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UPDATES ON PAEDIATRICS

QUIZ

Test Your Eye-Q (No 13)

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UPDATE ON PAEDIATRICS

Goh Lee Gan

This issue focuses on paediatrics. Rhinitis and school refusal are common problems. Child abuse needs to be considered as a differential diagnosis in childhood injuries that are unusual. Delivery room resuscitation of the newborn is relevant sometimes if a family doctor practices in a rural or remote setting. Antibiotics and vaccines have a role in the control of paediatric infections.

CHRONIC RHINITIS

The approach to chronic rhinitis in children is to exclude infective sinusitis, consider anatomic defects, foreign body, polyps, evaluate tympanic membranes and hearing, nasal obstruction and sleep apnoea and consider allergy evaluation. Rhinitis in children may be allergic or non-allergic in nature.

What is the role of allergen testing in rhinitis in children? To establish the diagnosis of allergic rhinitis with certainty, allergy testing needs to be considered. Inhalant allergens are the most frequent triggers of allergic rhinitis in children. Housedust mite and cockcroach allergens are the common causes. Food allergy should be considered in infancy or early childhood. The common ones are cow's milk and egg. In allergic rhinitis, environmental control, antihistamines, cromolyn and topical steroids need to be considered.

BETTER ANTIBIOTIC PRESCRIBING

Currently thousands of courses of antibiotics are given each year. One main problem in paediatrics is the diagnostic uncertainty of whether the child has a viral or bacterial infection. The rationale against presumptive antibiotic use are: no evidence for clinical efficacy because impending bacterial secondary infections are not aborted or diminished; there is no difference on rate of return visits; overuse of antibiotics promotes bacterial resistance in the long term; and antibiotics are associated with side-effects and add to cost of treatment. The need for antibiotics should therefore be evaluated based on the likelihood, individual risks and the choice of which one to use.

SCHOOL REFUSAL

Two groups of pupils can be differentiated: those who are truanting — not in school and not at home; and those who are at home. For those who truant, many do not have anything wrong psychiatrically. The strategy lies in unraveling social reasons. For those who are found at home, the underlying reason may be physical ill health or anxiety about school. The attitudes of parents may encourage or condone the absence of the child from school. Some parents give in to demands because of the fears of putting too much pressure on the child or because of their own difficulties in separation engendered b over-close emotional attachments. There is therefore a need to unravel the emotional issues surrounding the school refusal.

DELIVERY ROOM RESUSCITATION OF THE NEWBORN

The resuscitation of the newborn involves a series of well-defined steps based on repeated evaluation and assessment of airway, breathing and circulation, drugs and environment. Whilst not all family physicians may be dealing with this as a day-to-day problem, it is good to have an understanding of the subject.

CHILD ABUSE

For the family physician, a diagnosis of a possible child abuse is a judgment call. The family physician who is in direct contact and care of children has a duty to ensure that the alleged abused child is taken out of harm's way. A good history and observant examination is

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important. Some injuries are suspicious: bruises and welts, burns from cigarettes or patterned, rope burns, external genitalia, palate and mouth burns, abdominal injuries, cerebral injuries, and unusual fracture patterns e.g. fracture of femur in children less than 3 years old. It is also noteworthy that mistakes may be made in diagnosing child abuse. Beyond diagnosis lies the struggles in deciding how to deal with the situation.

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RHINITIS IN CHILDREN – ROLE OF ALLERGEN TESTING

B W Lee

ABSTRACT

To establish the diagnosis of allergic rhinitis with certainty, allergy testing is recommended. Inhalant allergens are the most frequent trigger of allergic rhinitis in children, however, food allergy should also not be ignored in infancy or early childhood. The importance of making a diagnosis of allergic rhinitis lies in its implications on the clinical course of disease, as well as therapeutic options. This paper will focus on the diagnostic approach of chronic rhinitis in children, with particular emphasis on allergy testing.

INTRODUCTION

Rhinitis is one of the most prevalent of respiratory diseases. In a schoolchildren survey in Singapore, 37% reported having had symptoms in the year previous of rhinitis, which is not related to an acute respiratory illness [1]. However, as it is not a life-threatening condition and children often do not verbalise the impact of their symptoms, chronic rhinitis often goes unnoticed and inadequately treated. It therefore should be emphasised that chronic rhinitis can affect a child's physical and psychosocial well-being, quality of life, and capacity to function and learn. Further, it may also result in significant sequelae such as sinusitis and serous otitis media.

CLINICAL CLASSIFICATION OF RHINITIS

Until now, there is no worldwide consensus for the classification, definition and diagnosis of rhinitis. Rhinitis may be classified first according to the clinical presentation (acute or chronic) and then to its etiology (Table 1). The clinical definition of a minimal of 12 weeks of symptoms for chronic rhinitis is based mainly on the clinical approach to sinusitis [2]. In chronic rhinitis in children, concomitant sinusitis is usually present and therefore the term 'rhinosinusitis' is often used.

The most common causes of chronic rhinitis in children are allergic and non-allergic vasomotor rhinitis. In very young infants, structural abnormalities such as choanal atresia, and gastroesophageal reflux should be considered, and may require specific evaluation. Nasal polyps are rare below the age of 10 years, and when diagnosed, cystic fibrosis should be excluded.

Table 1: Classification of Rhinitis

Clinical Presentation	Etiology
Acute* rhinitis	Infectious
Chronic* rhinitis	Infectious (sinusitis) Allergic Non-allergic • Vasomotor • NARES (nonallergic rhinitis with eosinophilia) Drug-induced • Aspirin sensitivity Gastroesophageal reflux
	Secondary causes • Polyps • Mechanical Factors - Deviated septum - Adenoidal hypertrophy - Foreign bodies - Choanal atresia • Tumours • Granulomas - Wegener's granulomatosis - Infectious • Ciliary defects • Cerebrospinal rhinorrhoea

** The cut-off between acute and chronic rhinitis has been arbitrarily defined as 12 weeks.*

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CLINICAL EVALUATION AND DIAGNOSIS

The most common symptoms of rhinitis are nasal obstruction, rhinorrhoea, pruitus and sneezing. They are however not highly specific for any particular etiology. Further, the classic signs of allergic shiners and an allergic crease, with or without the presence of high arched palate and a constantly open mouth only identify children with nasal obstruction; they do not necessary indicate an allergic etiology [3]. The concomitant presence of other atopic symptoms such as asthma and eczema, are highly suggestive of allergic rhinitis. However, to establish the diagnosis of allergic rhinitis with certainty, allergy testing is recommended.

The character of nasal secretions should also be evaluated. The presence of large amounts of mucopurulent secretions is often seen with infective rhinosinusitis. It should however be noted that pale yellow secretions may be indicative of high concentrations of eosinophils rather than an infective etiology.

Precipitating and aggravating factors are an important aspect of the history in the assessment a patient with chronic rhinitis. Besides providing information on relevant environmental exposure, children with older siblings or attending childcare are likely to have an infectious cause of rhinitis, which may or may not coexist with other forms of inflammatory rhinitis.

Finally, the evaluation of complications associated with nasal obstruction is important in the child with rhinitis. Adenoid hypertrophy is a common associated feature. As a result of relatively narrow air passages, and short and more horizontally positioned Eustachian tubes, children are particularly prone to complications such as serous otitis media, and infective sinusitis. Although less commonly observed, obstructive sleep apnea may occur in severe airway obstruction. An outline of the diagnostic approach to chronic rhinitis in children is shown in Figure 1.

WHICH ALLERGENS TO TEST FOR?

Like in adults, inhalant allergens are the most frequent trigger of allergic rhinitis in children. Locally, it is the perennial allergens that are most important. Sensitisation to house dust mite allergens is the most important. There are a large number of species of dust mites present in our environment. Of these, Dermatophagoides pteronyssinus and Blomia tropicalis are the most prevalent [4]. Allergy testing should include both these allergens as these mites have little cross reactivity [5]. Other indoor allergens that are of relative importance are the cockroach allergens from the species Periplenata americana and Blattela germanica. Animal dander allergy is less of a problem locally, however, for those with pets at home, evaluation for these allergies should be carried out.

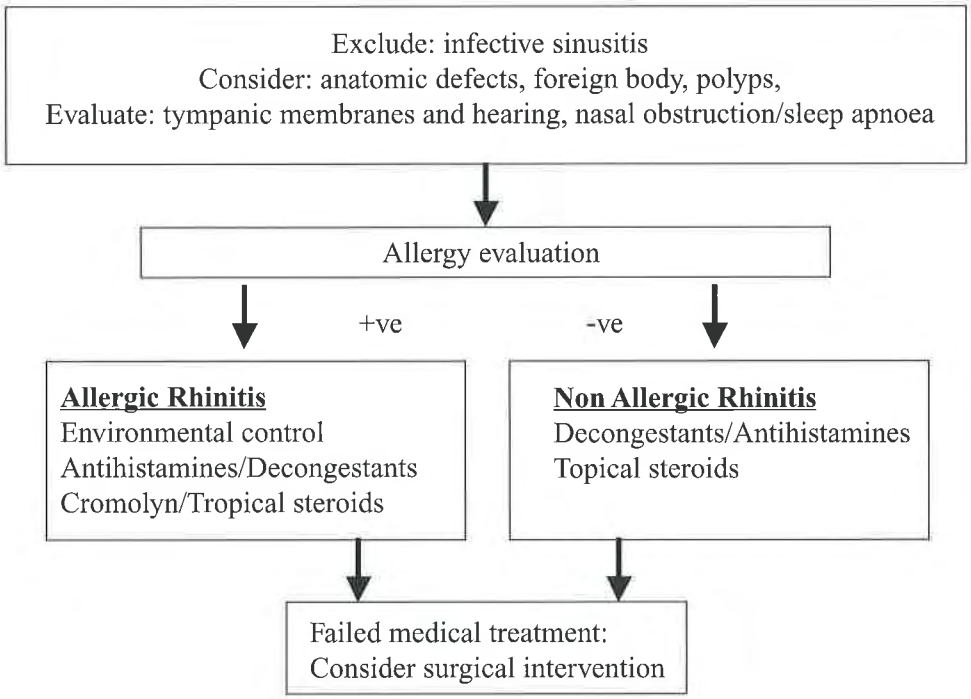
Food allergy as a trigger for rhinitis is less common, but should not be ignored in infants and children less than 2 years old. The most common allergens that young children are sensitised to are cow's milk and egg. These appear to be universal allergens as they cause food allergy in all populations including ours [6].

Allergy testing may be carried out skin prick testing or in-vitro testing (RAST). Both tests generally correlate well with each other. It should be noted that a positive test indicates sensitisation but not necessarily allergy. Strong positive tests (weal of at least 3mm for skin tests and RAST class (3 out of 4) are generally more clinically significant that weak positive tests. The results should be correlated with the clinical picture and in food allergy testing, the need for food challenge may have to be considered.

IMPLICATIONS ON THERAPY

The pharmacological treatment of allergic and non-allergic rhinitis is quite similar, although not identical (Figure 1). Topical nasal steroids should be used with caution in children below the age of 2 years, as data on its safety is lacking. The response to antihistamines is generally better in those with allergic rhinitis rather than in those with non-allergic. Further, the importance of environmental exposure to allergens, including food, is an important aspect of the management of children with allergic rhinitis. In addition, it will also provide means of prognostication and alert physicians and parents about the possibility of developing other forms of allergic problems such as asthma.

Figure 1: Approach to Chronic Rhinitis in Children



Therapy should also be tailored according to the severity of symptoms. The clinical definition of mild, moderate and severe rhinitis has been outlined by the European Academy of Allergology and Clinical Immunology [7]. In this position paper, mild was defined as few symptoms not interfering with daily activities and sleep; moderate as symptoms sufficiently severe to interfere with daily activities and/or sleep; and severe as symptoms sufficiently pronounced that the patients is unable to function properly without any therapy.

In conclusion, chronic rhinitis is a very common problem in childhood. The clinical approach includes a diagnostic evaluation, which includes arriving at an etiological diagnosis, classification of the severity symptoms, and exclusion of sequelae. Therapeutic measure would have to take into account each of these factors.

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CHILD ABUSE – A PHYSICIAN'S PERSPECTIVE

Ng Kee Chong

Summary

Child abuse can be potentially serious, if not fatal. Its early recognition by the physician is important, if only to ensure the abused child is not further hurt or damaged by the abuser.

The article summarises the approach to child abuse from a physician's perspective, with particular emphasis on history taking, and physical examination. It also summarises how the situation is managed in our local setting.

Key Words

- Child Abuse
- Non-accidental injury
- Battered Child Syndrome

INTRODUCTION

Child abuse has been described as the most common cause of death in Infants outside of the neonatal period and a leading cause of morbidity and mortality throughout childhood. In the United States alone, as many as 2.5% of children are abused or neglected yearly [1].

It was first described by Caffey [2,3] in 1946 and in 1962, Kempe proposed the term : " battered child syndrome" to "characterise a clinical condition in young children who have received serious physical abuse."

Child abuse is defined as any act of omission or commission by a parent or guardian which would endanger or impair the child's physical or emotional well-being, or that is judged by a mixture of community values and professionals to be inappropriate[4].

Over the years, the issue of child abuse in Singapore has come under increasing scrutiny, culminating recently in the Winny Ho case where a young child was severely abused by her mother.

TYPES OF CHILD ABUSE

The maltreatment may be either physical; sexual; emotional and psychological or through neglect [1,4,5,6,7].

Another presentation is the Munchausen [8-10] by proxy syndrome which was first described by Meadows in 1975. It is a condition where a parent or caregiver deliberately simulates or creates diseases in a child in order to attract the attention of the medical profession.

FACTORS CONTRIBUTING TO CHILD ABUSE

Various factors converge and contribute to a child being abused. They are usually a complex interaction [1,6,7] between the child, the caregiver and the innate family background (see Figure 1).

Figure 1: Factors Contributing to Child Abuse

Springthorpe et al in 1977 [11] identified several factors which had a significant association with child abuse. These included women who had had obstetric complications-, prolonged stay in hospitals; those with low maternal regard for

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children; unwed mothers; those with maternal social isolation and where there had been family disruption during the parent's own childhood.

Various characteristics of an abused child [1-6] include the following-.

- Premature birth
- Neonatal separation
- Multiple birth
- Congenital defects
- Mental Retardation
- Difficult Temperament
- Other conditions Interfering with Mother-Child bonding

Some characteristics of an abusive caregiver [1, 6] include:

- Previous aberrant childhood nurture or abuse
- Previous loss of child to foster care or avoidable death
- Fear of injuring child
- Violent behaviour towards others
- Substance abuser
- Mental illness or poor impulse control
- Young maternal/parental age
- Unrealistic expectations of child

The characteristics of an abusive family 1,6 may include:

- Socially isolated families with poor support system
- Financial stress or unemployment
- Marital problems (including spousal abuse)
- Inadequate child spacing or unwanted pregnancy
- Inadequate housing
- Stressful life events

In a series by Holloway et al [12], of the 49 cases of non-accidental injuries reviewed, 33 out of the 49 were under the care of their parents. Their ages ranged from 1 month old to 8 years old. 11 out of the 49 cases were already cases known to the Department of Community Services and 45% came from "socially stressed families". Retinal haemorrhages and Glasgow Coma Scores of less than 9 on arrival in the hospital were associated with poor outcomes. Cerebral edema on CT scan was associated with severe motor disability on discharge.

THE PHYSICIAN'S PERPECTIVE

For the physician, the diagnosis of a possible child abuse, however, provisional, is sometimes a difficult call to make.

Physicians, particularly those in direct contact and care of children, have a duty to ensure that the alleged abuse child is taken out of harm's way,

In Singapore, under section 27 of the Children & Young Persons Act (CYPA) [5], all government and restructured hospitals have been gazetted as "*places of safety*".

There are 2 important questions a physician must ask when approaching an allegedly abused child (see Figure 2) :

- Are the complaints (including signs and symptoms noted during the examination) consistent with alleged child abuse or are there other possible differential diagnosis for such complaints (for example uncommon blood dyscrasias or bony abnormalities)?
- Is the child safe to return home or should the child be admitted to a place of safety (that is, a hospital) until investigations are carried out to ensure the child does not continue to be abused?

Figure 2 - Diagnosis of Child Abuse

- Assess the child's immediate medical needs
- Obtain the past medical & social history of child & family
- Assess the plausibility of history being provided in light of any pre-existing medical conditions
- Determine level of risk to child if he/she returns home

APPROACH TO DIAGNOSIS OF CHILD ABUSE

The approach to an alleged case of child abuse must be managed with a good and sound history and physical examination.

However, as there is much stress and psychological overlay that will almost always be companion to such cases, extra care must be taken in handling and managing such cases.

a) Suspicious aspects in the history [1,6]

- Delay in seeking consult
- Account of accident is vague & inconsistent
- Discrepancy between history & degree of injury
- Parental behaviour is abnormal, lack of concern for child
- Interaction between child & parents is abnormal

b) Suspicious aspects in the physical examination [1,6]

- Injuries not consistent with history
- Multiple injuries in different stages of healing 13 (see Figure 4)
- Unusual and specific injuries

Figure 4: Determination of Age of Contusion

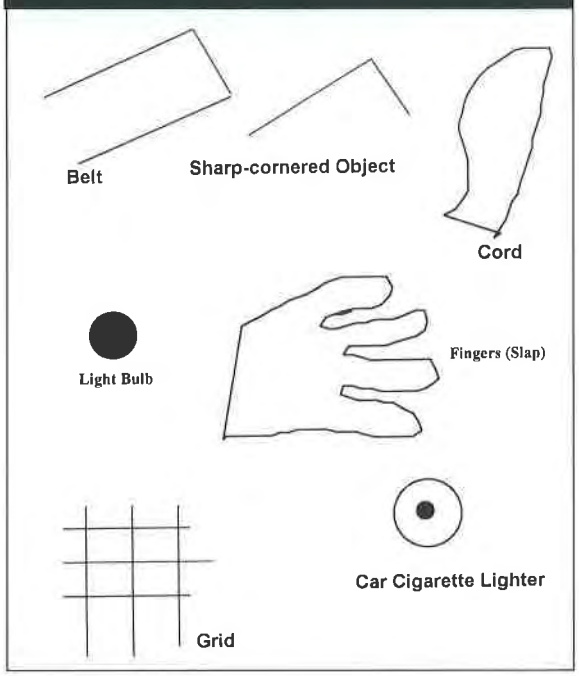
Days following Injury	Colour
0	**Red or red-blue**
1	
3	**Blue or purple**
4	
5	**Green**
6	
7	
8	**Yellow or brown**
9	
10	
14	**Normal skin colour**
21	

Robertson et al [14] in 1982 looked at the distribution patterns of normal and abnormal bruises. While almost 60% of children had normal bruises by 3 years of age, these were usually in the hands/feet and lower limbs. However, the distribution and the pattern of bruises differed in suspected non-accidental injuries with 60% of these cases having bruises to the face and head and 14% of those less than 5 years having lumbar bruises.

Unusual and specific Injuries include the following [1,613,15] (see Figure 3)

- Bruises & welts - forming regular patterns, often resembling shape of article used to inflict injury
- Burns - cigarettes, immersion injuries, patterned burns
- Lacerations/Abrasions - rope burns (on wrist/ ankles), external genitilia, palate and mouth
- Abdominal Injuries (both external and internal injuries)
- CNS - subdural bleeds, retinal haemorrhages, cerebral infractions etc.
- Unusual fractures patterns and skeletal injuries.

Figure 3: Examples of distinct contusions



Pointers in conducting and recording the physical examination [1,6]

- It should be conducted in a gentle & sensitive manner
- Should be conducted with consent of child
- Utilise no restraint or force
- Take sufficient time for child to be comfortable
- While interviewing the child
  - Attempt to establish an empathic & trusting relationship
  - Conduct interview in private
  - Reserve judgement till all facts are known
- Documentation
  - Standard & thorough assessment
  - Note statements made by child & caretakers
  - Observed behaviour
  - Note location of alleged abuse
- Detailed description of injuries (type, number, size, degree of healing, possible causes) properly recorded on charts

Skeletal Injuries and Child Abuse

This was part of the injuries described by Caffey in his original report. Skeletal injuries have been reported in less than half the cases of child abuses. In general fractures in children less than 1 year old are highly suspicious,

Unusual fractures include the following bones [1,6.]

- spinous processes
- sternum
- scapula
- femur
- rib fractures, especially posterior rib fractures
- fractures of epiphyseal-metaphyseal junction. These are virtually pathognomic of abuse with corner fractures occurring as a result of planar fractures through shearing forces when long bones are violently pulled or twisted.

Fractures of femurs in children less than 3 are often a result of abuse [1,616] . Recently however, a series by Schwend suggested that this is not as specific as it was previously thought [17]

Worlock et al [16] looked at 35 children with non-accidental injuries and fractures. All were under 5 years old. Such children were more likely to have multiple fractures with bruises of the head/ neck and fractures of their ribs.

Injuries to their long bones were invariably spiral or oblique with or without subperiosteal new bone formation. Spiral fracture of the humerus were more common in such children though the classical metaphyseal chip fracture were uncommon in his series. Worlock concluded that 1 child in 8 under 18 months of age presenting with a fracture may be a victim of child abuse.

Conversely, there have also been mistakes in

diagnosing child abuse. Wheeler et al [18] found that there had been 50 children in Leeds who had been wrongly diagnosed to have had non-accidental injuries over a 10 year period. Of the 50 cases initially labelled as non-accidental injuries, 18% actually had impetigo, 10% had blue spots, 10% had haemostatic disease and 16% had bony disorders. Figure 5 summarises some of the skeletal pathologies that might mimic non-accidental Injuries.

Figure 5: Differential Diagnosis of Radiological Findings in Abuse

Condition	Fractures Present	Confused with Bone Injury	Pain or Swelling (# =pain if fracture present)
1)Metabolic Defects			
eg Rickets	-	+	+
Mucolipodosis	+	+	#
2)Skeletal Disorders			
eg Osteogenesis Imperfecta	+	-	+
Caffeys	-	+	+
3)Infections Congental			
Syphilis	+	+	#
Osteomyelitis	-	+	+

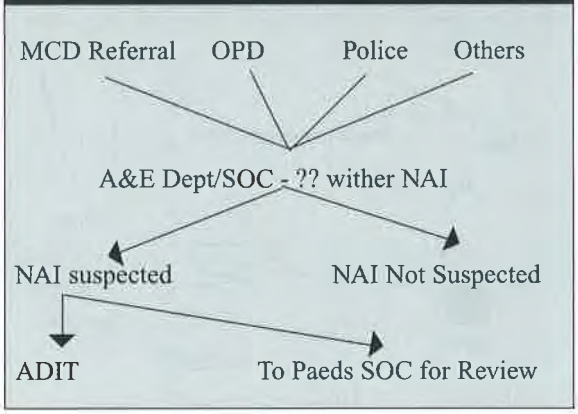
MANAGEMENT OF SUSPECTED CASES OF CHILD ABUSE IN THE HOSPITAL

Suspected cases are referred to physicians in the hospital from various sources. Following a careful assessment, they can either be admitted to the hospital both for diagnostic workup and clinical exclusion and to place the child in a place of safety till investigations are completed (Figure 6).

Management of suspected child abuse cases in KK Children's Emergency Department

Physicians at the emergency department, faced

Figure 6: How Alleged Cases of Child Abuse are Referred



with an alleged case of child abuse will need to do the following:

- Inform the police, that is make the case a "Police Case"
- Notify Department of Forensic Medicine (DFM)
- Notify the hospital medical social worker, which will in turn liaise with the Ministry of Community Development and Sports.

The admitting process is injury-specific (Figures 7 and 8). Those presenting with specific surgical complaints will be admitted to the surgical department whilst suspected female sexual abuse

Figure 7: Flow of Alleged Child Abuse Cases following Admission

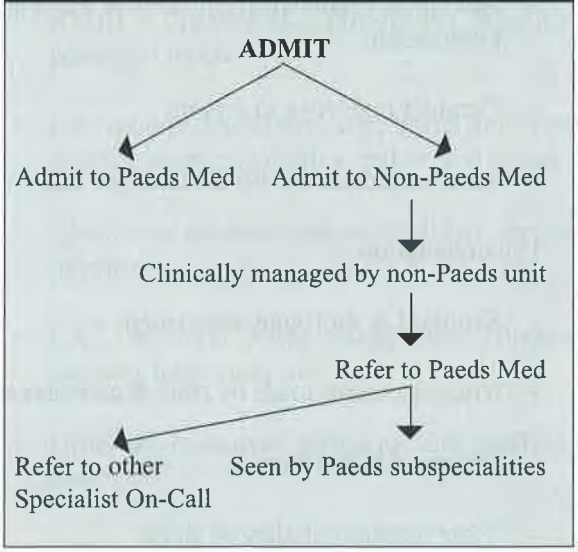
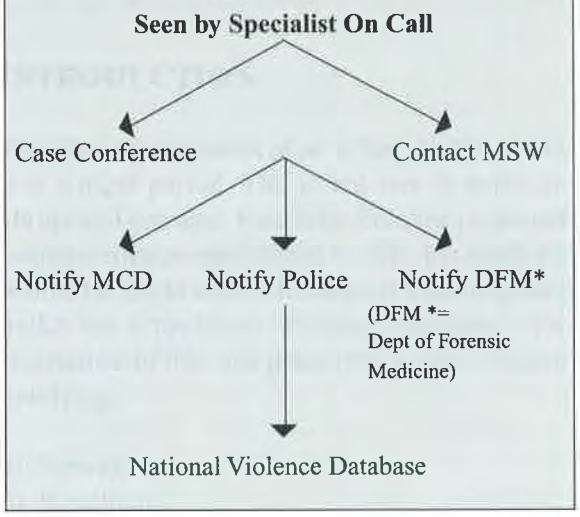


Figure 8



cases will be referred to Women's 24 hour clinic for assessment & management. All other cases are admitted to the General Paediatric Department.

Occasionally, after determining that the child is not in danger and can be managed as an outpatient, some cases of non-accidental injuries can be followed up at the outpatient level.

CONCLUSION

"Handling of child abuse requires judgement. It is not enough simply to comply with procedures, however important they are. Instead, there is a need to apply skill, judgement and experience. Judgement is exercised by the doctors (to decide whether the injuries/symptoms indicate child abuse) [19], ..."

"Because judgement is involved and cannot be avoided, there is no fool-proof solution to detect child abuse... We need a system that raises the probability of a correct assessment and of good judgements being made [19]."

The above statements were published as part of the recommendations from the Report of the Committee of Inquiry into the Winny Ho Case.

Child abuse is and will continue to be a difficult clinical problem to deal with. It involves a complex interplay of not just physical injuries but has significant serious psycho-social factors and effects as well.

In our Asian cultural context, where discipline forms a very important aspect of child-rearing, in particular, there is sometimes a very fine line between strict discipline and outright child abuse.

Dealing with alleged child abuse thus involves close co-operation between the clinicians on the ground with the specialists in the hospitals as well as with a team of dedicated social workers and law-enforcement officials.

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The Singapore Family Physician

Delivery Room Resuscitation of New Born

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INTRODUCTION

The first few moments of an infant life after birth is a critical period. The infant has to make an abrupt and dramatic transition from the protected in-utero environment to one outside the mother's womb. He has to establish adequate breathing, and make the circulatory changes necessary for sustenance of life. The principles of resuscitation involving:

a) Airway
b) Breathing
c) Circulation
d) Drugs
e) Environment

is also applied in the resuscitation of the newborn[1] Newborn resuscitation involves a series of steps, repeated evaluation and management.

Guidelines have been drawn up by the American Academy of Paediatrics and American Heart Association [2] as well as the International Liaison Committee on Resuscitation[3].

PHYSIOLOGY

After birth, the infant's lungs are filled with air. Fluid which previously filled the alveolar spaces and conducting passages during in-utero life leave the lung spaces. Considerable pressure is required to overcome the fluid pressure to open up the alveoli for the first time. If the infant falls to accomplish this then it is important to recognise that positive pressure applied for the first opening breath may require a higher pressure. This process is important for it allows adequate gaseous exchange to occur. Accompanying lung inflation with gas, a cascade of events occur, these include increased oxygenation, release of vasodilatory prostaglandins, nitric oxide and the shearing forces with lung inflation, all result in a dramatic decline in pulmonary vascular resistance and an increase in pulmonary blood flow. Blood which hitherto, has been shunted away from the lungs whilst in-utero now passes through the lungs allowing gaseous exchange to occur.

The pathophysiological consequence of disruption of gaseous exchange or circulatory processes at any stage during labour or the peri-partum period results in asphyxia with consequential hypoxemia, hypercapnia and acidosis[4]. The infant who suffer an asphyxia insult undergoes a sequence of rapid breathing, primary apnoea, gasping respiration, and secondary apnoea before terminal events occur. Heart rate, and blood pressure declines as the infant's hypoxemia persists. Intervention should be timely and as early as possible. Delay would not only make resuscitation more difficult but also may affect the outcome of the infant.

PREPARATION

Minimum preparation for every delivery should include.

1. a radiant warmer heated and ready for use
2. all resuscitation equipment immediately available and functional
3. at least one person skilled in neonatal resuscitation and one or two other persons available to assist in the resuscitation.

Delivery of asphyxiated infants can often be anticipated on the basis of the antepartum and intrapartum risk factors. Common risk factors include premature labour, growth-retarded infants, meconium-stained liqor and abnormal foetal heart rate patterns.

INITIAL STEPS IN RESUSCITATION

1 . ***Preventing Heat Loss***
Heat loss is prevented by placing the infant under a heated radiant warmer and quickly dry the infant of amniotic fluid. Remove wet towel and let the infant lie on another warm and dry towel.

2. ***Positioning***
For correct positioning, the infant is placed on his back or side, with the neck in a neutral position. This ensures a patent airway.

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3. ***Suctioning***
   As soon as the infant is properly positioned, he should be suctioned. The mouth should be suctioned first, followed by the nose. Be careful how deep you suction. Too deep suctioning and irritation of the pharynx may result in vagal induced bradycardia.

4. ***Tactile Stimulation***
   If any infant does not breathe immediately, tactile stimulation should be started in an attempt to initiate respiration. This involves slapping or flicking the soles of the feet and rubbing the back.

EVALUATION

After completing the initial steps, monitor and evaluate the infant on
the basis of three vital signs:

Respiration: Observe and evaluate the infant's respiration. If normal, go on to the next sign. If apnoeic or gasping, begin positive pressure ventilation.

Heart Rate: Check the baby's heart rate. If above 100 beats/min, go on to the next sign. If not, initiate positive pressure ventilation.

Colour: Observe and evaluate infant's colour. If central cyanosis is present, administer free flow oxygen.

FREE FLOW OXYGEN

Use if infant is centrally blue and has adequate respiration and heart rate above 100 beats/min. If infant remains centrally blue despite free-flow oxygen, a trial of positive-pressure ventilation is indicated.

Free flow oxygen can be provided using an oxygen tubing held half an inch from the nose and this will deliver to the infant 80% oxygen. Flow is adjusted at 5 litres per minute. The self-inflating bag should not be used to give free flow oxygen.

MECONIUM IN AMNIOTIC FLUID

When meconium has been expelled into the amniotic, fluid, there is a chance the meconium can be aspirated into the infant's mouth and potentially into the trachea and lungs. The initial steps of resuscitation have to be modified to allow removal of meconium from the pharynx and trachea. If the infant is depressed, suctioning of the trachea is indicated using a endotracheal tube connected to a meconium aspirator or directly with a suction catheter. However, if the infant is active and liqor has thick meconium staining, one should use clinical judgement whether the difficulty of intubating a vigorous infant outweighs the advantage of trachea suctioning. Following removal of meconium, the subsequent steps of resuscitation is as according to any normal infant.

BAG AND MASK PROCEDURES

Bag and mask ventilation is indicated when an infant, after the initial steps is assessed to have any of the following conditions:
1. apnoeic or gasping
2. heart rate less than 100/min
3. persistent cyanosis despite free flow oxygen

Bag and mask ventilation can be provided using an anesthesia bag or self-inflating bag. Before use, connect to an oxygen source. Select a mask of appropriate size which covers the mouth, nose and chin but not the eyes. If the self-inflating bag is used, ensure that the reservoir is connected. This will ensure that the infant will receive high concentration of oxygen. Test the bag and mask ventilation equipment on a firm surface before applying it on the baby.

The infant should be bagged with the neck in a neutral or slightly extended position to ensure an open airway. Stand at the head of the infant, and placed the mask in position. As you ventilate, observe for an appropriate rise of the chest. If the chest does not rise, it could be due to an **inadequte seal, blocked airway, or inadequate pressure.** Attempt to rectify the problem by the following sequence of actions:

a) Try reapplying mask- to the face
b) Repositioning the head

c) Suction if secretions are present
d) Open infant's mouth & lastly if still no chest excursion is observed, then
e) Increase ventilatory pressures

Infant should be ventilated at 40-60 breaths per minute. Ventilatory pressures should be enough to elicit appropriate chest excursion. After 15-30 seconds of ventilation with 10011/0 oxygen, check the heart rate for 6 seconds. A heart rate over 6 seconds multiplied by 10 would give a heart rate over a minute. Continue bag and mask ventilation until normal spontaneous breathing is present and heart rate is sustained above 100/min.

CHEST COMPRESSION

Chest compression is indicated if after 15-30 seconds of bag and mask ventilation, the heart rate is below 60 or between 60 and 80 and not increasing.

Chest compression is done with a firm support for the back. The sternum should be compressed to a depth of $^1/_2$ to $^3/_4$ inch or $^1/_3$ of anterior-posterior diameter of chest. Chest compression is interposed with ventilation in a 3:1 ratio. The compressor counts aloud " one-and-two-and-three-and-bag-and". The location for chest compression is Just below the inter-nipple line and at the sternum. Chest compression can be done using 2 fingers placed perpendicularly on the sternum or using the thumbs with the two hands enclosing the infant's chest. Ensure that the pressure is applied perpendicularly down at the sternum and not outside the sternum.

ENDOTRACHEAL INTUBATION

This is indicated when:
1) Prolonged positive-pressure ventilation is required.
2) Bag and mask ventilation is ineffective
3) Tracheal suctioning is required for meconim-stained liquor.
4) Diaphragmatic hernia requiring positive pressure ventilation.

Selecting an appropriate size endotracheal tube is important. Generally, a size 3.5 (internal diameter/mm) tube is used for infant of more than 2 kg birth weight. Size 3 tube is used if difficulty is encountered. The guide for endotracheal tube length in cm, to the upper lip (oro- tracheal tube) is 6 + birth weight (kg). After placement of the endotracheal tube, the tube position is checked by observing, for symmetrical chest rising and no gastric distension with ventilation. Further confirmation is obtained by ascultation with a stethoscope.

Medication	Concentration to Administer	Dosage/Route
Adrenaline	1:10,000	0.1-0.3ml/kg IV or ET (for ET; dilute with saline to 1-2ml)
Volume Expanders	Whole blood, 5% Albumin-saline, normal saline, Ringer's lactate	10 ml/kg IV
Sodium Bi-carbonate	4.2% solution	4 ml/kg IV
Naloxone Hydrochloride	0.4 mg/ml	0.25 ml/kg IV, ET, IM, SQ (IV, ET preferred)
	1.0 mg/ml	0.1 ml/kg IV, ET, IM, SQ (IV, ET preferred)

MEDICATIONS

Medications are indicated if the infant's heart rate remains below 80/min despite adequate ventilation (With 100% oxygen) and chest compressions for a minimum of 30 seconds or the heart rate is zero. The following medications are used during resuscitation:

1) Adrenaline
2) Volume Expanders
3) Sodium Bicarbonate
4) Naloxone Hydrochloride

(*Note* that atropine and calcium are not included as there is no current evidence that they are useful in the acute phase of resuscitation).

Indication for adrenaline includes an infant with no heart rate or heart rate less than 80/min after minimum of 30 seconds of ventilation and compression. Volume expanders are indicated if there is evidence or suspicion of acute bleeding with signs of hypovolemia. Sodium bicarbonate is indicated when there is prolonged arrest that does not respond to other therapy. Naloxone is used when there is severe respiratory depression and a history of maternal narcotic administration within the past 4 hours.

Drugs can be administered via the umbilical vein, peripheral veins and, for adrenaline and naloxone, endotracheal instillation can also be used.

CONCLUSION

The resuscitation of the newborn involves a series of well-defined steps based on repeated evaluation and assessment after each step. Every delivery room facility should be well equipped and have well trained personnel at hand. Team work is essential, and optimum management done in a timely manner can make a difference in the survival and the outcome of the new born.

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SCHOOL REFUSAL

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INTRODUCTION

For children, going to school usually is an exciting and enjoyable event. But for some it brings fear or panic. Yet others may simply detour to absent themselves from schools to play.

So what are the reasons and how do we evaluate non-attendance in schools by children?

Basically we need to ask two questions to separate the three main groups of children (truancy, kept at home and school refusers) who do not show up in schools:

1. Is the child at home?

2. Is the child kept at home with parents' approval?

TRUANCY

When the child is not at school and also not at home, then the child is most likely

to have played truant. As often found in truancy, the child engages in alternative activities without parental permission. Truancy is increasingly encountered in the secondary school students who are not good in study and, hence, consider schooling as unwelcome or irrelevant. The parents do not know where the child is. Usually the child spends the day in groups or in association with gangs. If there is anything wrong in terms of a psychiatric label in the child, it is linked to a conduct disorder. However, it is important to remember that many children who played truants do not have anything wrong psychiatrically.

Kept at home

If the child is at home, does he have the parents' approval? Physical illness, e.g. fever, coughs and colds, is the commonest reason for parents to keep their child at home. Sometimes the child stays at home to help parents look after the young siblings or in the preparation of festivals or to keep company for the depressed mother who is fearful of leaving the house.

SCHOOL REFUSERS

Children with emotional upsets are unable to go to school despite much coaxing and persuasion by parents. Among the younger children in the lower primary schools, the commonest reason for the child to refuse to go to school is a separation anxiety disorder. Fears of travel, bullies, a particular subject or teacher, or "spirits" in the school are fairly common reasons. Other emotional disorders include phobic disorders, dissociative disorders, and obsessive-compulsive disorders. In the adolescents, depression sets in as the cause for school refusal. Psychosis is infrequently encountered.

How severe is the problem?

About 5% of new cases at Child Guidance Clinics present with refusal to attend
school associated with anxiety or misery.

Prevalence

School refusal is most common in children aged 6 to 7 (Primary one or two) and 11 to 12 (Primary six or Secondary one). School refusal is not the same as school phobia as the child is not afraid when he is in the school.

Characteristics

Temperamentally, the child is usually timid and shy. He has few friends and is easily upset by trivial reasons. There is an equal sex ratio in boys and girls. As a group, school refusers are of average intelligence and academic ability.

WHAT MAKE THE PARENTS UNABLE TO GET THE CHILD TO GO TO SCHOOL?

The attitudes of parents may encourage or condone the absence of the child from school.

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Some parents give in to demands because of the fears of putting too much pressures on the child or because of their own difficulties in separation engendered by over-close emotional attachments. They share their child's anxiety about separation. They fear the child may go mad if forced to go to school. A depressed mother is unable to enforce the child to go to school either. Parents who are in conflict, especially over whether the child's abdominal pain is organic or functional, are ineffective in making the child go to school. Other parents worried that the child may be penalised by the teachers as they have problems in communication with the school staff.

Separation anxiety disorder

The child is frightened to leave home or attend school. Attempts by parents to force the child to attend school are met with tears, pleading, tantrums or physical resistance. The precipitating events could be a holiday break, following an illness, the death of a pet or a relative, a move to a new neighbourhood, a change of teacher or school, too much homework, examination approaching, or disturbed relationship with the teachers or peers. The child may complain of bodily pains and aches before leaving for school or once at school. At weekends or during school holidays, the child is perfectly well and has no complaints.

Case example- "Where is mummy?"

Judy Lim, a 6 year-old Primary one girl, had a persistent fear that her mother would leave her and not return anymore. This had lasted about a month without any signs of improvement. She had some unrealistic fears that her mother would meet with a road traffic accident. Despite continuous reassurances, she could not be pacified.

She was reluctant to go to school. She wanted her parents to accompany her to assembly and then to her primary one classroom. When she was in the school, she would phone home several times to check on how her mother was doing. She felt relieved to hear her voice. During the night, she would get up several times to check if her mother was well. Occasionally she would go and sleep beside her. Her mother thought that the child was purposely trying to be difficult and by shadowing her, give the mother no peace of her mind. She frequently had recurring nightmares when she wakes up crying, "Where is mummy?". She would dream that her mother was kidnapped or had a severe illness that required prolonged hospitalisation.

Temperamentally, she was a timid and sensitive girl. Her illness was precipitated by high fever for about a week. Shortly thereafter, her father had to leave for an overseas assignment.

When I first saw her, she was afraid that I would force her to go to school without her mother. She could not explain why she was afraid. Her fear that something bad will happen to her mother was born out of the stress in her life; the acute illness and the father's overseas trip. With counselling and support, she became less fearful and soon returned to her normal self in a few weeks.

DISSOCIATIVE DISORDERS

Children faced with insurmountable stress whether in study, in interpersonal relationship with the parents or peers, or having high expectations unmet, may resort to a loss of mental or physical functions to resolve the conflict. The child may develop a sudden loss of memory or weakness of limbs or body so that they do not have to face the current difficulty in life and, in return, they may be showered with excessive attention because of the dramatic presentation of symptoms and disability.

Case example - "I don't know who I am!"- dissociative fugue

Li Lian was a 16 year-old secondary four girl who excelled in study. She felt the pressure academically to perform to please the parents who wanted her to become a doctor one day. Her parents expected excellent results in the O Level examination. On the morning of the first day of the examination, she was very nervous and felt so weak that she could hardly walk. She forced herself to leave the house to go to school. On the way she was giddy and wandered into the Mac Ritche Reservoir Park which was near her school.

She had a sudden loss of memory as to who and where she was and could not get out of the park. For hours she tried desperately to get out but failed. Towards the evening she was scratched and bitten by a monkey and fell to the ground. She screamed loudly and this attracted the attention of a policeman who came to her Rescue. She was brought to the hospital for treatment. With rest and support by the Family and counselling she gradually regained her memory and identity in two weeks.

Case example-"I can't walk!"-dissociative motor disorder

Kok Hua was a 15 year-old secondary three boy in the express stream. He developed a sudden clawing of toes and fingers, which incapacitated him from walking or writing. He had to be wheel chair bound. As a result he could not go to school. He was admitted to a hospital and extensively investigated but no physical lesion was found.

He revealed to me that he had a very high self-expectation not only in study but also in singing and sports. He was deeply disappointed by the mid year examinations results in which he failed three subjects. He thought he had let the parents and family down. He could not bring himself to face his friends and teachers in the school.

After a few counselling sessions, he agreed to continue his study in the normal stream next year and accepted the need to lower his expectation. He was also treated with anti-depressant Prozac 20-mg daily for his depression. He showed quick recovery and regained his physical power completely within a month.

Assessment

Physical conditions e.g. chronic viral infections, gastro-enteritis, peptic ulcer, migraine and cerebral tumour, which are rare causes that can present with school refusal and involve a physical symptom in presentation, should be excluded with the necessary investigations as quickly as possible.

Then it is useful for the therapist to clarify the nature of problems by interviewing the family and child. The focus is on looking for a special relationship and interaction between the child and the parents and their views of the aetiology of the problems. The child's mental state, maturity, IQ and academic attainment are then ascertained. A report from the school is sought with regards to the details of attendance, current academic and social functioning and the attitude of the child to school.

Treatment

A rapid return to school is generally indicated in mild cases and those of acute onset and where physical illness has been excluded.

Gradual return to school is to be entertained if the anxiety level in the child and parents is particularly high, the child has been out of school for a long time, in the older child aged 10 or more, the child expresses suicidal ideation and where there is intractable family problems.

Family therapy is frequently used to empower the parents to set firm boundaries, exert control over the child and reduce emotional over-involvement with the child. The parents are aware of the academic disadvantage but often need help to see the detrimental effects of social development if the child does not go to school.

Liaison with school principals and teachers are helpful to get their support in reducing the child's academic and relationship difficulties in school and in preparing the child to accept the idea of returning to school.

Drugs are not effective unless depression is evident. The use of a short-acting anxiolytic mediation on the morning of return to school and a hypnotic to ensure a good night sleep before starting school again may occasionally be justified.

Where the school refusal is severe or deeply entrenched, not responding to other forms of therapy, family environment actively maintains the disorder and blocks effective treatment, hospitalisation in a psychiatric inpatient unit may be indicated.

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How about a transfer of school or home tuition?

A change of school is not advisable unless there is serious bullying. This is because with a change of school the child has to face a new environment, new curriculum, new rules and a strange peer group.

Home tuition gives the child the impression that it is all right not going to school to study. If any study is to be attempted, it may be advisable for the child to attend a specialised classroom attached to a child guidance clinic under the supervision of a teacher so as to emulate the normal school condition.

Prognosis

Most mild and acute cases, 70% or more, returns to school without much problems. The prognosis is good if the child is young (less than 9 years old), the symptoms are minimal, the family problems are mild and the intervention is early.

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ANTIBIOTIC THERAPY FOR OUT-PATIENT CHILDREN

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Abstract

With increasing antibiotic resistance rates, we need to be judicious in our use of antibiotics. The principles of antibiotics include: Use of antibiotics only when bacterial and not viral infection is suspected, use appropriate antibiotics for the suspected organisms at the correct dose and duration, use as narrow-spectrum antibiotic as possible so as not to disrupt the normal flora and promote antibiotic resistance. In this article, the guidelines proposed are for respiratory tract infections (tonsillo-pharyngitis, acute otitis media, acute sinusitis, acute pneumonia) and urinary tract infections.

Keywords: Respiratory tract infections, urinary tract infections, children, antibiotic-resistance, S. pneumoniae

RATIONALE FOR JUDICIOUS USE OF ANTIBIOTICS

Currently thousands of courses of unnecessary antibiotics are given each year. If unnecessary antibiotics use can be curtailed, the community as well as the individual patient will benefit. In Japan, 62% of group A streptococcus (GAS) were resistant to erythromycin in 1974 when macrolides accounted for 22% of all antibiotic use. By 1988, macrolides accounted for only 8% of antibiotic use and < 2% of GAS isolates were resistant to erythromycin.[1] In Iceland, public campaigns directed at the problem of pneumococcal resistance and its relationship to antibiotic use resulted in a decrease in sales of antibiotics and a concomitant decrease in the resistance rates of pneumococci. [2] One of the main problems in paediatrics is the diagnostic uncertainty of whether the child has a viral or bacterial infection. The indicators of a viral infection are in table 1. Other pressures for prescribing antibiotics include sociocultural and economic pressures e.g. parents' expectations, approaching a long week-end; avoiding the costs of return visits, need for rapid recovery due to exclusion of sick children from child-care centres and lastly litigation concerns.

Table 1: Indicators of viral infections

- Runny nose, sneezing
- Cloudy/ discoloured nasal discharge for < 10 days
- Conjunctivitis- serous discharge
- Wheezing
- Bronchiolitis, Bronchitis
- Croup/ Acute laryngotracheobronchitis
- Watery diarrhoea
- Antierior stomatitis, mouth ulcers

A recent local questionnaire survey of parents revealed that when the parents expected antibiotics, they were more likely to be prescribed antibiotics; parents who expected antibiotics tended to be younger. [3]

The rationale against presumptive antibiotic use include:

1. No evidence for clinical efficacy: Impending bacterial secondary infections are not aborted or diminished. [4]
2. No difference on rate of return visits. [5]
3. Overuse of antibiotics promotes bacterial resistance in the long term
4. Antibiotics are associated with side -effects and add to the cost of treatment.
5. The primary determinant of patients' satisfaction is: Effective communication about patient's illness and not the prescription of antibiotics. [6]

Tonsillopharyngitis

The majority of tonsillo-pharyngitis are due to viruses (30-45%) especially if < 4 years old. This is followed by group A streptococcus

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(GAS)(12%), rarely (5%) due streptococcus group C or G, Mycoplasma pneumoniae, Chlamydia pneumoniae/ Chlamydia psittaci, Arcanobacterium hemolyticum and C. diptheriae. Patients with GAS are usually between the ages of 5 to 15 years and commonly present with acute onset of sorethroat with fever, headache and pain on swallowing and have none of the features indicative of a viral infection as in table 1. Vomiting and abdominal pain are common in children. On examination there are tender enlarged cervical lymph nodes, tonsillar erythema with exudates, a beefy red swollen uvula and occasionally, a scarletiniform rash. It is recommended that a throat swab be done for GAS culture or rapid antigen detection test for patients with possible GAS before starting antibiotics.[7] When obtaining a throat swab culture, vigorously swab both tonsillar surfaces and posterior pharnyx. Other areas should not be swabbed as this would dilute the inoculum.

Antibiotics are given for GAS tonsillo-pharyngitis only to reduce the complication of rheumatic fever and to decrease carriage. GAS pharyngitis is usually a self-limited disease; fever and constitutional symptoms disappear spontaneously within 3 -4 days of onset, even when antibiotics are not administered. [8] It has been shown that antibiotics can be safely postponed up to 9 days after the onset of symptoms and still prevent the occurrence of acute rheumatic fever.[9] The recommended antibiotics for GAS pharyngitis are in Table 2. Penicillin remains the drug of choice for GAS pharyngitis. [10]Although broader spectrum antibiotics e.g. first, second generation cephalosporins have been shown to be as efficacious as penicillin, there are no added advantages to use of these newer agents with increased costs incurred, except for patients with non-immediate type hypersensitivity to penicillins. [11] Shorter courses of penicillin V (5-7 days) have been shown to have lower eradication rates (50-82%) compared to the standard 10-day course (89-94%). [11] Amoxycillin for 6 days produced an 84% bacteriologic success rate compared with 85% of 10 days of penicillin. [12] For patients who have failed first-line drugs, a 10 day course of clindamycin or amoxycillin-clavulanate may be indicated if the throat culture shows persistence of GAS. [7]

Otitis media

The major pathogens involved in acute otitis media (AOM), acute sinusitis include: Streptococcus pneumoniae, H. influenzae, M. catarrhalis and viruses. In AOM, viral, H. influenzae and M. catarrhalis can spontaneously resolve as opposed to S. pneumoniae which is least likely to resolve (40-50%). Overall 80% of untreated cases of AOM will resolve by day 7-14 as compared with 95% of AOM given antibiotics. [13] Therefore antibiotics will only provide a 15% benefit as compared to no treatment. Due to this marginal benefit, many European countries do not recommend routine antibiotics for AOM but adopt a wait-and-see approach, whereby the child only gets antibiotics if the symptoms persist for > 48 hours.

The recommended antibiotics for AOM are in Table 2. Data from clinical otitis media trials suggest that 80-85% efficacy is achieved with oral antibiotics when the antibiotic reaches a time above MIC for 40-50% of the dosing interval. Among all the available antibiotics, amoxycillin still has the best pharmacokinetic profile in the middle ear, with the drug being above the MIC 90 for 40-50% of the dosing interval, even for penicillin-resistant S. pneumoniae. 14,15 For the cephalosporins, only cefuroxime, cefprozil (not available here) are adequate for penicillin-susceptible pneumococci, however the time above MIC 90 for penicillin-resistant strains only reached 33%, 28% respectively of the dosing interval. [14,15] The following children are at higher risk for penicillin-resistant pneumococci and need a higher amoxycillin dosage (80-90 mg/kg/day) and longer duration of treatment (10 days): < 2 years old; attend child-care centres; previous antibiotics in the past 3 months.[16, 17] Although erythromycin is a potential candidate if the patient has penicillin-allergy, it does not perform well against H. influenzae. Erythromycin also has an "all or none" effect whereby if S. pneumoniae (including all streptococci and staphylococci) are resistant to erythromycin, the drug-resistance cannot be overcome by increasing the dose nor by switching to a second generation macrolide.

Table 2: Antibiotic treatment for out-patient paediatric infections

Infection	1st-line antibiotics	Alternative*	2nd-line antibiotics**
GAS pharyngitis	Penicillin V 250 bds or tds x 10 days OR Amoxycillin 50 mg/kg/day div bds or tds x 6 days	Erythromycin estolate 20-40 mg/kg/day x 10 days OR Erythromycin ethylsuccinate 40 mg/kg/day x10days Alternative: < 27 kg: I/M Benzathine Penicillin 0.6 MU, > 27 kg: 1.2 MU	Clindamycin 20-30 mg/kg/ day x10 days Amox/Clav 40 mg /kg/day (of amox-ycillin) x 10 days
Acute Otitis media	Amoxycillin 60-90 mg/kg/day x 7 days †	Erythromycin TMP-SMX	Amox/Clav at 80-90 mg/kg/day (of amoxy-cillin) Cefuroxime
Acute sinusitis	Amoxycillin 50-60 mg/kg/day x 10 days	TMP-SMX	Amox/Clav or Amp/Sulb
Acute pneumonia	Age < 2 years ¶ and 2-5 years §: Amoxycillin 50-60 mg/kg/day x 7-10 days Age > 5 years: Subacute onset: Macrolide x14 days Acute onset: Amoxycillin 50-60 mg/kg/day x 7-10 days	Erythromycin x 7-10 days	Age < 5 years: Amox/Clav or Amp/Sulb
Urinary tract infection	TMP-SMX Cephalexin Nitrofurantoin Parenteral: Gentamicin ± Ampicillin ◊	Trimethoprim alone (G6PD deficiency, child < 2 months old)	Parenteral: Ceftriaxone ± Ampicillin◊

GAS= Group A Streptococcus; Amox/Clav= Amoxycillin-Clavulanate; Amp/Sulb= Ampicillin/ Sulbactam; TMP-SMX= Trimethoprim-Sulfamethoxazole; G6PD deficiency = Glucose-6 -phosphate dehydrogenase deficiency; MU= Million units

* *Alternative antibiotics are for patients with penicillin/ß-lactam allergies , except in the case of UTI*

** *2nd-line antibiotics should only be used if the patient has failed 1st-line therapy*

† *If patient is < 2 years old, attend child-care centres, had previous antibiotics in the last 3 months, consider higher dose of amoxycillin (80-90 mg/kg/day) for 10 days.*

¶ *Lower respiratory tract infections in this age group are predominantly viral in origin. Consider antibiotics only if: 1) Fever > 1 week; 2) Prolonged symptoms > 1 week; 3) Presence of localizing signs suggestive of lobar consolidation; 4) Toxic appearance or unwell; 5) High white cell count > 20,000; 6) CXR shows lobar consolidation.*

§ *In a patient < 5 years old, M. pneumoniae is less likely unless there is a positive family contact, gradual onset and low-grade fever.*

◊ *Ampicillin is added for suspected Enterococcus infection*

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Acute sinusitis

Most pre-schoolers and school-aged children have 3-8 upper respiratory tract infections (URTI) per year; bacterial sinusitis only complicates 0.5-10% of them.[18] After an URTI, the nasal discharge frequently turns discoloured or opaque after 1-3 days. This contains desquamated epithelial cells, polymorphs and colonizing bacteria and lasts 2-7 days. Therefore bacterial sinusitis should only be considered if the discoloured nasal discharge persists > 10 days and in association with persistent fever, facial pain/ tenderness, headache or halitosis. [19] The duration of treatment varies from 7-10 days (Canadian guidelines) to 10-14 days (US guidelines); however, the duration should not exceed > 7 days beyond clinical improvement. The antibiotics recommended are in table 2.

Acute pneumonia

Respiratory tract infections that are viral in nature include: Bronchiolitis, croup and bronchitis. Antibiotics are not routinely recommended in acute bronchitis [20] / bronchiolitis unless a bacterial superinfection is suggested by persistent fever > 1 week or prolonged symptoms lasting > 3 weeks. Pneumonia in a neonate needs admission to hospital as he / she requires intravenous antibiotics. The main pathogens in pneumonia beyond the neonatal period are: S. pneumoniae, H. influenzae, M. catarrhalis, S. aureus (in infancy) and Mycoplasma pneumoniae.

Typical pneumonia with acute onset of high fever, dyspnoea/ tachypnoea, toxicity, pleuritic chest pain and a productive cough is often caused by S. pneumoniae. Atypical pneumonia with gradual onset, low-grade fever and a persistent cough in a child > 5 years old may be caused by Mycoplasma pneumoniae. Although less common in the age group 2-5 years, M. pneumoniae should also be considered if there was a positive family contact with features suggestive of an atypical pneumonia. The antibiotics for the various age groups are given in table 2. Recent studies done locally showed an increasing antibiotic resistance pattern for S. pneumoniae, H. influenzae and M. catarrhalis. [21,22] In 1995, TTSH paediatric isolates of S. pneumoniae were resistant as follows: 17% to penicillin, 30% to erythromycin, 23% to trimethoprim-sulfamethoxazole (TMP-SMX). [21] From 1997 to 1999, hospital isolates of S. pneumoniae had the following resistance pattern: 63% to penicillin, 88% to TMP-SMX, 68% to erythromycin. [22] Although the penicillin-resistance of S. pneumoniae is increasing, based on revised susceptibility guidelines, the majority (95%) remain sensitive to amoxycillin (personal report). In our acute respiratory tract infection study, the majority of complicated cases were from S. pneumoniae with an increased incidence of empyema (personal report). There was no difference in clinical outcome between penicillin-resistant or susceptible strains, as proven in other studies for non- central nervous system pneumococcal infections. [23,24] Therefore, among all the pathogens causing pneumonia, it is most important to treat S. pneumoniae due to its associated higher rate of morbidity; however, the good news is that amoxycillin given in adequate dosing is good enough for this pathogen.

In a child < 6 months old, one needs to consider Chlamydia trachomatis as a cause of pneumonitis. This condition is characterised by a staccato dry cough, the absence of fever, bilateral interstitial infiltrates on CXR. This diagnosis is also suggested by a past history of eye discharge after day 5-7 of life; the treatment is erythromycin for 2 weeks. The other differential diagnosis for a child < 6 months old with tachypnoea and interstitial infiltrates is Pneumocystis carinii pneumonia (PCP). One needs to consider PCP if the child has underlying failure to thrive, oral candidiasis beyond 3 months old, chronic diarrhoea or fever for > 1 month, or if the parents are known to be HIV-infected and the mother did not receive anti-retroviral treatment during pregnancy. When PCP is suspected, admission to hospital is required for assessing the degree of hypoxemia, TMP-SMX treatment and for the work-up of the underlying immunodeficiency.

Urinary tract infection

Accurate diagnosis of urinary tract infection (UTI) is important in paediatrics because the treatment, further evaluation and long-term prophylaxis

Figure 1. Algorithm for UTI

Fever			
No		Yes	
⬇		⬇	
Lower tract infection		Upper tract infection	
⬇		⬇	
Age		Age	
⬇		⬇	
< 12 years	> 12 years	< 28 days	> 28 days
⬇		⬇	⬇
Treat 7-10 days	Consider 3 days abx	Admit <-	Toxic / Not toxic
			⬇
		Septic work-up	+/- Admit
Antibiotics		Antibiotics	
TMP-SMX*		Parenteral until afebrile then PO	
Nitrofurantoin*		to complete 10-14 days	
Cephalexin		Gentamicin +/- Ampicillin	
Trimethoprim		Ceftriaxone +/- Ampicillin	

** Contraindicated in patients < 2 months old and in Glucose-6-phosphate dehydrogenase deficiency*

demands accuracy. One must not depend on urine dipstick/ labstix tests to make a diagnosis; however, these tests are useful in screening but need confirmation with a midstream or catheterized urine culture. E. coli is the predominant organism, followed by Klebsiella sp, Proteus sp, Citrobacter sp, Enterococcus sp. The algorithm for treatment of UTI is found in figure 1. [25]

Admission to hospital is required if: 1) Neonatal age- 12 months old; 2) Febrile patient who is toxic-looking; 3) Unable to tolerate oral medications; 4) In shock or dehydrated. When the patient has improved clinically, the treatment can be continued as an out-patient to complete 10-14 days for upper tract infection, 7- 10 days for lower tract infection. Once UTI has been documented, antibiotic prophylaxis is recommended while awaiting the radiologic investigations if the child is < 2 years old or male sex (any age) with either: TMP-SMX, nitrofurantoin, trimethoprim alone (if G6PD deficiency or if child is < 2 months old) or cephalexin. Radiologic investigations include: Renal ultrasound, micturating cystourethrogram for vesico-ureteric reflux and dimercaptosuccinic acid (DMSA) scan for renal scarring. [26]

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Ministry of Health Antibiotics Clinical Practice Guidelines Subcommittees of Respiratory tract infections and Urinary tract infections.

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NEW TRENDS IN NEONATAL INFECTIONS

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SUMMARY

Perinatal infections are still common problems in neonatology, despite the improvements in the standard of care. This article looks at the role of obstetric practice in improving the incidence and severity of perinatal infections as well as the present situation regarding the causative organisms, diagnosis, prevention and therapy. Perinatal AIDS will also be discussed.

Keywords: infections, neonatal, perinatal

NEW TRENDS IN NEONATAL INFECTION

Despite the improvements in the field of neonatology, infections continue to cause mortality and morbidity to newborns. The incidence of neonatal sepsis ranges from 2.7 – 6.6/1000 newborns in neonatal units. [1,2] The common sites affected are blood, lungs, meninges, eyes and skin. The renal tract, bones and joints are less commonly affected.

The role of obstetricians

Obstetricians have made important contributions to the reduction of early neonatal sepsis. 2 examples will clearly illustrate this. Management guidelines for maternal intra-partum prophylaxis to prevent Group B streptococcal (GBS) disease in the newborn were formulated in 1996[3]. The incidence of early onset GBS sepsis (<7 days of life) was 2/1000 live births.[4] After the implementation of the prophylaxis regimes, the risk of GBS sepsis fell by 36%.[5] The second example is the management of preterm prelabour rupture of membranes. Maternal antibiotic treatment not only reduced maternal infection and chorioamnionitis but also reduced the risk of neonatal pneumonia and sepsis by 68%. [6,7]

In many perinatal centers, there is now an era of open communication between the obstetrician and neonatologist. Both have a significant stake in the outcome - the obstetrician hopes to prevent infection in the mother or deliver at the appropriate time if infection does occur; the neonatologist wishes to ensure that neonatal infection is attenuated if not prevented. Such rapport augurs well for both mother and child.

The high risk newborn

The newborns that are managed in hospitals today certainly are at greater risk of infection than before. Most neonatal intensive care units (NICUs) have a large proportion of premature babies whose weights can be as low as 500-600g and whose gestations can be as low as 23weeks. These premature babies have poor immunity and often have numerous invasive procedures carried out (intubation, intravenous access, venepunctures etc). 1.9 – 3% of all very low birth weight infants (<1500g) had early onset sepsis (<48hours of birth).[8,9] Many neonatal units now use percutaneously inserted central catheters for parental nutrition. While these catheters reduce the need for short-lived peripheral drips in tiny veins and stay in situ for weeks, there is no doubt that they increase the risk for sepsis.[10] Furthermore, with improved survival, the threat of late onset sepsis is always present. 8% of survivors had late onset sepsis.[9]

Changing trends in infective organisms

With time, organisms change in pattern, frequency and resistance. Table 1 highlights the different infective organisms in the nosocomial isolates from the NICU of the KK Women's & Children's Hospital. It is worthwhile to note that while Methicillin Sensitive Staphylococcus was present in 1992, it is far less common today. Methicillin resistant Staphylococcus epidermidis is the most prevalent organism today in late onset sepsis.

In early onset sepsis, Group B Streptococcus remains an important pathogen.[8,9,11] However, the widespread use of antepartum ampicillin has resulted in the emergence of Escherichia coll as a predominant pathogen.[12]

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Table 1: Changing trends in infective organisms (in decreasing importance)

1992	1995	1999
MSSA	MRSE	MRSE
MRSE	Enterobacter	E coli
Enterobacter	MSSA	Pseudomonas
MSSE		Klebsiella
Acinetobacter		MRSA

Source: Dept of Neonatology, KK Women's & Children's Hospital

MSSEIMRSE: Methicillin sensitivelresistant Staphylococcus epidermidis
MSSAIMRSA :Vethicillin sensitivelresistant Staphyloccocus aureus

Candida infection does occur, usually in very small, very ill infants who have been on multiple antibiotics for some time. These are difficult infections to diagnose, as the cultures can be negative in up to 50% of cases.

Of the viral infections, enterovirus causes the most concern. It can cause a shock-like syndrome that is very similar to a severe bacterial infection. The virus can be isolated from the stool. Unfortunately, specific anti-viral therapy is very difficult.

Another infection that has generated a great deal of interest is Ureaplasma urealyticum. It has been implicated as a cause of chronic lung disease (CLD), one of the main respiratory complications in ventilated premature babies as well as perinatal death. [13,14] In a prospective study conducted in KK Women's & Children's Hospital, 80% of premature babies who developed CLD were colonized at birth compared to only 50% who did not develop CLD.[15] Treatment of colonized premature infants with erythromycin did not reduce the incidence or severity of CLD.[16]

With the establishment of the Neonatal Emergency Transport Service (NETS) neonates today can be transferred to other hospitals after birth. Newborns are also transferred into KK Women's & Children's Hospital from the neighboring countries after being transferred by an air ambulance. This allows the introduction of organisms not usually seen in the hospital

Bacterial resistance

Methicilin resistance in Staphylococcus is well established. Extended spectrum beta lactamase is seen in some of the gram-negative organisms. Ampicillin resistant E coli is now more common and this is thought to be related to prolonged antepartum exposure to ampicillin.[17] There has also increased in vitro resistance of GBS to clindamycin and erythromycin, which are the recommended antibiotics for those allergic to penicillin.[18]

Because of the changing patterns of infective organisms and the development of resistance, the Hospital Infection Control Committee of the KK Women's & Children's Hospital draws up an antibiogram on a yearly basis. The appropriate empiric antibiotic combination for nosocomial infection has changed from vancomycin/ cefotaxime in 1992 to gentamicin/cefotaxime in 1995 and cloxacillin/gentamicin in 1999.

Diagnosis

In clinical practice, the new and most promising test is the PCR (polymerase chain reaction) which is being used for more and more organisms today.[19,20] The other investigations have not changed much. The full blood count (total white count, the ratio of immature to mature white cells, peripheral blood film and platelet count) continue to be extremely useful. CRP (C Reactive Protein) is very useful to monitor the response to treatment.[21] Isolation of the infective organism by cultures and immunoflorescence remain the mainstay of diagnosis, assisted by serology and antigen studies. Unfortunately, the use of maternal intraparturn antibiotics interferes with early blood culture results. A combination of clinical, hematological and other microbiological evidence should be used when diagnosing early neonatal sepsis.[22]

The newer markers of infection e.g. Interleukin I and 6, tumor necrosis factor are still only used in research and have not been established in clinical practical practice.

There are 2 areas where significant improvements have been made in the battle against infection. In

the clinical laboratories, the range of available investigations has widened considerably, the quality of results has improved and the waiting time for results has shortened. The other area of vast improvement is the skill of the neonatal intensive care nurse. Very often, it is the primary care nurse who first becomes suspicious of infection in the baby, by noticing that the activity of the baby has diminished, that the abdomen has become distended or that the general condition has deteriorated slightly. Very often, this starts the investigative process that leads to the diagnosis of infection.

The volume of blood needed limits the number of investigation that can be done. A baby weighing 700g has a blood volume of 56mls. It is common practice to replace the volume with packed cells when 10% has been utilized or lost in a short time. Blood cultures need 1 ml, Urea-Electrolytes-Creatinine, Ca/Mg, FBC, CRP, Group and cross matching need at least 0.5ml. Arterial blood gases use 0.2ml of blood. These small babies require blood transfusion very frequently; this of course increases the risk of transfusion related infections.[23]

Treatment options

The use of antimicrobials in the newborn is greatly limited by numerous factors. There are few reliable studies in newborns as most new drugs are tested on adults first. Even pediatric usage is often not recommended. G6PD deficiency also poses some problems as up to 3-5% of Singapore males have this condition. Drug levels for drugs with known effects on organs are not always available. Drug interactions and clearance in the small premature infant with immature organs are not well documented.

There is often insufficient knowledge about the best treatment regimes. E.g. Should treatment with amphotericin be guided by total accumulated dosage or by duration of treatment? While there are working guidelines for many drugs, few are well tested by therapeutic trials.

Because premature babies have developing organs, it is also important to ensure that drugs used do not cause permanent damage or adversely affect their long-term neurodevelopment outcome. What has developed over the years is the improvement of supportive care of the ill newborn. Most modem neonatal intensive care units are well equipped with up-to-date monitoring devices, external as well as invasive. The mechanical ventilators have improved. There are more modem types of ventilation e.g. high frequency oscillatory ventilation, continuous positive airway pressure, synchronized ventilation, which are either more effective or less traumatic to the lungs. Support of the blood pressure with inotropes is commonplace. Better intravenous access and methods of intravenous delivery ensure that drugs are administered effectively.

Persistent pulmonary hypertension of the newborn (PPHN) is a common complication of infection. The associated high mortality and morbidity make it a dreaded problem. The treatment is often long and arduous. It is caused by the effect of toxins, asphyxia or hypotension on the pulmonary arteriolar bed, leading to constriction and pulmonary hypertension. This in turn causes right to left shunting across the patent ductus arteriosus which is usually anatomically and functionally open after birth. The ensuing cyanosis can be severe and difficult to reverse. Extra corporeal membranous oxygenation (ECMO) or nitric oxide are the 2 most commonly used treatment modalities, with varying results. Unfortunately, in Singapore the former is not available at all and the latter is used only in one center. Locally, tolazoline, a pulmonary and systemic vasodilator and Magnesium sulfate are the drugs of choice. A higher index of suspicion and an aggressive, early treatment policy have helped us to deal with this condition.

Immunoglobulins (polyclonal, non-specific) have not been shown to be cost-effective in prophylaxis against infection. Although they caused a marginal reduction in sepsis, the expense of its use for the large premature population is not justified.[24] As a therapeutic modality, the available but scanty data does reduce mortality.[25] At present, the International Neonatal Immunotherapy trial is in progress. It will also study the long-term neurodevelopment outcome of the infants in the study.

There is some early data that suggests that granulocyte-colony-stimulating factor may be useful in the management of neonatal sepsis complicated by neutropenia. [26]

Preventive strategies remain pertinent today. Handwashing is the cornerstone of infection control and staff is constantly reminded by education and by the use of prominent signs in the patient care areas. [27,28] Routine surveillance for MRSA carriage is carried out. Varicella immunization for non-immune staff is offered. Visitors are curtailed. Parents are encouraged to wash their hands before entering the patient care areas. Cohorting of patients and staff is carried out when particular infections are encountered e.g. varicella zoster, MRSA, enterovirus etc.

Perinatal AIDS

Of the children who are HIV positive in the world today, the majority have been infected by the mothers.[29] The social burdens of perinatal AIDS are huge. Not only do they require treatment but also their parents may succumb to AIDS and leave them orphans. The most welcome news in this area of medical care was the result of the landmark AIDS clinical trial group 076 which showed that with maternal treatment, the transmission of HIV from mother to child fell from 25% to 8.3%.[30] Based on this trial, pregnant mothers who are HIV positive are given oral zidovudine from 14 – 26 weeks gestation and intravenous therapy during labor. The infant is started on zidovudine after birth and bactrim prophylaxis against Pneumocystis carini infection from 6 weeks of life. The infant is tested at birth, I week, monthly intervals from 1 – 3 months, and then 6 monthly from 6 to 18 months. With the use of caesarian sections especially in women with high viral loads, the transmission rates can halve the transmission rate.[29] Because of the prohibitive cost of combined maternal and newborn therapy, numerous trials using shorter courses of zidovudine or alternative drugs e.g. nevirapine have been conducted. Results have also shown reduction in the transmission rate.[31,32]

Breast-feeding is thought to be responsible for a significant proportion of transmission of HIV to the child and is therefore not recommended if a reliable alternative formula source is available.[33]

International benchmarking

There are 2 large international benchmarks. The National Nosocomial Infection Surveillance (NNIS) from the Center for Disease Control in the USA releases combined data on rates of infection, catheter related infection and ventilator related pneumonia.[34] The other benchmark is the huge Vermont-Oxford Network, consisting of more than 350 neonatal intensive care units. Both of these networks provide a benchmark for audit and quality control.

Outcome

The mortality from neonatal infection is very variable, ranging from 15 – 37% in early onset sepsis 8 – 14% in late onset sepsis. [2,8,11] The morbidity is wide-ranging, from short-term problems including respiratory, renal failure, hematological abnormalities and their individual sequelae to long term neurological sequelae including convulsions, cranial nerve palsies, cerebral palsy, hearing impairments and cognitive delay. Because many of these newborns were premature, it is sometimes to differentiate between the effects of infection and prematurity. One of the newer issues in infection is the possible correlation of sepsis and cerebral palsy.[35]

Infection control in the neonatal period is a team effort. The hospital administrators, the medical and nursing team, the parents and visitors and the any other person who participates in the care of the ill neonate all have important roles in the prevention of infection in the little ones they care for.

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Paediatric Vaccines

WinstonNg

INTRODUCTION

We have seen the success of Haemophilus influenzae type b (Hib) conjugate vaccines in preventing invasive disease. Newer conjugate vaccines to be discussed include pneumococcal and meningococcal conjugate vaccines. Varicella vaccine was introduced a few years ago but it is still being infrequently administered. We will look at some potential barriers to varicella immunisation. More combination vaccines are becoming available which have tangible public health benefits, benefiting both the patients and their parents. Finally, despite measles-mumps-rubella (MMR) vaccine being a part of our national immunisation schedule, a measles outbreak occurred in 1997 and there was a resurgence of mumps in 1999.

PNEUMOCOCCAL VACCINES

The 23-valent pneumococcal vaccine was the first generation vaccine which contained pneumococcal serotypes responsible for 85-90% of adult infections and virtually 100% of invasive disease in children. However, the efficacy data for preventing bacteremia and meningits in immunocompetent adults is only 61 to 75%; and the efficacy for all persons >5 years of age is only 57%. This vaccine is not immunogenic in children less than 2 years of age; it offers limited protection in patients with immunodeficiencies and hematologic malignancies, and does not reduce mucosal carriage of pneumococci. As 80% of disease burden in children occurs in those less than 2 years of age, this vaccine therefore has limited indications.

The new pneumocccal conjugate vaccine produces good antibody response in persons at the extremes of age (i.e. young infants and elderly), the immunocompromised and those who have had recurrent infections with poor immunologic response to the 23- valent pneumococcal vaccine. This improved immunogenicity is the result of a T cell- dependent antibody response which is elicited, as compared to only a T cell- independent response seen with the 23-valent pneumococcal vaccine. Even though there are at least 90 pneumococal serotypes, the new Food and Drug Administration (FDA) approved heptavalent conjugate pneumococcal vaccine would cover an estimated 52 to 81% of the pneumococci causing invasive infections in children. In a large trial involving infants vaccinated at 2, 4 and 6 months of age with a booster at 12 to 15 months, efficacy of the heptavalent conjugate vaccine in preventing invasive disease due to vaccine serotype versus any serotype was 97.4% versus 89.1%, respectively.[1] The vaccine also reduces nasopharyngeal colonization of serotypes contained in the vaccine; however there is an increase in carriage of nonvaccine serotypes. The long term colonization effects of the pneumococcal conjugate vaccines will be the subject of additional surveillance.[2] In general, the conjugate vaccine appears to be well tolerated with a safety profile similar to other routine paediatric vaccines.[2]

MENINGOCOCCAL VACCINES

Systemic infection with Neisseria meningitidis (N. meningitidis) is not commonly seen, cases encountered may give a history of travel to Mecca to participate in the Hajj or had close contact with such a traveler. The quadrivalent meningococcal A/C/Y/W135 polysaccharide vaccine is approved for use in children 2 years of age and older.[3] Routine use is not recommended. Indications include persons with asplenia, terminal complement or properdin deficiencies. The vaccine is also used for travellers to areas with epidemic or hyperendemic meningococcal disease and as a possible adjunct to chemoprophylaxis when an outbreak is caused by a serogroup contained in the vaccine. Immunization of college students is recommended by the American College Health Association.

New conjugate vaccines for serogroups A and C meningococci have been made and a serogroup Y conjugate vaccine is under development. They are immunogenic in young children and have the

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potential to prevent one-third of deaths from N. meningitidis in developed countries.[4]

In the UK because of a recent increase in serogroup C disease, meningococcal C conjugate vaccine is currently being offered to all infants from November 1999.[5] The primary series is given at 2, 3 and 4 months of age. A catch up programme to immunize all school age children and young adults to the age of 20 years is also planned.[6] The implementation of this program is based on excellent immunogenicity and safety data for this vaccine. There is no data yet on the efficacy of this vaccine from Phase III trials. It is likely that the vaccine would protect against serogroup C meningococcal disease. However would a reduction in nasopharyngeal carriage of group C meningococci lead to a replacement with other pathogenic meningococci such as group Y, W135 and B? Such strain replacement has been observed during trials of pneumococcal conjugate vaccine but not after immunisation with Hib conjugate vaccines.

VARICELLA VACCINE

A vaccine against varicella has been available for the past five years but many children remain unimmunized. There are at least five reasons cited as potential barriers to varicella immunization which are discussed below. [7]

1. **Varicella is a mild disease**

Varicella is a common childhood disease that infects almost everyone who is not immunised. Despite more than 90% of cases occurring in childhood, the morbidity and mortality risk is lower in this age group as compared to an adult. However in children, varicella is one of the most important risk factors for severe, invasive, group A streptococcal disease. [8,9] The incidence of varicella among adults is low, but morbidity and mortality is up to 20-fold higher compared to children.

2. **Vaccine effectiveness and safety**

The vaccine is 70 to 90% effective in preventing varicella, and more importantly more than 95% effective for preventing severe varicella. The rate of breakthrough disease following exposure to wild type virus is about 1 to 4% and the rate does not increase with length of time post-vaccination. Even if breakthrough disease occurs, it is a mild infection with < 50 lesions, of short duration with low-grade or no fever.

3. **Duration of immunity**

Follow up studies of children in the United States and Japan have shown that the vaccine is protective for at least 11 and 20 years respectively. These studies were performed at the time when a substantial amount of wild type varicella-zoster virus (VZV) was circulating in the community with opportunities for subclinical infections and boosting of the immune system to occur. The experience from other live vira vaccines such as measles, mumps or rubella suggests that immunity remains good throughout life though. Follow up studies are currently underway to determine if additional doses of varicella vaccine are needed.

4. **Effect of universal vaccine on the epidemiology of varicella**

There is concern that the use of varicella immunization in children will create a cohort of adults susceptible to serious varicella disease. As more children are vaccinated against VZV, the circulation of wild type VZV will decrease and the likelihood of children who are not immunized and have no exposure to natural infection to enter adolescence and adulthood will increase.

Mathematical models predict that if varicella vaccine coverage in children is more than 90%, there will be a greater proportion of susceptible adults, but varicella disease burden will decrease for both children and adults [10] (Table 1). However, if vaccination rates remain low (<90% coverage), this will lead to an increase in the number of children who become susceptible adults; leading to increased opportunities for these susceptible adults to contract varicella from unimmunized children.

5. **Cost-benefit of varicella vaccine**

A cost-benefit analysis of immunising all children less than 6 years old in the United States has been reported by Lieu et al. [11] Direct medical costs (ie cost of the vaccine and its administration minus cost of varicella disease prevented) is calculated to be US $8 million. The savings from a decrease in the number of days taken for sick leave works out to US $392 million. Therefore the overall net savings would be US $384 million. The theoretical savings per vaccine dose given would be US $96.

The vaccine is about 90% effective if given within 3 days and possibly within 5 days of household or hospital exposure. There is no evidence that administration of the vacccine during the presymptomatic or prodromal stage will lead to an increased risk of an adverse event or more severe natural disease. In 2000, the American Academy of Pediatrics (AAP) recommended that the vaccine be used for postexposure immunization. [7] The vaccine has shown good safety data, adverse event are generally mild and occur in 5 to 35% of cases. 20% are minor injection site reactions and 3 to 5% have a localised rash. Another 3 to 5% may develop a generalised varicella-like rash, typically consisting of only 2 to 5 lesions and are papular in nature; lesions appear 5 to 26 days post vaccination.

COMBINATION VACCINES

An increasing number of vaccines are currently being introduced and the benefit of a combination vaccine to patients and parents would be a decreased number of injections and health care visits. Tangible public health benefits include: decreased cost of administration, increased compliance, and improved record keeping and tracking. Given the option of multiple injections or multiple office visits, parents refer multiple injections [12]. Therefore there is a demand for new combination vaccines.

Newer combination vaccines under active development or developed include diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP)-hepatitis B (Hep B) vaccine (DTaP-Hep B), DTaP-trivalent inactivated polio vaccine (IPV) (DTaP-IPV), hepatitis A (Hep A) vaccine-Hep B (Hep A-Hep B), DTaP-IPV-Hib, DTaP-Hep B-IPV, Hib-Hep B-IPV, DTaP-Hib-IPV-Hep B, DTaP-Hib-IPV-Hep B-Hep A, MMR-varicella (V) vaccine (MMR-V), Hib-pneumococcal conjugates-Hep B, meningococcal conjugates and pneumococcal conjugates.

Administering an extra dose of live, attenuated virus vaccine to immunocompetent persons who already have vaccine-induced or natural immunity has not been demonstrated to increase the risk of adverse events. [13]

When inactivated vaccines (which are adsorbed to aluminium-salt adjuvants) are administered, the reactogenicity of the vaccine must be balanced with the benefits and risks of extra doses. The extra antigen contained in these combination vaccines is justified if products containing only needed antigen are unavailable and the benefit of giving extra antigen outweighs the risk of adverse events. Because clinical experience suggests low reactogenicity, an extra dose of Hib or Hep B vaccine may be administered as part of a combination vaccine to complete a vaccination series for another component of the combination.

Extra doses of tetanus toxoid vaccines need to be administered with caution, as there is an increased risk of hypersensitivity reactions when given earlier than the recommended intervals. Extra doses of tetanus toxoid-containing vaccines might be appropriate if a child has only received diphteria and tetanus toxoids (DT) vaccine and needs protection from pertussis or immigrants with uncertain immunization histories. [13] Even though the antibody titers to one or more components of the combination vaccine may be significantly lower as compared to antibody titers if a monocomponent vaccine had been used; the antibody titers induced are still well within adequate protection levels.

MMR Vaccine

In 1997, there was a measles outbreak locally. Even though 96% of persons given MMR seroconvert to the measles component, a large

pool of non-immune persons to measles will still develop over a 10 year period (4% non converters x 145 000 births/year x 10 years = 58 000 non-immune persons). This large pool of non immune persons to measles led to a drop in herd immunity, which manifested in the outbreak seen. Therefore, in 1998, a second dose of MMR vaccine was recommended for all children in primary 6, so as to seroconvert the group of initial primary failures to measles vaccination.

There was an increase in mumps from 674 cases in 1997 to 1183 cases in 1998, and to 2586 cases for the first 7 months of 1999.[14] The reason for this increased incidence is as follows. The egg-free MMR vaccine containing the highly attenuated Rubini mumps virus strain was used from 1993 to 1995. It was later found to confer no protection against acute mumps parotitis in vaccinated children in Singapore. Its introduction into the national immunisation programme has resulted in a reduction in the seroprevalence of mumps to prevaccination levels. The egg-free MMR vaccine containing the Rubini strain was deregistered in Singapore in May 1999.

The currently available MMR vaccine (MMR II", Merck & Co., Inc.) contains insignificant amounts of egg white (ovalbumin) cross-reacting proteins. Except for children with an anaphylactic or a severe reaction (generalised urticaria, shock, wheeze or upper respiratory obstruction) after egg ingestion, the rest should receive MMR. Also, skin testing of children to eggs is not predictive of reactions to the MMR vaccine.

THIMEROSAL

Thimerosal, a mercury-containing preservative has been used as an additive to vaccines since the 1930s for preventing bacterial contamination. The organic mercury is associated with neurotoxicity in high doses and definitive data regarding the doses at which developmental effects occur in infants are not available [15]. For vaccines containing the recommended dose of thimerosal, hypersensitivity has been noted but no other harmful effects have been reported. In 1997, the FDA determined that infants who receive thimerosal-containing vaccines at several visits may be exposed to more mercury than recommended by federal guidelines for total mercury exposure. Some vaccines that contain thimerosal are: all diphtheria and tetanus toxoids and whole-cell pertussis vaccines (DTwP), Hep B vaccines, influenza vaccines, pneumococcal polysaccharide vaccines, meningococcal polysaccharide vaccines, some of the DTaP and Hib preperations. Currently the various pharmaceuticals involved in vaccine production and the FDA are working to remove thimerosal from the various products. One should use a thimerosal-free product if available. Until thimerosal has been removed from all vaccine products, the use of products containing thimerosal is preferable to withholding vaccinations; as the larger risks of not vaccinating children far outweigh any known risk of exposure to thimerosal-containing vaccines.

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UPDATE ON TRAVEL VACCINES

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INTRODUCTION

Advising international travelers on vaccine-preventable diseases is one of the major services provided by travel medicine specialists.

Immunization advice needs to be individualized. To quote Prof. Keystone, Vice President of the International Society of Travel Medicine, we should immunize according to risk, not according to the destination country. Prioritizing vaccine recommendations based on health risk factors is a major challenge. Risk assessment for travel vaccines depends on geographic destination and reported endemic and epidemic diseases; the level of anticipated contact with the local residents, the mode and conditions of travel (luxury hotels versus camping), duration of stay, kind of activities etc. Also other factors such as traveler's budget and health insurance coverage, time before departure (last minute consultations naturally exclude vaccinations requiring a series), known allergies, other health conditions and pregnancy influence pretravel immunization advice. In order to have a rational approach to travel vaccines, it is essential to know the risks of vaccine preventable diseases in travelers.

Table 1: Risk of vaccine preventable diseases in international travelers (Monthly incidence rate) [1]

Influenza	1%
Hepatitis A	300/100,000 (Backpackers: 2000/100,000)
Hepatitis B	200/100,000 in Asia 80/100,000 in Africa, South America
Animal Bite	20/100,000 (India: 8-14% of dogs are rabid)
Typhoid fever	3/100,000 30/100,000 (India, Peru, West Africa)
Meningococcal meningitis	0.4/100,000 2000/100,000 in Hajj travellers
Cholera	0.3/100,000
Japanese Encephalitis	Unknown (around 40 reported cases worldwide)

CATEGORIES:

Travel Vaccines can be categorized into Required, Recommended and Routine Vaccinations

Required:

The only mandatory vaccination is the Yellow Fever vaccine which is required for travellers arriving in endemic areas for Yellow Fever (certain countries in South America and Africa) as well as for travellers returning from endemic areas.

In view of the high incidence of meningococcal meningitis in Hajj pilgrims (see above table), Saudia Arabia has introduced meningococcal vaccination as prerequisite for all Hajj and Umrah pilgrims arriving in Saudi Arabia. Until May 2000, in Singapore we used the bivalent meningococcal vaccine (A/C). However, after the year 2000 Hajj outbreak of meningococcal disease with serogroup W-135, a switch in the recommendation to the quadrivalent meningococcal vaccine (A/C/Y/W-135) was indicated [2;3].

Table 2: Required Travel Vaccines

Yellow Fever	vaccine	Live attenuated
		Residual egg protein
	regimen Duration of protection	Single dose 10 years
	Efficacy	>98%
	Adverse Effects	
	Contraindications	Pregnancy, Immunsupression, egg allergy
Meningococcal Vaccine *(required for pilgrims to Saudi Arabia only) recommended for Sub-Saharan Africa*		Live inactivated
	Regimen	Single dose
	Efficacy	85-90%
	Onset of protection	10-14 days
	Duration of protection	3 years

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Recommended Vaccinations

Hepatitis A

Hepatitis A infection is highly endemic throughout developing countries but of lower endemicity in most developed countries. The Case-fatality rate of hepatitis A is 0.3%, however, it is 1.8% for reported cases in persons age 50 years and older. The hepatitis A vaccine is highly immunogenic and safe and can be coadministered with other travel vaccines. Protection starts 2-4 weeks after a single intramuscular injection. Booster is required 6-12 months (Havrix, SKB) or 6-18 months (Vaqta, MSD) later. Duration of protection is one year after initial dose, after booster it is 10-30 years according to current extrapolations, maybe even lifelong. It is not necessary to test anti-HAV after immunization, as vaccine efficacy is close to 100%.

Hepatitis B

Close to 40% of the world's population has experienced infection with HBV, and there are an estimated 20 million new infections per year worldwide. The highest HbsAg seroprevalence rates, reaching 15%, are found in Asia. In the context of travel Hepatitis B vaccine in adults is indicated for short-term travelers with high risk sexual behaviour or professional exposure to blood products. The risk of HB is low in tourists without sexual risk behaviour or professional exposure if the stay is of short duration. Among long-term residents in endemic areas, the incidence rate of symptomatic HB ranges from 0.2 per 1000 per month to 0.6. The rates of seroconversion, including asymptomatic infection, are 0.8 and 2.4, respectively. Therefore, for travel for more than 6 months to endemic areas, Hepatitis B is indicated. The disadvantage of Hepatitis B vaccinations for the traveller is the vaccination schedule of 0-1-6 months. Studies have shown that the accelerated schedule with 0-1-2 months and even 0-7-21 days PLUS shot after 1 year is as effective as the old schedule.

With Hepatitis A and B being indicated fairly frequently for travellers, there is now a combination vaccine on the market, Twinrix from SKB. The schedule is the same as for Hep. B , that is 0-1-6 months. But there is an accelerated regime with 0-1-2 (with booster at 12 months) [5], and now also 0-7-21 days plus at 12 months [6]. The latter vaccine schedule is not registered yet in Singapore.

Typhoid fever

The classic inactivated whole-cell parenteral typhoid vaccine with frequent side effects has been largely replaced by two newer vaccines, the oral typhoid vaccine, and the typhoid Vi capsular polysaccharide vaccine. The oral typhoid vaccine consists of a series of three enteric-coated capsules that are taken orally on an empty stomach (at least 1 hour before a meal) on alternate days. The vaccine consists of a live attenuated bacterial strain of Salmonella typhi, strain Ty21a. Although the oral vaccine is often the preferred vaccine for travelers anxious to avoid too many injections, it requires a high level of patient compliance to ensure potency of the capsules. Once dispensed, refrigeration is recommended. Concurrent use of antibiotics, mefloquine and oral polio should not be advised. Published studies from field trials in endemic areas have reported a protective efficacy range of 43-96%, the wide range of results probably being caused by variations in intensity of exposure at geographic sites and the prevailing health status of the study populations. The protection afforded by oral typhoid vaccine in nonimmune travellers may be less than that reported in semi-immune endemic study populations. The official booster interval is 5 years, requiring an entire three capsule series.

The parenteral Vi capsular polysaccharide vaccine was introduced in 1995. Protective efficacy rates of 60-72% have been reported in published studies of field trails in endemic countries, although seroconversion rates of greater than 95% have been measured in volunteer subjects. The vaccine is safe and well tolerated. Immunization with typhoid Vi vaccine is not affected by concurrent administration of antimicrobials or antimalarials.

Typhoid vaccination does not give complete protection. The importance about food and water hygiene needs to be emphasized in all clinics offering pre- travel advice.

Cholera Vaccine

V. cholera is divided into two serogroups, 01 and 0139, and the 01 serogroup is further characterized by two serotypes, Inaba and Ogawa, and the two biotypes, classical and El Tor. El Tor is the most predominant biotype.

The cholera epidemic that began in Peru in 1991 and then spread throughout Latin America has been well publicized and is due to V. cholera 01 Inaba El Tor. In 1992, V. cholera 0139 was detected during a cholera outbreak in Calcutta. The 0139 serogroup spread to Bangladesh in 1993, but has been limited to sporadic outbreaks in countries of Southeast Asia only.

Cholera vaccine was required by many WHO member countries until the late 1980s when the cholera vaccine requirement was officially dropped because of the lack of efficacy of the parenteral inactivated whole-cell cholera vaccine. Newer oral cholera vaccines have been developed since, but the WHO does currently not recommend cholera vaccines to the general traveler for two reasons:

1) risk for cholera in travelers is very low

2) current parenteral and live attenuated oral vaccine do not offer good protection and duration of protection is limited to 6 months. Cholera vaccination is recommended to special high-risk groups only, such as workers in refugee camps.[4]

The most recent advancement in cholera vaccinology is the development of an oral inactivated whole-cell/recombinant B-subunit of cholera toxin in Sweden. This vaccine is reported to provide 86% protection. The additional benefit is a protective efficacy against ETEC diarrhoea of about 60%. Enterotoxin producing E. coli is a common cause of "travellers' diarrhea". The whole-cell/recombinant B subunit cholera vaccine is not registered yet in Singapore.

Japanese Encephalitis

JE is a leading cause of encephalitis in Asia. Although most infections with the virus are asymptomatic, among those who develop clinical illness, the disease has a case fatality rate as high as 30%, and 50% of survivors may have residual brain damage. Highest incidence in China, Korea, India, Thailand, Vietnam. Lower frequency in Japan, Hong Kong, Taiwan. Among travellers reports of JE have been scant. It is more frequent in expats and military personnel with intensive exposure. Risk of transmission is higher in rural areas, especially where pigs are raised and where rice paddies, marshes and standing pool of water provide breeding grounds for mosquitoes and food for birds. Transmission is highest during the rainy season and early dry season.

Indications for JE vaccine:

1) Travellers >1 month in endemic areas during the transmission season, especially if travelling to rural areas

2) Travellers < 1 month if at high risk of exposure (i.e. outdoors activities with intense exposure to mosquito bites, during rainy season)

The JE vaccine with worldwide distribution is the vaccine manufactured by Biken; it is an inactivated virus vaccine purified from mouse brain cultivation. The vaccine is given as a series of three s.c. injections (0-7-21/28 days). Efficacy is 90%, duration of protection 3 years.

Systemic side effects (fever, headache, myalgia, chills, dizziness, nausea, vomiting, malaise) occur in approximately 10% of vaccines. Because of the possibility of generalized urticaria, angioedema, respiratory distress and anaphylaxis that could be life threatening, persons receiving this immunization should be observed in the medical office for 30 minutes. They should defer international travel and remain in areas with ready access to medical care for 10 days after receiving any dose [7]. JE vaccine related encephalitis occur in 1 to 2.3 vaccinees per million.

Contraindications to JE vaccination is a history of urticaria, allergy to beestings. A history of previous reaction to JE is an absolute contraindication.

Rabies

Rabies is an underestimated risk for adventuresome travellers and long-term expatriates. Due to a lack of dog vaccination and control programs, dogs remain the major vector in developing countries. In the USA, the principal vectors are wild animals-especially skunks, raccoons, bats and foxes. Singapore has been declared rabies free.

Every animal bite in an endemic country needs to be treated as potential risk for rabies. As rabies leads almost inevitably to death, rabies vaccination needs to be taken seriously. There is pre- and post-exposure prophylaxis.

Preexposure Rabies Vaccination is indicated for:

1) Travellers who are likely to come in contact with animals in areas of enzootic rabies

2) Certain occupations or activities with frequent risk of exposure (i.e. veterinarians, animal control personnel, park rangers, wildlife workers, hunters, spelunkers etc.)

3) Travellers in isolated areas where vaccine is not readily available or postexposure therapy may be delayed

4) Travellers going to rabies-endemic areas in which postexposure rabies care is likely to be suboptimal.

5) Long-term travellers/expatriates in endemic areas for more than 3 months

Vaccines:
In the USA there are 3 inactivated-virus, cell culture vaccines (for pre and postexposure prophylaxis): Chick Embryo Cultura Vaccine (PCEC), Human Diploid cell vaccine (HDCV) (available for both i.m. and i.d. formulations), and Rabies Vaccine Adsorbed (RVA). Human Rabies Immune Globulin (RIG) is for postexposure prophylaxis only. In Singapore, we have HDCV (currently only i.m. formulation) and Rabies immunglobulin. In some developing countries, the original rabies vaccine, known as Semple vaccine, is still available be should be avoided. It has a lower protection and is associated with a high rate of severe side effects.

Preexposure immunization consists of 3 doses of HDCV, PCEC or RVA 1.0ml i.m., one dose each on days 0.7. and 21 or 28. Only HDCV may be administered by the intradermal route. The intradermal route is cheaper, however, it is contraindicated for those on concurrent malaria medication as this appears to interfere with antibody production.

Postexposure prophylaxis [8;9] consists of a regime of 0-3-7-14-30 days (all i.m. doses!) and depending on size and site of animal bite, passive immunization with human rabies immunglobulin needs to be given at a dose of 20IU/kg . Rabies immunglobulin (RIG) should be infiltrated around the wound, and the remainder given as a deep intramuscular injection distant from the active vaccine.

Following animal bite, persons fully immunized with the preexposure rabies vaccine would need to receive two additional intramuscular doses of HDCV or RVA or PCEC given on days 1 and 3; and rabies immune globulin is not required.

Influenza

Although influenza is a very common illness encountered in international travelling, it is probably still an underrecognised vaccine in the travel medicine setting. Mortality caused by influenza in travellers is extremely uncommon; however, the impact it may have on lost vacation days may be substantial. Influenza vaccination is mainly recommended for all persons with chronic illness, especially cardiopulmonary conditions, and for all adults 65 years of age and older. But it should also be offered to persons who cannot afford lost vacation days.

A summary of Recommended Travel Vaccines is given in Table 3.

Table 3: Recommended Vaccines			
Vaccine	**Onset of protection**	**Duration of protection**	**Efficacy**
Hepatitis A	2-4 weeks	> 10 years (if booster given 6-18 months after primary dose)	>98%
Hepatitis B	After 2nd dose ~80%, after 3rd dose >95%	>10 years	After 2nd dose ~80%, after 3rd dose >95%
Oral typhoid	2 weeks after 3rd oral dose	3 years	50-80%
Typhim Vi	2 weeks	3 years	55-75%
Oral live attenuated cholera vaccine	8 days after single	6 months	Challenge 62-100%, field trials <20% (prevents mainly serious illness)
Cholera parenteral	6 days after primary series	~ 3 months	50%
Oral Cholera: Whole-cell recombinant/ B subunit (not registered in Singapore)	7 days after second dose	?> 1 year	Field efficacy 85% Plus ~60% protection against ETEC
Japanese Encephalitis	2 weeks after c completion of series	3 years	>90%
Rabies- HDCV	2 weeks after 3rd dose	~ 3 years	Postexposure: 2 doses of HDCV required

Routine Vaccinations

A consultation for travel health advice is an opportunity to ascertain that routine childhood immunizations and boosters have been performed. Travellers should have protective immunity against tetanus, diphtheria, measles, mumps, rubella, chickenpox and polio. Details about DPT, MMR, Polio vaccine etc. would be beyond the scope of this article. It needs to be briefly mentioned, though, that in most developed countries booster with polio vaccine is not part of the national programs anymore. Although polio has been eradicated in many developed countries, it is still a risk in Asia and Africa. Updating immunity against polio with a booster dose of poliovirus vaccine using the trivalent inactivated eIPV vaccine, which is safe in all adults, is recommended before travel to the latter areas.

VACCINE INTERACTIONS

1) Avoid concurrent administration of oral typhoid and oral polio vaccine

2) Do not take oral typhoid vaccine with antibiotics and antimalarials

3) Malaria prophylaxis interferes with intradermal rabies vaccination response. Either schedule at least an interval of 3 weeks, or give the intramuscular dose instead of the intradermal dose.

4) Tuberculin skin test and live virus vaccines should be given simultaneously or alternatively an interval of 4-6 weeks between the skin test and virus vaccine should be kept.

5) Yellow Fever and cholera vaccines should be administered at least 3 weeks apart since antibody response is diminished if given simultaneously.

6) Vaccines and immunoglobulins should be administered at different injection sites

7) Inactivated vaccines may be given simultaneously at separate sites

8) OPV and MMR can be administered together, however, other live virus vaccines should best not be administered within 30 days of each other.

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The Singapore Family Physician

VIRAL HEPATITIS - AN UPDATE

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SUMMARY

Issues of current interest in viral hepatitis include hepatitis C virus genotypes 6-11, which are unique to our region, and the emergence of various hepatitis B mutant virus, either spontaneously or treatment-induced. Hence, despite new therapeutic agents and regimen, these viruses continue to pose management challenges. It is also important to keep acute hepatitis A and E in mind as our population travels frequently and yet has a dropping seroprevalence of anti-HAV IgG. There were also sporadic incidences of, probably indigenous, acute hepatitis E. Finally, we should be aware that some new viruses, namely hepatitis G and TT viruses, have been described. Unfortunately, they still cannot account for our non A-E hepatitis and cryptogenic cirrhosis.

INTRODUCTION

This paper will focus on aspects of various viral hepatitides that are of relative current interest, such as the changing seroepidemiology of hepatitis A in our community and its impact on us. The local prevalence and incidence of hepatitis E, will be highlighted. There is a need to include Hepatitis E in our list of differential diagnoses when we encounter patients with acute non-A, non-B hepatitis. In addition, two relatively new viruses, namely hepatitis G virus (HGV) and TT virus, which were discovered among the patients with non A-E hepatitis by genetic sequencing in the recent years will be briefly mentioned. As for chronic hepatitis B and C which we are familiar with, the emergence of hepatitis B virus mutants and new hepatitis C virus genotypes that has posed new therapeutic challenges despite new therapeutic agents or regimens which promised better response rates will be discussed.

HEPATITIS A

Changing seroepidemiology and its implications

With improved sanitation and as our people enjoy living in a better environment, our young Singaporeans are less exposed to infective agent, such as hepatitis A virus. It is therefore no wonder that the seroprevalence of hepatitis A (anti-HAV IgG) has been falling progressively in our population. 1,2 In the sero-epidemiological survey in 1994 '3 the prevalence of anti-HAV IgG among those who were less than 35 years old was only 37.5 %. This implies that many in the younger cohort of our population are susceptible to development of acute
hepatitis A when they travel to highly endemic areas. This is highly likely with our mobile, young adults who travel frequently for work or leisure. It is important to note that while hepatitis A virus infection may be subclinical in many children, as the age of acquisition of the infection advances, the symptoms of acute hepatitis become more marked. The patients are more likely to develop prolonged jaundice from cholestasis and acute fulminant hepatic failure, if they are aged more than 40 years.

Atypical clinical manifestation

While most patients are expected to have uneventful recovery from acute hepatitis A, there is a small proportion of patients who may develop a relapsing course with resurgence of s. transammases before complete resolution that may take as long as a year.[4,5,6]

In recent years, I have observed persistent fever in some patients who had acute hepatitis A even after the onset of Jaundice. This is against the description of classical presentation of acute viral hepatitis. Concurrent sepsis and other causes of fever were excluded in these cases. The fever usually resolved spontaneously within one to two weeks after the onset of jaundice, with no particular complication. History from these

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patients suggested foreign acquisition of these infections (unpublished data).

Rational approach to hepatitis A vaccination
Based on the epidemiological data, it would seem logical to vaccinate the young adults who travel frequently to hepatitis A - endemic areas. It is probably reasonable and cost-effective to omit prevaccination serological test for anti-HAV IgG in those who are below 35 years of age. Patients with chronic viral hepatitis B or C make up the other at-risk group. [7] Some of them, especially the older patients and those with underlying liver cirrhosis, may risk hepatic decompensation with acute hepatitis A super-infection causing acute-on-chronic hepatitis. However, for the older patients, it may be worthwhile checking their serological status for anti-HAV IgG before any attempt of vaccination which may prove unnecessary.

HEPATITIS E

Epidemics of hepatitis E were first described in the Indian subcontinent and travellers to endermic areas may acquire the infection. A study on acute hepatitis E was carried out in the department of Gastroenterology, Singapore General Hospital, between 1993 and 1995 and we found an incidence of 0.83 case per month during this period.[8] We also found the seroprevalence of anti-HEV IgG among patients with or without underlying liver disease to be 10.5 % and 14.7 % respectively.[9] The difference in seroprevalence between the two groups was not statistically significant.

Over the years, epidemiological surveillance in Singapore has reported acute hepatitis E making up 0.4 % to 6.3 % of the reported cases of acute hepatitis annually. 10 While a proportion of these cases were travel-related, there were sporadic cases originated locally.[8, 10] It is, therefore, worthwhile to keep this condition in mind when we encounter patients with non-A, non-B acute hepatitis. The condition can be diagnosed by serological tests for anti-HEV IgG and IgM. Both of which are present early in the clinical course of acute hepatitis. The patients should be warned of prolonged period of cholestasis, lasting for, on average, more than a month.

NON A-E HEPATITIS

Despite the discovery of hepatitis A, B, C, delta and E viruses, there are still some cases of acute and chronic hepatitis of which the etiology are unknown and some cases of hepatocellular carcinoma which cannot be accounted by known etiology. It is believed that some of these idiopathic hepatitis are caused by a yet unknown parenterally transmitted hepatitides virus, and there are still other cases which are caused by another unknown enterally transmitted hepatifides virus.

With the advent of molecular biological techniques, sequences of new viruses have been found in patients with non A-E hepatitis. To date, they include the hepatitis G virus and the TT virus which were reported in 1995 & 1996 [11,12] and 1997, [13] respectively. The former is an RNA virus, like the hepatitis C and dengue viruses, belonging to the family of flavivirus; and the latter a DNA virus. Both of which are parenterally transmitted. While they are commonly found either isolation or in co-existence with chronic hepatitis B or C, there is no sufficient evidence to believe that they are pathogenic independently. Thus, the etiology of acute non-A, non-B fulminant hepatitis and cryptogenic chronic hepatitis / cirrhosis remains unresolved.

CHRONIC HEPATITIS C

The overall prevalence of hepatitis C is not very high in our country. Previous study done in the blood donor population found a seroprevalence of 0.3 %.14 However, in a public hospital setting, it is disproportionately represented by patients with chronic renal failure undergoing dialysis or patients post-renal transplantation. This poses a difficult management problem as these patients tend to respond poorer to standard therapeutic regimen for hepatitis C. In addition, there is also a therapeutic dilemma in managing patients post-renal transplantation as treatment of hepatitis C with interferon will risk renal allograft rejection. The current recommended treatment for chronic hepatitis C is injection interferon and oral ribavirin combination for 6 to 12 months, depending on hepatitis C virus (HCV) genotype and viraemic

load, with longer duration of treatment recommended for patients with high viral load and genotype 1 infection. [15] These recommendations are based essentially on studies done in the West where HCV genotypes 1, 2 and 3 are found.

Unfortunately, previous local study[16] has found our patients to be infected mainly by HCV genotype I that has worse response to the currently available treatment and consequently require a more prolonged and costly treatment. In addition, ribavirin is generally contraindicated for renal failure patients, thus further decrease the sustained response rates in the bulk of our patients who can only receive interferon monotherapy. In recent years, HCV genotypes 6-11 were reportedly found uniquely in our part of the world. We too have found HCV genotype 6 infection, which is common in Hong Kong and Southern China, in our local patients who had renal failure and have undergone renal transplantation Guangzhou, China.[17] Due to the lack of data from regional studies, the response of HCV infection caused by these more recently described genotypes to the currently recommended treatment regimen needs to be ascertained.[18] It is hoped that with the availability of the long-acting pegylated interferon in the near future, and perhaps novel combination treatment, we will be able to see better therapeutic outcome in the coming years.

CHRONIC HEPATITIS B

On the topic of hepatitis B, I shall concentrate on discussing the molecular variants of the hepatitis B virus (HBV) which poses diagnostic and therapeutic challenges in the recent years. I will describe three variants, each caused by mutations at a different genetic site of the virus but, independently, all has given rise to practical problems of management:

The HBV surface (HBs) mutant

With the mutation of the common epitope, the "a" determinant, of the surface gene of HBV, routine ELISA test for HBsAg may be falsely negative in patients who actually have chronic HBV infection caused by such mutants. Thus, this may prevent us from recognising HBV infected patients who actually requires follow-up and possibly, treatment. We may also unintentionally, as a result, give these patients a false sense of security. Therefore, it is important that we are aware of such an entity in at-risk patients who are HBsAg negative but who have elevated s. ALT. If in doubt we should screen for the presence of anti-HBc (total) antibody which suggests patients' once exposure to HBV. If positive, serum for HBV DNA should be done to confirm the presence of ongoing HBV infection. This includes children who are born to HBV infected mothers, as the commonly used hepatitis B vaccine, containing only 's' antigen, will not protect the children from being 'infected by HBV surface mutants from their mothers. In a local study,[19] albeit small, 20% and 13% of the vaccinated children and adults, respectively, were found to be infected by HBs mutant.

HBV precore mutant

In the traditionally hepatitis B endemic countries, such as Italy and Greece, majority (50 - 80 %) of their HBV infected patients are now infected by HBV precore mutant. Similarly, the precore mutant virus has replaced the wild type HBV in a significant proportion of our HBV infected patients in Asia (see table 1).[20] This is associated with HBeAg negative viraemia, as confirmed by the presence of HBV DNA. It may be confusing for some as we were traditionally taught that the loss of HBeAg is a reflection of quiescent viral activity. In this case, however, HBV is still actively replicating and translation of HBeAg was merely disrupted due to mutations at either the core promoter or precore regions of the virus (see Fig. 1). Hence, if the patients' s. transaminases are inexplicably elevated long after the loss of HBeAg, HBV DNA should be done as part of the investigation for such a situation. The patients may benefit from treatment if they indeed have significant HBV precore mutant - related hepatitis. Unfortunately, sustained response rate was limited with interferon treatment in these cases, based on limited studies.

Nucleoside analogues selected HBV polymerase variants

Due to the advent of nucleoside analogue, which acts at the polymerase gene of HBV, employment of such therapeutic agents has led to rapid and effective suppression of HBV replication. However, selection pressure sets in with prolonged treatment, and this leads to development of HBV mutant virus. One of these agents that is currently available is lamivudine. Its prolonged usage can lead to mutation at the YMDD motif of the HBV polymerase gene, thus the emergence of the so-called HBV YMDD variants. Their emergence is usually associated with increase in serum transaminases and relapse of viraemia, as suggested by recurrence of serum HBV DNA. The pathogenicity of these YMMD variants is variable. While initial observation seemed to suggest low pathogenicity, compared to the wild type HBV, there were some more recent reports of acute flare of hepatitis, and even hepatic decompensation, associated with YMDD variants. Therefore, despite the initial therapeutic success, one will need to continue to exercise caution, and patients monitored closely, particularly if we persist with treatment beyond nine months.[12]

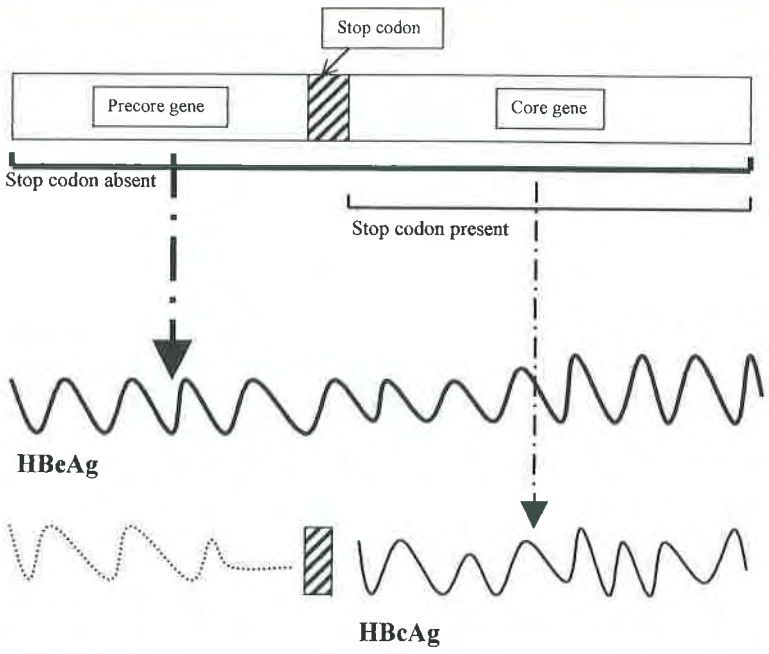
Hence, while the advent of nucleoside analogue is unarguably a breakthrough in the treatment of chronic hepatitis B, we are still far from arriving at an optimal therapeutic plan for all the patients. Perhaps, combination treatment, with varying concoction appropriate for the different subgroups of patients, as suggested by Shaw and Locarnini, will offer the final solution. [22]

Table 1: Prevalence of precore hepatitis B mutant virus (HBV mutant) in some Asian countries

Country	Prevalence of pre-core HBV mutant
China	30%
Korea	38%
Japan	54%

Translation of the precore and core regions of HBV gives rise to the final product, HBe antigen (HBeAg), as found in the patients' sera. The functional role of HBeAg is not clear but it is not essential for viral replication; whereas, translation of just the core region of HBV per se gives rise to

Fig 1: Schematic representation of translation of precore and/or core genes of hepatitis B virus without and with stop codon mutation.



hepatitis B core antigen (HBcAg) which is an essential element in, H-BV replication. A classical precore HBV mutant involves a nucleotide mutation at codon 28 of the precore region leading to the formation of a stop codon. Hence, translation of the final HBeAg product is disrupted. However, translation of HBcAg is uninterrupted, thus viral replication persists.

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URINARY TRACT INFECTION – PERSPECTIVE 2001

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INTRODUCTION

Urinary tract infection (UTI) is an extremely common clinical entity, accounting for 7 million US physician visits each year [1]. Approximately 20% of women will develop UTI sometime during their lifetime.

PATHOPHYSIOLOGY

Infectious organisms gain entry to the urinary tract through two mechanisms:

1. Ascending route - more than 95% infections occur by bacteria travelling from the urethra to the bladder or up the ureter to the kidney.

2. Hematogenous - less than 5% of UTI result from bacteremia with relatively virulent organisms such as Staphylococcus aureus.

Risk Factors

The shorter female urethra predisposes women to UTI. Women are 30 times more likely than men to develop UTI [2]. Women who are sexually active and those using diaphragm and spermicide for contraception are at increased risk. Pregnancy presents an increased risk with 4% to 10% of pregnant women and 25% to 38% of postpartum women developing bacteriuria [3]. Catheterisation increases the risk for UTIs. A single catheterisation is associated with 5% infection rate and if the catheter remains indwelling, there is a 5% increase per catheter day in the rate of UTI [4]. Incomplete emptying of the bladder in neurogenic disorders, urinary retention and obstruction allows for bacterial growth and prolonged contact with the bladder mucosa.

DIAGNOSIS

Microscopic examination of the urine is the first step in the laboratory. Pyuria is diagnosed as 10 or greater leukocytes per high-power field in centrifuged mid-stream urine.

The dipstick leukocyte esterase test is a rapid screening test for detecting pyuria. Test sensitivity is 75% to 96% and specificity is 94% to 98% for detecting more than 10 WBC/mm^3 of urine [5].

Isolation of significant numbers of bacteria in urine culture makes it possible to separate contamination from urinary tract infection. A clean-catch midstream urine is the standard collection technique. The threshold for significant bacterial count is 10^5 CFU/ml [6].

The Infectious Diseases Society of America (IDSA) consensus definition of cystitis for use in antibiotic treatment studies is (10^3 CFU/ml (sensitivity 80%, specificity 90%) and for pyelonephritis: (10^4 CFU/ml (sensitivity 90%, specificity 95%) [7].

CLASSIFICATION OF UTI

UTIs may be categorized into the following:-

1. Adult women with acute uncomplicated cystitis

2. Adults women with acute uncomplicated pyelonephritis

3. Adults with complicated urinary tract infection

4. Adults with asymptomatic bacteriuria

5. Recurrent urinary tract infection

ACUTE UNCOMPLICATED CYSTITIS (AUC)

AUC is defined as UTI limited to the bladder involving only the mucosal surface with sudden onset in a previously healthy adult.

In women, colonization of the vaginal introitus and periurethral region by Enterobactericeae is critical in the pathogensis of UTI [8]. An increase in vaginal pH due to diminished circulating levels

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Table 1: Infectious causes of acute dysuria in women

Condition	Pathogen	Urine culture CFU/ml	Symptoms and signs
Cystitis	E. coli (88%) 9 S. saprophyticus (7%) Klebsiella spp (3%) Proteus spp (2%) Enterococcus (2%) Enterobacter spp (1%)	10^2 to $\geq 10^5$	Dysuria, increased frequency and urgency, suprapubic or low back pain. Suprapubic tenderness (exam). Pyuria present
Urethritis	C. trachomatis	$< 10^2$	Vaginal discharge or bleeding Lower abdominal pain, new sexual partner. Cervicitis or vulvovaaginal herpetic lesions (exam). Pyuria present
Vaginitis	Candida sp Trichomonas vaginalis	$< 10^2$	Vaginal discharge or odour, pruritus, dyspareunia, dysuria increased frequency or urgency. Vulvovaginitis (exam).

Table 2: Treatment regimens for acute uncomplicated cystitis

Agent	Dose/frequency	Duration (days)
Trimethoprim-sulphamethoxazole	160/800mg bid	3
Trimethoprim	200mg bid	3
Norfloxacin	400mg bid	3
Ciprofloxacin	250mg bid	3
Ofloxacin	200mg bid	3
Nitrofurantoin	100mg qid	7

of estrogens in postmenopausal women is an important factor in introital and perineal colonization. The rationale is that decreased estrogen is associated with a decreased introital colonization of hydrogen peroxide-producing lactobacilli and increased colonization of E. coli leading to bacteriuria and UTI.

Women with cystitis, urethritis or vaginitis can be differentiated on the basis of their presenting symptoms and signs and findings on urinalysis and urine cultures. (Table 1)

Gupta et al studied the increasing prevalence of antimicrobial resistance among uropathogens causing AUC in 4082 women from 1992-1996. The prevalence of resistance among E. coli and all isolates was more than 20% for

ampicillin, cephalothin and trimethroprim-sulphamethoxazole in each year studied. The prevalence of resistance to nitrofurantoin, gentamicin and ciprofloxacin was less than 10% among E. coli and all isolates.

Treatment

In AUC, in young women, the current management is to omit urine cultures and utilise empiric short-course antibiotic therapy. (Table 2) The usual organisms causing acute cystitis have predictable antibiotic sensitivity. In addition, cultures are insensitive and expensive and empiric antibiotic therapy is effective. No follow-up visit or testing is recommended unless symptoms persist or recur [11].

In healthy adult, non-pregnant women with AUC a 3-day antimicrobial therapy is optimal [12]. Single-dose therapy is generally less effective especially with drugs such as amoxicillin and oral cephalosporins which are very rapidly excreted and often ineffective in patients with occult renal infection. Three day therapy with trimethoprim, trimethoprim-sulphamethoxazole and fluoroquinolones are equally effective to 7 day regimen and more effective than single-dose therapy 12. Side effects are reduced with single-dose and 3-day therapy.

Fluoroquinolones are more expensive than trimethoprim-sulphamethoxazole and trimethoprim. Initial empiric therapy with a fluoroquinolones is not recommended in order to postpone emergence of resistance to these drugs.

'Long-Count' Bacteriuria in Young Women with Acute Urinary Symptoms

Stamm et al demonstrated in young women, bacterial concentrations as low as 102 CFU/ml of urine were significantly associated with symptoms of cystitis [13]. In a study of women coming to a university health clinic for any reason, Kunin et al demonstrated that stepwise increases in bacterial counts from 10^2 to 10^5 CFU/ml were significantly associated with an increased incidence of symptoms and pyuria [14]. By incubating urine in vitro for 20 hours, they demonstrated that the 'low count' bacteriuria increased to (10^5 CFU/ml. These findings suggested that low count bacteriuria represent an early phase of UTI.

ACUTE UNCOMPLICATED PYELONEPHRITIS (AUPN)

The diagnosis of acute pyelonephritis requires a clinical presentation of acute onset fever, chills, rigors and flank pain accompanied by positive urinalysis and urine culture.

Common pathogens in AUPN include: Escherichia coli (80%), Proteus mirabilis, Klebsiella pneumoniae and Staphylococcus saprophyticus. About 20% of patient with AUPN have urine cultures < 10^5 CFU/ml and a negative gram stain of urine. Positive blood culture is obtained in 15-20% of patients [7].

Treatment

In the absence of nausea and vomiting and if the patient's illness is mild, oral antibiotic can be given in an outpatient setting. Such antibiotics include trimethoprim-sulphamethoxazole, amoxicillin-clavulanic acid or fluoroquinolones for 10-14 days.

For women with moderate to severe pyelonephritis who have high fever and leukocytosis and evidence of sepsis, admission to hospital and initiation of intravenous antibiotic therapy is indicated. Initial empiric therapy pending urine cultures include aminoglycoside with or without ampicillin, fluoroquinolone (e.g. ciprofloxacin, oxacillin) or a third generation cephalosporin (e.g. ceftriaxone, ceftazidime) with or without aminoglycoside. When the symptoms and signs improve or resolve after 48 to 72 hours, the antibiotic can be changed to an oral form [15].

Recent studies suggest that most healthy young women with AUPN will have a satisfactory outcome with 2 weeks of antimicrobial therapy [16,17]. For a highly active agent such as fluoroquinolone, a 7-day therapy maybe sufficient for mild or moderate pyelonephritis.

In a comparison of ciprofloxacin (7 day) and trimethoprim-sulphamethoxazole (TMP-SMX)

(14 days) for acute uncomplicated pyelonephritis in women. Talan et al demonstrated a higher clinical cure rates for ciprofloxacin (96%) than for TMR-SMX (83%) [18]. The clinical, bacteriologic and cost outcome analysis all showed significant health benefit in the use of ciprofloxacin especially for patients with TMP-SMX resistant uropathogens.

If fever and flank pain persist after 72 hours of therapy, cultures should be repeated and ultrasonography or computed tomography should be considered to rule out obstruction, unrecognized urologic abnormalities, perinephic or intrarenal absceses. The urine culture should be repeated 2 weeks after completion of therapy to document clearing of the infection. If the culture remains positive, a deep tissue infection is likely and a 4-to 6-week course of antibiotics is recommended.

COMPLICATED URINARY TRACT INFECTION

Complicated urinary tract infections are those that occur in a patient who has a functionally, metabolically or anatomically abnormal urinary tract (Table 3). A wide range of bacteria can cause complicated infections namely Escherichia coli, Proteus spp, Klebsiella spp, Pseudomonas spp, Serratia spp and entercococci.

For empirical therapy in patients with mild-to-moderate illness, oral medication with fluoroquinolones for 10-14 days provide a broad spectrum of activity against most expected pathogens. For initial empirical therapy in seriously ill, hospitalized patients, parenteral ampicillin plus gentamicin, ceftriaxone, piperacillin-sulbactam or imipenem-cilastatin for 14-21 days provides coverage against most expected pathogens[19].

ASYMPTOMATIC BACTERIURIA

Asymptomatic bacteriuria in nonpregnant patients presents a diagnostic and therapeutic dilemma. The diagnosis implies absence of symptoms, urinalysis without pyuria and urine culture with bacterial growth of > 10^5 CFU/ml from 2 separate clean-catch urine specimens.

Table 3: Underlying conditions predisposing to complicated urinary tract infections

- Infections in pregnancy
- Diabetes mellitus
- Neurogenic bladder
- Chronic bacterial prosatitis
- Vesico-ureteric reflux
- Structural urological anomalies
- Indwelling urethral catheter
- Urological instrumentation
- Renal transplant
- Immunosuppressive drugs
- Urinary calculi

The prevalence of asymptomatic bacteriuria in healthy women 18 to 40 years of age is approximately 5% and it increases with age to 20% or more in ambulatory elderly women [20].

There is no urgency in treating patients with asymptomatic bacteriuria. Therapy should be delayed until 2 cultures have been obtained for confirmation of bacteriuria. Asymptomatic bacteriuria in elderly patients need not be treated as it is a benign disease and antimicrobial treatment carries the risk of drug toxicity.

Since screening and treatment of asymptomatic bacteriuria had been shown to prevent pyelonephritis, treatment with an appropriate antibiotic is recommended for all pregnant women with significant bacteriuria.

Treatment of asymptomatic bacteriuria is beneficial in:

1. clean intermittent catheterization
2. abnormal urinary tract eg congenital polycystic, medullary sponge kidney or nonfunctioning segments of the kidney
3. acquired abnormalities eg obstruction, renal calculi or papillary necrosis

4. prior to urinary instrumentation or manipulation

5. underlying medical problems that may complicate the treatment course of a subsequent UTI eg diabetes, mechanical prosthesis and immunosuppression

RECURRENT URINARY TRACT INFECTION

The most likely causes of a relapse after therapy for symptomatic urinary tract infection:

1) renal involvement

2) a structural abnormality of urinary tract (eg calculi)

3) chronic bacterial prostatitis

People who relapse after a short course therapy should be considered for a 2-week course. Turck et al demonstrated that a 6-week course of therapy resulted in a higher cure rate than a 2-week course in patients who relapsed after a 2-week therapy[21]. If relapse occurs after a 6-week course, therapy lasting 6 months or even longer may be considered.

Reinfection of the urinary tract can be divided into 2 groups:

1) those with relatively infrequent reinfection (less than 2 per year) and

2) those who develop frequent reinfection

With infrequent reinfections, each episode can be treated with short course of antibiotics based on past culture results. Many patients with frequent reinfections are middle-aged or elderly women with lower urinary tract infections. Symptomatic reinfections are associated with sexual intercourse in some women. The patient may benefit from postcoital prophylaxis with a single dose of TMP-SMX, cephalexin, nitrofurantoin or ciprofloxacin[22]. Voiding immediately after intercourse may help prevent reinfections.

In other patients with frequent symptomatic reinfections with no apparent precipitating event, 6 month daily chemoprophylaxis may be instituted. Antibiotic choices include trimethoprim, TMP-SMX, nitrofurantoin, norfloxacin and cephalexin [23].

Another approach to preventing reinfections in postmenopausal women with frequent recurrent UTI is the use of oral or intravaginal estrogens. Estrogen therapy decreases the vaginal pH, increases colonization of the vagina with lactobacilli and decreases colonization with Enterobactericeae [24].

CONCLUSION

There is abundant new research in urinary tract infections which will provide insights to maximise therapeutic benefits while reducing costs and the incidence of adverse reactions.

The clinical presentation, together with the results of diagnostic studies helps to guide the antibiotic choice for treatment of UTI.

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The Singapore Family Physician

TEST YOUR EYE-Q (NO. 13)
A Superior Visual Field Defect in a Middle-aged Woman

Au Eong KG, Mathur R***

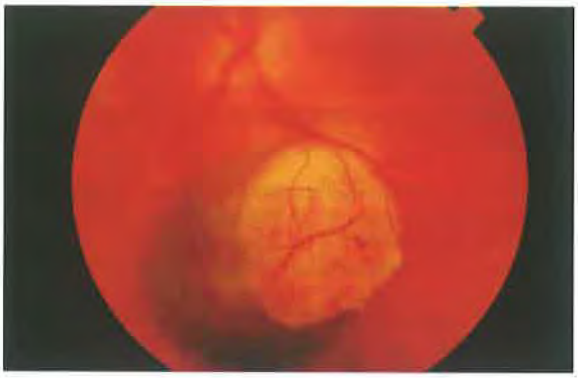

Figure 1. Colour photograph of the left eye showing the inferior part of the ocular fundus below the optic disc.

A 40-year-old woman complained of a superior visual field disturbance and decreased vision in her left eye for several weeks. Her visual acuity was 6/36 in the left eye. Figure I is a photograph of her left eye showing the ocular fundus inferior to the optic disc. Her right eye was normal.

Questions

1. What does figure I show?
2. What is the likely diagnosis?
3. What is the cause of the patient's symptoms?
4. What are the consequences if this condition is untreated?
5. What treatment modalities are available for this condition?

Answers

1. Figure 1 shows an elevated (detached) retina with a whitish mushroom-shaped mass just beneath the retina. The mass arises from the choroid. There are several small haemorrhages on the surface of the mass.
2. The diagnosis is a choroidal melanoma with secondary (exudative) retinal detachment. The tumour arises from the choroid. It has broken through Bruch's membrane and caused an exudative retinal detachment. Primary cancer of the eye is rare. Between 1968 and 1995, the average annual age standardised incidences of eye cancer for male and female Singapore residents were 1.89 and 1.81 per million respectively.' The most common eye cancer among persons 15 years or older was malignant melanoma while the most common cancer among persons younger than 15 years was retinoblastoma.
3. The patient's superior visual field defect is due to the inferior exudative retinal detachment. This is because the inferior part of the retina is responsible for the superior visual field. Her impaired visual acuity is due to a shallow detachment of the fovea (not shown in figure).
4. The choroidal melanoma, being a malignant tumour, can cause local invasion as well as distant metastasis. The most common site for metastasis is the liver.
5. Treatment options include enucleation, radiation therapy and local resection. The overall survival rates for choroidal melanoma following enucleation is about 75% at 5 years, 65% at 10 years, and 60% at 15 years.

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2. Legend for Figure I

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PRESENTATION ON THE MANUSCRIPT

The Whole Paper

- Normally the text should not exceed 2000 words and the number of illustrations should not exceed eight.
- Type throughout in upper and lower case using double spacing, with three centimetre margins all round. Number every page on the upper right hand corner, beginning with the title page as 1.
- Make all necessary corrections before submitting the final typescript. Headings and subheadings may be used in the text. Indicate the former by capitals, the latter in upper and lower case underlined.
- Arrange the manuscript in this order: (1) title page (2) summary (3) text (4) references (5) tables and (6) illustrations.
- Send 3 copies of all elements of the article: summary text, references, tables and illustrations. The author should retain a personal copy.
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- The summary should state the purpose of and give the main argument or findings.
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The text should have the following sequence:

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  Drugs must be referred to generically; all the usual trade names may be included in parentheses.

  Dosages should be quoted in metric units.

  Laboratory values should be in SI units with traditional unit in parentheses.

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