an extra dose of medication. This may be due to almost a third of intravenous medication being prescribed at doses less than one tenth of the vial, thereby increasing the risk of a tenfold or 100-fold dosing error on administration. Almost 50% of the administration errors have been found to be tenfold dosing errors [6].

Dispensing errors

Dispensing errors were found in almost 12-25% of neonatal prescriptions due to mistakes in labelling and dilution of formulations. It was associated with delays in the dispensing time of more than 2 hours [6].

Transcription errors

Transcription errors accounted for 12-18% of total errors where commissions and omissions were equally common. Use of incorrect units, recording of incorrect weight, omission of recording of the administered dose were the commonest transcription errors that were observed. These errors were associated with neonates with a higher number of medications, vascular lines and longer hospitalization [6].

- NICU setting is a high risk setting for medication errors
- Dosing errors are the commonest
- Smallest babies are at highest risk
- Use the neonatal formulary or national neonatal guideline to calculate drug doses based on weight, gestation and day of age NICU
- Use a standard dilution method when preparing all infusions
- Have clear written instructions on how to prepare the standard dilutions

- Have a dedicated calculator for calculating drug doses
- Have a minimum of two health care workers for each step to countersign each other and minimize errors at each step
- Regular training and assessment for neonatal unit staff to increase awareness

Overprescribing is common in neonates

Overprescribing includes unnecessary prescriptions as well as inappropriate prescriptions, where the harm outweighs the benefit.

Chlorpheniramine and saline nose drops / spray for nasal congestion

Presence of nasal secretions is a normal phenomenon soon after birth, due to presence of excess amniotic fluid that has not been absorbed yet. Nasal secretions and nose block in otherwise well neonates are mostly due to common cold which is a self-resolving viral illness.

Saline nose drops which are is very commonly prescribed has no proven benefit and is likely to do more harm than good. Saline drops wash away lysozymes which are both bactericidal and bacteriostatic, thereby lowering the local immunity. It also dries the nasal passageways, by washing away the natural mucus blanket that protects the delicate cilia and the nasal mucous membrane. In addition, saline nasal sprays will spread the purulence from one area to all areas in the nose as well as the sinuses [7].

Chlorpheniramine which is also commonly used to treat nasal symptoms in neonates despite not been recommended for use under one moth of age, has been associated with life threatening apnoea as well as sudden infant death [8].

- Neither chlorpheniramine nor saline nasal drops / spray should be used to treat nasal symptoms in neonates

Lactulose for 'constipation'

Parents worrying that an otherwise well neonate has reduced stool frequency and hence constipation, is a common reason for an outpatient consultation. This frequently results in the neonate being prescribed a laxative, most commonly lactulose by a health care worker.

While breastfed neonates have higher stool frequency and more liquid consistency than formula fed neonates, some have no bowel movements or infrequent stools for several days or weeks. A French study demonstrated that 28% of exclusively breastfed infants open bowel once in 3-5 days. Furthermore, stool frequency and consistency change with age and should not be misinterpreted as constipation [9].

Constipation is defined as a delay or difficulty in daefecation, present for 2 weeks or more, sufficient to cause significant distress to the patient [10]. Hence reduced bowel frequency in an otherwise well neonate who is not distressed, is not constipation. While crying following daefecation until the dirty nappy is cleaned is a normal phenomenon, crying during daefecation and persistent crying after the nappy is cleaned indicates examination for anal fissures. History of delayed passage of meconium after the 48 hours of age in a neonates suspected to have constipation warrants careful evaluation for Hirschsprung disease.

Lactulose is an osmotic laxative and is not licensed for use in neonates. It causes flatulence and bloating that will lead to further confusion if attributed to reduced stool frequency instead as an adverse effect of the medication.

Glycerin suppositories to hasten the passage of meconium in preterm neonates

Glycerin suppositories are commonly prescribed to preterm neonates who don't pass stool during the first few days. However, an metanalysis by Buchard et al, did not demonstrate any benefit. Furthermore, long-term use has been shown to cause dependence and interfere the development bowel habits. In addition, the dosage recommended for very and extreme preterm neonates is a 'chip' which is very subjective [11].

Antibiotics for 'diarrhoea'

Infective diarrhoea does not occur in exclusively breastfed neonates where a stool frequency of 10-15 times per day or passage of stool during / after each breastfeed is due to the immature gastrocolic reflex and is considered normal. The consistency of each stool varies with the water content of each breastfeed and should not be misinterpreted as diarrhoea.

Stool colour also changes through the neonatal period and commonly changes from blackish- green to yellow with establishment of breastfeeding. Green stool in a well neonate does not indicate pathology and does not warrant antibiotics.

- Stool frequency, consistency and colour are highly variable during the neonatal period
- Use extreme caution in diagnosing constipation and diarrhoea in exclusively breastfed neonates
- Lactulose is not licensed for use in neonates
- Long term glycerin use interferes with the development of normal bowel habits
- Use glycerin suppositories only if coupled with significant abdominal distension
- Increased stool frequency and green stool in a well neonate should not be mis interpreted as diarrhoea and does not warrant antibiotics

Gripe water for 'stomachache'

Excessive crying in the evening is frequently thought to be due to stomachache or due to difficulties in digestion for which parents often administer gripe water with the misconception that it relieves stomachache. Excessive crying in the evening in neonates is due to air swallowing due to an imperfect seal during breastfeeding. There is no evidence that gripe water is beneficial. In fact, it has been found to significantly increase infantile colic, vomiting and constipation. Improving attachment to have a tight seal around the areola, spacing breastfeeds, not using the breast to as a pacifier nor to put the baby to sleep, keeping the baby prone after feeds and winding / burping effectively will help these babies [12].

- Excessive crying in the evening is not due to stomachache
- It is due to swallowing air during feeding
- Gripe water should not be prescribed for neonates
- Gripe water causes vomiting, constipation and colic

Antibiotic eye drops for eye discharge

The commonest cause for eye discharge is blockage of the nasolacrimal duct. This is characterized by unilateral discharge / crusted eyelids, without evidence of acute inflammation i.e., erythema, eye lid swelling, purulent discharge, periorbital swelling etc. Therefore, antibiotic eyedrops should only be reserved for babies whose eye discharge is accompanied with features of acute inflammation.

- Unilateral eye discharge or crusting of eye lids are usually due to nasolacrimal duct obstruction and does not warrant antibiotics
- Presence of conjunctival erythema and purulent eye discharge are suggestive of bacterial infection, where antibiotic eye drops are indicated

Antibiotics for umbilical discharge

The umbilical cord is colonized with potential bacterial pathogens soon after birth. These bacteria attract polymorphonuclear leukocytes. The granulocyte influx and phagocytosis in addition to desiccation and tissue necrosis lead to separation of the umbilical cord by 7-10 days after birth resulting in a sticky umbilicus that provides an excellent ground for bacterial invasion. This is best prevented by keeping the umbilical cord clean and dry by bathing the baby every day after the first 24 hours. There is no place for topical antibiotics.

Purulent discharge and periumbilical erythema are danger signs suggestive of bacterial infection i.e., omphalitis which needs to be treated with intravenous antibiotics, as it has the potential to spread to fascial planes (necrotizing fasciitis), muscles (myonecrosis) and invade the umbilical vessels (phlebitis) as well as the blood stream (sepsis).

- Umbilical area is sticky due to ongoing necrosis in preparation for separation
- Umbilical cord should be kept clean and dry to prevent secondary bacterial infection
- Local application of antibiotics are not recommended
- Purulent discharge and periumbilical erythema indicate bacterial infection and should be treated with intravenous antibiotics

Use of 'Off label' medication is common in neonates.

'Off label' refers to the usage of a medication for an indication or age group that is not included in the package insert. However, labeling with paediatric information exists for less than 50% of products. Off label use is not necessarily a bad practice and is common in neonates due to the difficulty of conducting clinical trials in this age group. However, it is done on an individual basis and is only justified when there is a benefit over risk for that individual neonate as per best available clinical evidence and / or clinician experience [13].

- Off label medication can be used in a specific situation for a specific neonate where there is a clear benefit more than the risk

Rational use of antibiotics

Antibiotics are commonly overprescribed in neonates. Rational use has been defined by the World Health Organization to assure that each patient receives the medication they need, in a dose appropriate for his / her individual characteristics, for the appropriate duration [14].

A study in Pakistan showed that 85.5% of children with COVID 19 were prescribed 'watch' antibiotics, to prevent secondary bacterial infections, although secondary bacterial infections was found only in 3.7% [15]. However, a study done in Australia revealed that more than 95% of therapy for neonatal sepsis was deemed appropriate by local assessors and in accordance with their guidelines despite only 4% of neonates having microbiologically confirmed infection [14].

Neonatal sepsis has a high mortality; clinical features are not specific; anti-inflammatory markers are nonspecific and frequently lag behind the clinical features; blood cultures are often negative due to small volume of blood; treatment during the golden hour improves prognosis; treatment delays result in morbidity and mortality. Therefore, intravenous antibiotics need to be commenced as soon as possible on suspicion of sepsis. Early onset sepsis is treated with narrow spectrum antibiotics like benzyl penicillin and gentamicin, whereas late onset sepsis may require more broad-spectrum antibiotics. Choice of antibiotic should be based on the National Guideline for newborn care. Strict antibiotic policy helps to prevent / minimize the development of resistance. Antibiotics should be given for the minimum duration needed, decided as per improvement of clinical features as well as

normalization of investigation results. Beware of normal ranges for neonates, as these are age specific.

- The appropriate antibiotic, in the appropriate dose, should be administered intravenously, for the minimum duration, to treat neonatal sepsis effectively, while minimizing the adverse effects and development of antibiotic resistance
- Neonatal drug doses do not have a linear relationship with body weight or age and cannot be extrapolated from adult doses
- Use a neonatal formulary or the latest national guideline on newborn care or the paediatric BNF in that order of preference when prescribing for neonates

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Pharmacological management of polycystic ovary syndrome

SUMMARY

Polycystic ovary syndrome is a common and frequently undiagnosed female endocrine disorder that is associated with diverse symptoms and features, and an increased risk of long-term chronic diseases such as type 2 diabetes and cardiovascular disease. Pharmacotherapy for polycystic ovary syndrome should be directed at the key concerns of the individual patient. The combined oral contraceptive pill or metformin may be prescribed for irregular periods. The combined oral contraceptive pill is preferred over antiandrogens for treatment of hirsutism and acne. Metformin is of benefit for reducing excess body weight and improving hormonal and metabolic outcomes in those with high metabolic risk (e.g. body mass index greater than 25 kg/m^2). Inositol appears to have limited benefits for metabolic outcomes, although it is associated with fewer adverse effects than metformin. Modification of lifestyle factors is important as part of a holistic approach to managing polycystic ovary syndrome. Anti-obesity drugs may be considered for weight management in addition to lifestyle interventions.

Keywords

antiandrogens, anti-obesity drugs, combined oral contraceptive pill, inositol, metformin, polycystic ovary syndrome, women's health

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Introduction

Polycystic ovary syndrome (PCOS) is a common female endocrinopathy with reproductive, cardiometabolic, dermatological and psychological features. The key concerns of women with PCOS include subfertility, loss of feminine identity, irregular periods, excess body weight, hirsutism and acne, all of which can have a significant negative impact on the patient's emotional wellbeing.[1,2] Despite affecting around 1 in 8 women globally with significant public health impacts,[3] women with PCOS have reported diagnostic delays, which are commonly due to a lack of knowledge about PCOS, particularly low awareness of diagnostic criteria, among primary care clinicians.[4,5] Even at the time of diagnosis, women are sometimes not provided with adequate information about PCOS and the initial information given can vary among medical practitioners.[6] The International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome 2023 integrates the best available evidence with multidisciplinary expertise and consumer preferences, to provide guidance on diagnosis, assessment of PCOS-related concerns and optimal treatment.[7] Nonpharmacological and lifestyle interventions are an essential part of management and are discussed in the international guideline. This article focuses on the current diagnostic criteria and key considerations for the pharmacological management of PCOS based on the guideline. In this article, the term 'woman' is used to encompass all genders affected by PCOS and the term 'female' is used where biological sex is most relevant.

Diagnosis

The diagnosis of PCOS now includes using antiMullerian hormone concentration as an alternative to ultrasound in adults (Box 1). If used for diagnosis, ultrasound may be transabdominal or transvaginal; transvaginal ultrasound is the most accurate.[7] The use of ultrasound or anti-Mullerian hormone concentration to diagnose polycystic ovaries is not recommended in adolescent females within 8 years of menarche because there is a risk of overdiagnosis.

Assessment for comorbidities

As PCOS is strongly associated with an increased risk of type 2 diabetes and cardiovascular disease, diagnostic assessment of women with PCOS should

also include assessment of glycaemic status (preferably with an oral glucose tolerance test) and cardiovascular disease risk. Lifestyle interventions (exercise alone or combined with dietary measures and behavioural strategies) are recommended for all women with PCOS to improve their metabolic health, including reducing central adiposity and improving their lipid profile.

Women with PCOS should be informed about the increased premenopausal risk of endometrial cancer (twofold to sixfold), although the absolute risk is low and routine screening is not recommended. Informing women about this risk can help guide decisions regarding pharmacological treatment.7 Obstructive sleep apnoea is a common comorbidity in women with PCOS, and clinicians should assess patients for symptoms of obstructive sleep apnoea (e.g. snoring, waking unrefreshed, daytime sleepiness, fatigue). Women with PCOS have a high prevalence of anxiety and depression, and assessment for psychological symptoms at the time of diagnosis is recommended.

Box 1 Diagnostic criteria for polycystic ovary syndrome[7]

Diagnosis of polycystic ovary syndrome in **adult** females requires **two** of the following criteria after exclusion of other aetiologies:

- oligo-anovulation or anovulation [NB1]
- clinical and/or biochemical hyperandrogenism [NB2]
- polycystic ovaries on ultrasound or elevated anti-Mullerian hormone concentration. [NB3]

Diagnosis of polycystic ovary syndrome in **adolescent** females requires **both** of the following criteria after exclusion of other aetiologies:

- oligo-anovulation or anovulation [NB1]
- clinical and/or biochemical hyperandrogenism. [NB2]

NB1: Anovulation is a condition in which the ovary does not produce and release an egg each menstrual cycle. Oligo-anovulation refers to irregular cycles lasting less than 21 days or more than 35 days, less than 8 periods per year, or an absence of raised serum progesterone 7 days before a period.

NB2: Clinical hyperandrogenism includes acne, female pattern hair loss (adults only) and hirsutism. Biochemical hyperandrogenism refers to elevated serum androgens such as total serum testosterone or elevated free androgen index; reference ranges vary depending on the assay used – seek advice from the laboratory.

NB3: The polycystic ovarian morphology threshold is a follicle number per ovary of 20 or more and/or an ovarian volume of 10 mL or more (with transvaginal ultrasound), or follicle number per section of 10 or more and/or an ovarian volume of 10 mL or more (with transabdominal ultrasound). Reference ranges for anti-Mullerian hormone concentration are population- and assay-specific – seek advice from the laboratory.

Table 1 Pharmacological management of symptoms of polycystic ovary syndrome[7]

Symptom	First-line therapy	Second-line therapy	Third-line therapy
irregular periods	combined oral contraceptive pill	metformin	–
excess body weight and metabolic effects (e.g. insulin resistance)	metformin	anti-obesity drugs	inositol
clinical hyperandrogenism, including hirsutism and acne	combined oral contraceptive pill	antiandrogens	–

Following initial assessment, women with PCOS should be monitored for these comorbidities based on their individual risk factors.

Principles of pharmacological management

Effective pharmacotherapy for symptoms of key concern to women with PCOS focuses on patient entred care, where treatments are tailored to individual needs, goals and preferences.7 Monitoring of response to treatment, identifying adverse reactions and adjusting therapy will support patients in achieving their desired health outcomes. Discussions around management of PCOS and related concerns should be conducted in a sensitive manner. For example, clinicians should be aware of their own potential biases about weight and aim to promote and adopt weightinclusive practices that advocate for the acceptance of, and respect for, people of all body sizes.

The recommended preferences for pharmacological therapies for irregular periods, excess body weight and metabolic effects, and clinical hyperandrogenism are summarised in Table 1 and discussed in more detail in the individual sections on each therapy below.

Subfertility can be a key concern in women with PCOS; however, not all women with PCOS will experience subfertility. Women should be reassured that pregnancy can often be successfully achieved either naturally or with assistance. The management of subfertility in women with PCOS requires

optimising healthy lifestyle behaviours and metabolic health before conception. If pharmacological management of subfertility is required, patients should be referred to a specialist. Contraception should be considered in women with PCOS who do not wish to conceive.

Combined oral contraceptive pill

The combined oral contraceptive pill (COCP) is usually the first-line treatment to ameliorate symptoms of irregular periods or clinical hyperandrogenism, such as hirsutism or acne, in women with PCOS.[7] The COCP can improve symptoms through multiple pathways including:

- direct inhibition of ovarian androgen production
- increased hepatic production of sex hormone–binding globulin, which reduces free androgen availability
- direct antiandrogenic effects of newer progestins.[8,9]

Despite the common perception that the COCP is the first-line treatment for any woman with PCOS, the COCP should only be used in patients who have concerns about irregular periods or clinical hyperandrogenism, or who are already on a COCP for another indication.

General population guidelines should be followed when prescribing the COCP for women with PCOS. Formulations containing low-dose estrogen are preferred as high-dose estrogen formulations do not confer additional clinical benefits. Apart from minimising the use of preparations containing cyproterone acetate because of its less favourable adverse effect profile (e.g. increased risk of venous thromboembolism), no specific types of COCP are recommended as none of them have demonstrated superiority in the context of PCOS.[7-9]

Progestogen-only oral contraceptives may be considered for endometrial protection in women with contraindications to, or who are intolerant of, the COCP. Evidence of other benefits, such as regulating menstrual cycles or improving clinical hyperandrogenism, in women with PCOS is limited.

Metformin

In women with PCOS, metformin is used off label as first-line treatment for excess body weight and metabolic effects. Metformin can improve the underlying insulin resistance that is characteristic of PCOS. Its action primarily involves improving insulin sensitivity in the liver and peripheral tissues, and reducing hepatic glucose production.[10]

Metformin has demonstrated significant efficacy in improving various anthropometric outcomes, including reducing body weight, waist–hip ratio and body mass index (BMI), in addition to improving metabolic parameters (e.g. blood glucose concentrations, lipid profile).[7,10] These therapeutic effects are particularly pronounced among adults with a BMI greater than 25 kg/m^2.[7] Combining metformin with lifestyle interventions has demonstrated better outcomes compared with lifestyle interventions alone, suggesting synergistic effects.[10]

Additionally, metformin may exert beneficial effects of restoring menstrual cyclicity and ovulation, and can be considered in preference to the COCP in women wishing to conceive.

There is conflicting evidence on whether metformin use in pregnant women with PCOS can prevent gestational diabetes, late miscarriage, hypertension, pre-eclampsia or macrosomia; however, there is evidence that metformin reduces gestational weight gain and decreases the risk of preterm delivery. These effects warrant further research and clinical consideration in this context.[7]

Inositol

Inositol is a nutrient supplement that acts as an insulin sensitiser and is thought to promote glucose uptake and reduce androgen production in ovarian granulosa cells.[11] In Australia, inositol is available without a prescription and is a 'listed' medicine on the Australian Register of Therapeutic Goods, meaning it has not been assessed for efficacy.

A 2024 systematic review and meta-analysis reported inconclusive evidence of benefit for inositol in women with PCOS.[11] The most commonly used forms of inositol, myo-inositol and D-chiro-inositol, may have limited benefit for some metabolic outcomes in PCOS, including reduced fasting insulin concentration and increased insulin sensitivity. Metformin appears to be superior to inositol for hirsutism and central adiposity, although metformin has more adverse effects such as gastrointestinal effects. It is unclear if there is any benefit in adding inositol to metformin. Specific types, doses or combinations of inositol cannot currently be recommended because of a lack of high-quality evidence.

Clinicians should discuss with patients the potential benefits and harms of using inositol, including cost and the relative lack of regulation, while acknowledging and respecting the individual's values and preferences.

Anti-obesity drugs

There is limited evidence for the efficacy of antiobesity drugs, such as orlistat and glucagon-like peptide-1 (GLP-1) receptor agonists (e.g. liraglutide, semaglutide), specifically in women with PCOS, including for reproductive outcomes.[12] However, based on guidelines in the general population, orlistat and GLP-1 receptor agonists can be considered for management of excess body weight in adults with PCOS alongside lifestyle interventions.[13]

Concurrent effective contraception is required if pregnancy is possible because there is insufficient safety data on the use of GLP-1 receptor agonists in pregnancy. Gastrointestinal adverse effects, such as diarrhoea and vomiting, are common with GLP-1 receptor agonists and gradual dose escalation is recommended. Women should be counselled about the lack of long-term safety data and the high risk of weight regain after discontinuation.

Anti-obesity drugs are not recommended in adolescents as no evidence for efficacy or safety was identified in this age group.[7]

Antiandrogens

Antiandrogens play a role in managing clinical hyperandrogenism in PCOS via diverse mechanisms, such as:

- competitive inhibition of androgen receptors
- suppression of androgen synthesis
- inhibition of 5-alpha-reductase activity, which converts testosterone to its active metabolite, 5-alpha-dihydrotestosterone.[14]

Spironolactone is the most frequently prescribed antiandrogen because finasteride, flutamide and bicalutamide have an increased risk of causing liver toxicity. Prolonged use of cyproterone acetate is associated with development of meningioma.[7] While there is some evidence for antiandrogens in managing hirsutism,[14] they are reserved for cases where the COCP is contraindicated, or where there is suboptimal response after a minimum of 6 months of the COCP or cosmetic therapy.[7] This cautious approach stems from potential teratogenicity of antiandrogens, which can cause hypovirilisation of male fetuses. Concurrent use of effective contraception is imperative for women taking antiandrogens in whom pregnancy is possible. Although evidence in treating female pattern hair loss in PCOS is limited, the combination of

antiandrogens with the COCP should be considered given the significant psychological impact of alopecia on affected patients.[7]

Conclusion

Management of PCOS requires a comprehensive patient-centred approach, incorporating education, empowerment and shared decision-making to

optimise the patient's experience and health outcomes. The International Evidence-based Guideline for the Assessment and Management of PCOS 2023 provides guidance on nonpharmacological and pharmacological management of PCOS. Choice of pharmacotherapy is driven by the individual patient's symptoms and may include the COCP, metformin, inositol, anti-obesity drugs and antiandrogens.

Conflicts of interest

Carolyn Ee and Chau Thien Tay were both authors on the International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome 2023.

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