MARCH 2010 • VOL. 2 • NO. 2

Journal of THE SOCIETY OF PHYSICIANS OF HONG KONG

ISSN 2072-4209

- **Sleep Apnoea and Arrthymias**
  Dr Lam Tse Fun, Cathy (林紫芬醫生)
- **The Use of Topical and Oral Drug Therapies in Acne Vulgaris**
  Dr Chan Pui Yiu, Nicola (陳珮瑤醫生)
- **Infant Feeding in the First Year – Breastfeeding, Infant Formula, Nutritional Additives and Special Formula (Part I)**
  Dr Lam Cheung Cheung, Barbara (藍章翔醫生)

香港內科學會
THE SOCIETY OF PHYSICIANS OF HONG KONG

www.soPHYSICIANSHK.org

Visit the web site for our regular CME programmes for doctors

Rapidly reduces acne lesions from the first week*

Epiduo™ Gel

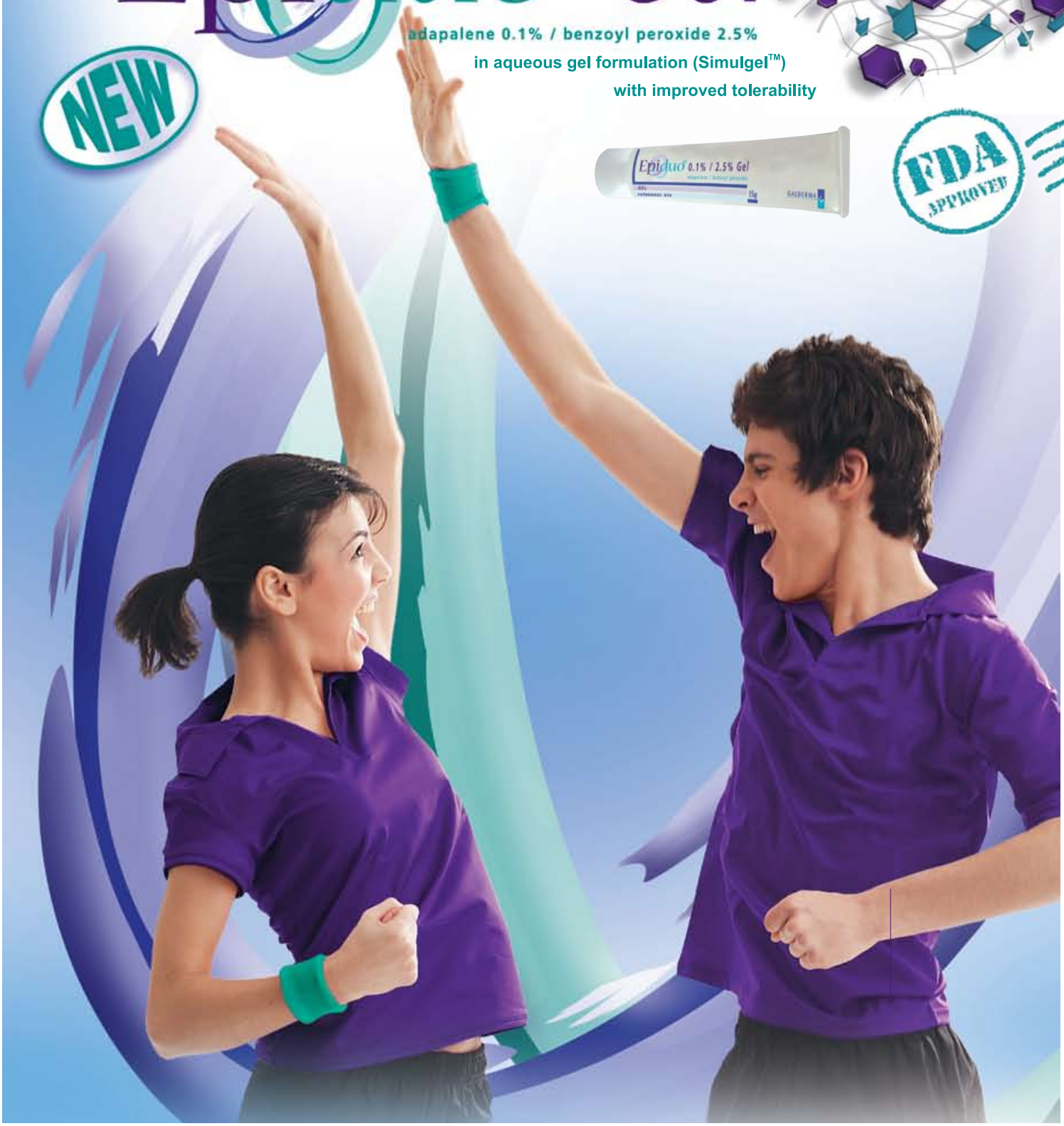
adapalene 0.1% / benzoyl peroxide 2.5%

in aqueous gel formulation (Simulgel™)

with improved tolerability

NEW

FDA APPROVED



Epiduo™ removes the risks of promoting antibiotic resistance

* Thiboutot DM, Weiss J, et al; for the Adapalene-BPO Study Group. J Am Acad Dermatol. 2007;57(5);791-9.

Full prescription information is available on request

GALDERMA
Committed to the future of dermatology

Galderma Hong Kong Limited
Room 1401, 14th Floor, Phase I, Ming An Plaza,
8 Sunning Road, Causeway Bay, Hong Kong.
Tel: (852) 2824 0333 Fax: (852) 2827 7760

EPI-AD001-0210

香港內科學會
THE SOCIETY OF PHYSICIANS OF HONG KONG

www.soPHYSICIANSHK.org

Journal of
THE SOCIETY OF PHYSICIANS OF HONG KONG

MARCH 2010 • Vol. 2 • No. 2

EXECUTIVE COMMITTEE

PRESIDENT
Dr Lam Tat Chung, Paul
林達聰醫生

VICE PRESIDENT
Dr Tsang Wah Tak, Kenneth
曾華德醫生

HON. SECRETARY
Dr Shiu Cho Tak, Wesely
邵祖德醫生

HON. TREASURER
Dr Lam How Mo, Ignatius
林孝武醫生

CHIEF EDITOR
Dr Lau Chu Pak
劉柱柏醫生

EDITORS
Dr Chan Chun Kwong, Jane
陳真光醫生
Dr Chan Hin Lee, Henry
陳衍里醫生
Dr Chan Kwok Wing, Fredriech
陳國榮醫生
Dr Chan Pui Yiu, Nicola
陳珮瑤醫生
Dr Chan Tak Hin
陳德顯醫生
Dr Chen Yi Tin
陳以天醫生
Dr Lam Cheung Cheung, Barbara
藍章翔醫生
Dr Lam Tat Chung, Paul
林達聰醫生
Dr Lam Tse Fun, Cathy
林紫芬醫生
Dr Leung Wai Keung
梁偉強醫生
Dr Li Siu Lung, Steven
李少隆醫生
Dr Shea Tat Ming, Paul
佘達明醫生
Dr Shiu Cho Tak ,Wesely
邵祖德醫生
Dr Tam Kwok Kuen, Vincent
譚國權醫生
Dr Tsang Wah Tak, Kenneth
曾華德醫生

CMPMedica
United Business Media

Editorial Office:
CMPMedica Pacific Ltd
9th Floor, CNT Tower, 338 Hennessy Road, Wan Chai, Hong Kong
T +852 2559 5888 F +852 2559 6910

Advertising Enquiries:
Ms Chloe Wong
T +852 2155 8557
e-mail: chloe.wong@asia.cmpmedica.com

© 2010 The Society of Physicians of Hong Kong. All rights reserved. No part of this publication may be reproduced in any language, stored in or introduced into a retrieval system, or transmitted, in any form or by any means (electronic, mechanical, photocopying, recording or otherwise), without the written consent of the copyright owner. Permission to reprint must be obtained from the publisher. Advertisements are subject to editorial acceptance and have no influence on editorial content or presentation. The Society of Physicians of Hong Kong does not guarantee, directly or indirectly, the quality or efficacy of any product or service described in the advertisements or other material which is commercial in nature.

Editorial

In this issue of the Journal we are pleased to feature the article in Paediatrics by Dr Barbara Lam. Paediatrics is an integral and important part of the work of physicians. Without healthy children, we cannot have healthy adults. The Society has always included Paediatrics as one of the important areas of our work. We hope in future we will have more activities in this area, and there will be more Paediatricians participating and contributing to the work of the Society.

Dr Lam Tat Chung, Paul
林達聰醫生

FRCP, FHKAM (Medicine),
FHKAM (Psychiatry)
President

Dr Lau Chu Pak
劉柱柏醫生

FRCP, MD, FHKAM (Medicine)
Chief Editor

CONTENTS

15 **Sleep Apnoea and Arrthymias**
Dr Lam Tse Fun, Cathy (林紫芬醫生)

19 **The Use of Topical and Oral Drug Therapies in Acne Vulgaris**
Dr Chan Pui Yiu, Nicola (陳珮瑤醫生)

23 **Infant Feeding in the First Year – Breastfeeding, Infant Formula, Nutritional Additives and Special Formula (Part I)**
Dr Lam Cheung Cheung, Barbara (藍章翔醫生)

Sleep Apnoea and Arrhythmias

Dr Lam Tse Fan, Cathy
(林紫芬醫生)

MBBS (HK), FHKCP, FHKAM (Med), FRCP (Edinburgh, London)

Specialist in Cardiology

Honorary Clinical Assistant Professor, Department of Medicine & Therapeutics, Chinese University of Hong Kong

Key words:
Sleep apnoea (睡眠窒息), arrhythmia (心率不正)

Sleep-related breathing disorder is a common clinical problem that is often underdiagnosed. Two percent of women and 4% of men in the middle-aged work force met the minimal diagnostic criteria for the sleep apnoea syndrome.[1]

Case 1

A 29-year-old non-smoking gentleman was referred for management of hypertension. He had had tonsillectomy in his early teens, and has adopted an inactive lifestyle over the last few years. He started to gain weight progressively, putting on >20 kg in 8 years, mainly related to adopting a diet of fast food high in fat and carbohydrates.

He experienced frequent headache and dizziness in the morning. He had difficulty concentrating in work due to headache. He experienced occasional fatigue and daytime somnolence.

Physical examination showed a young gentleman of medium built with body weight of 80 kg and a body mass index (BMI) of 27.7. His blood pressure (BP) was 148/110 mm Hg with a regular sinus rhythm of 68 bpm. Examination of the cardiovascular, respiratory and abdominal systems was unrevealing.

An angiotensin receptor blocker was started for BP control. With the strong clinical suspicion of significant sleep apnoea, polysomnography was performed. The study revealed 28 episodes of apnoea/hypopnoea per hour, with a maximum duration of 87 seconds. There were 26 episodes of oxygen desaturation per hour, and the minimum SpO_2 was 74%. (Figure 1)

After assessment by ENT and respiratory specialists, the patient was diagnosed to have moderate obstructive sleep apnoea (OSA), with contributing factors including overweight, macroglossia and teeth overjet. He was recommended to have nasal continuous positive airway pressure (CPAP) therapy.

He was reassessed after 3 months. His BP was well controlled in the range of 120–130/75–85 mm Hg. Symptoms of morning headache improved significantly. However, compliance with and efficacy of nasal CPAP were limited by unintentional removal of mask during sleep.

Case 2

The patient was a 79-year-old gentleman, who was an ex-smoker with a long-standing history of hypertension, bilateral carotid stenosis with recurrent cerebrovascular accidents, coronary artery disease, renal impairment and peripheral vascular disease. He became chair-bound and aphasic after the second stroke 6 years ago. His medications included acetyl salicylic acid, β-blocker for ischaemic heart disease, and multiple antihypertensives.

He was hospitalized for management of urinary sepsis. During hospitalization, he was witnessed to have frequent hypopnoea/apnoea episodes during sleep. Telemetric monitoring showed frequent atrial and ventricular ectopics, sinus tachycardia with first degree and Wenckebach phenomenon, and nonsustained and sustained runs of paroxysmal atrial arrhythmias/fibrillation. There was one documented conduction pause of 3.6 seconds during underlying atrial arrhythmia. (Figure 2)

Table 1. Signs, symptoms and risk factors of obstructive versus central sleep apnoea

Obstructive sleep apnoea	Central sleep apnoea
Disruptive snoring	Congestive heart failure
Witnessed apnoea or gasping	Paroxysmal nocturnal dyspnoea
Obesity and/or enlarged neck size	Witnessed apnoea
Hypersomnolence (not common in children or in heart failure)	Fatigue/hypersomnolence
Other signs and symptoms include male gender, crowded-appearing pharyngeal airway, increased blood pressure, morning headache, sexual dysfunction, behavioral changes (especially in children)	Other signs and symptoms include male gender, older age, mitral regurgitation, atrial fibrillation, Cheyne-Stokes respiration while awake, periodic breathing during exercise, hyperventilation with hypocapnia

These two cases represent patients commonly seen in medical wards and daily practice. They have different types of sleep-related breathing disorders and associated medical comorbidities.

Normal Physiology of Sleeping

Sleep is a state of partial unconsciousness, characterized by inactivity of nearly all voluntary muscles and suspension of most sensory and motor activity.

Sleep is a dynamic and complex process divided into two broad types: rapid eye movement (REM) and non-rapid eye movement (non-REM) sleep. During REM sleep, parasympthetic tone decreases while sympathetic tone varies. Surges of sympathetic activity and decreased baroreceptor regulation were postulated to account for the higher incidence of nonfatal myocardial infarction (MI), implanted defibrillator discharges, and sudden cardiac death (SCD) at night. Non-REM sleep is further divided into the three stages of N1,N2 and N3 by the American Academy of Sleep Medicine. The overall parasympathetic tone increases and sympathetic tone decreases in non-REM sleep with diminished arousability.

Normal rhythm changes during sleep in healthy subjects include sinus bradycardia and pauses of up to 2 seconds. It was reported that sinus bradycardia at a rate <40 bpm could be found in 24% of normal healthy adults. First-degree atrioventricular block and Wenckebach block are not uncommon in healthy subjects with no apparent heart disease.[2]

Sleep-related Breathing Disorders

Sleep apnoea is associated with cardiovascular diseases (CVDs) including systemic hypertension, congestive heart failure, myocardial ischaemia, arrhythmia and SCD. Evidence on the direct relationship between mortality and severity of sleep apnoea remains diversified. As various CVDs and sleep apnoea share similar clinical factors, it is difficult to establish a direct causal relationship.

Definitions

Sleep-related breathing disorders can be obstructive or central. (Table 1) OSA results from partial or complete airway obstruction caused by collapse of the pharyngeal airway. An obstructive apnoea episode is defined as a 10-second pause in respiration associated with ongoing ventilatory effort, with an associated fall in oxygen saturation or arousal. A diagnosis of OSA syndrome is accepted when a patient has an apnoea-hypopnoea index (AHI; number of apnoeas and hypopnoeas per hour of sleep) of 5 and symptoms of excessive daytime sleepiness.[3]

Central sleep apnoea (CSA) is characterized by repetitive cessation of ventilation during sleep resulting from loss of ventilatory drive. A central apnoea episode is a 10-second pause in ventilation with no associated respiratory effort. CSA syndrome is present when a patient has five episodes of central apnoea per hour of sleep and the associated symptoms of disrupted sleep (frequent arousals) and/or hypersomnolence during the day.[3]

Central apnoeas may also occur in an individual with obstructive apnoeas. Although there is no absolute standard in this regard, studies of patients with CSA require that 50% of all events be central, with 80% of central events often being required in most clinical trials.

Figure 1. One example of apnoea associated with nonsustained atrial arrhythmia during hypoxia

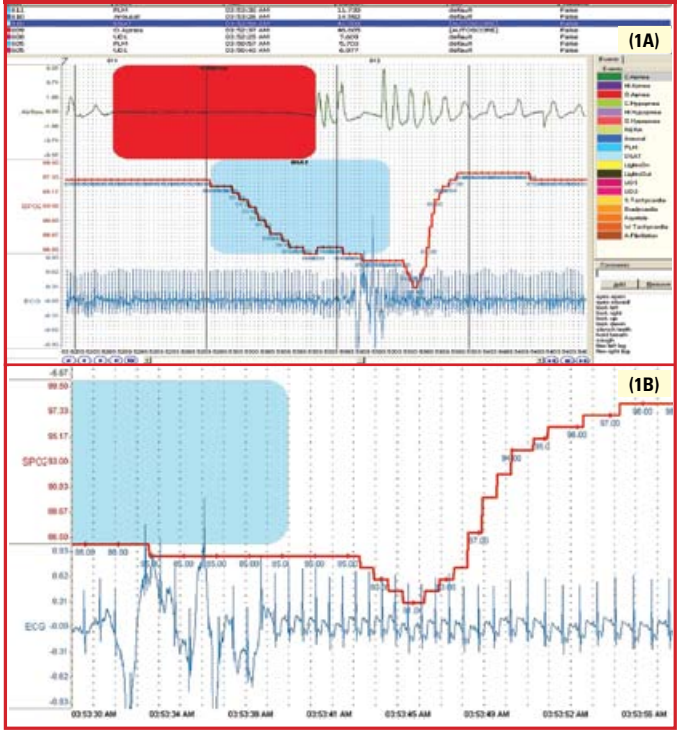
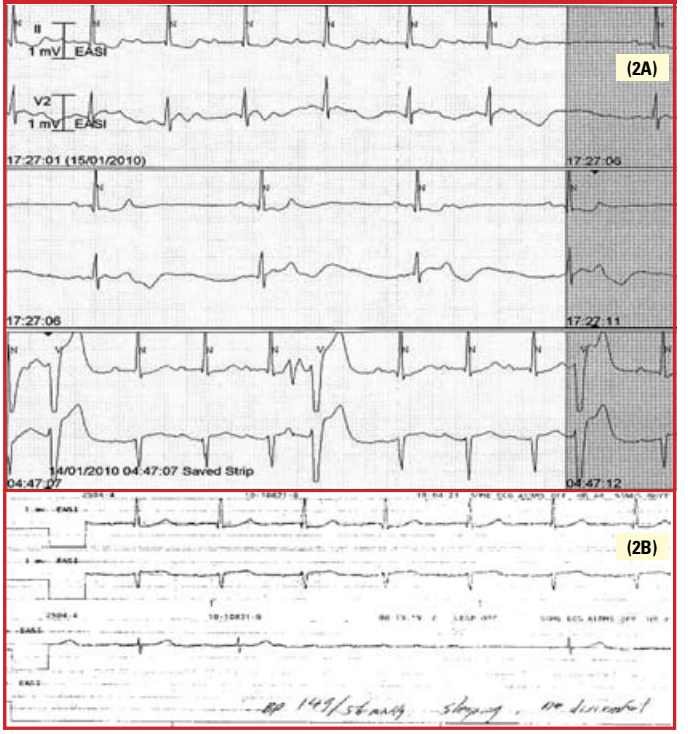


Figure 2. Documented arrhythmia and conduction pause up to 3.6 seconds



Arrhythmia and Sleep Apnoea

Nocturnal arrhythmias occur in up to 50% of OSA patients.[4] Cardiac arrhythmias associated with sleep disorders include sinus bradycardias and pause, sinus tachycardia, heart block, junctional rhythm, premature ventricular contractions and complex ventricular arrhythmia, supraventricular tachycardia, atrial fibrillation (AF), and sudden arrhythmic death.

Recent data from the Sleep Heart Health Study, comparing 228 subjects with sleep-disordered breathing (SDB) and 338 subjects without SDB, suggested that those with severe SDB had a two- to four-fold higher risk of nocturnal complex arrhythmias.[5]

Atrial Fibrillation

Patients with AF are likely to have OSA.[6,7] In individuals <65 years of age, OSA strongly predicts the incidence of AF within about 5 years of its diagnosis, and the degree of nocturnal oxygen desaturation independently correlates with the risk of incident AF.[8]

Hypoxaemia, sympathetic activation, pressor surges, transmural pressure changes and systemic inflammation that occur in OSA may be the mechanisms that predispose to the development of AF.

Ventricular Arrhythmias

Ventricular arrhythmias, primarily premature ventricular contractions, have been reported in up to 66% of patients with sleep apnoea, which is significantly higher than the rates reported in persons without sleep apnoea (0% to 12%).[9,10]

Recent data suggest that in heart failure patients with OSA who are in normal sinus rhythm, ventricular ectopic beats occur more frequently during the apnoeic phases than during hyperpnoea.[11] This is in contrast to patients with CSA, in whom ventricular ectopy was noted to occur more frequently during hyperpnoeas than apnoeas.

A higher frequency of ventricular ectopies coupled with higher sympathetic activity caused by longer apnoea episodes in REM sleep may be one reason for increased nocturnal death in apnoeic patients.[12]

Sudden Cardiac Death

An undiagnosed sleep apnoea syndrome was found to be a contributing pathogenetic factor in unexpected sudden postoperative death.[13] Twenty percent of MIs and 15% of SCDs occur between midnight and 6:00 am.[14] The risk of nocturnal SCD may be especially high in patients with coronary disease confounded by apnoea, heart failure, recent MI, pause-dependent Torsade de Pointes, and near-miss victims or the siblings of sudden infant death syndrome (SIDS). In non-REM or slow-wave sleep, hypotension may lead to malperfusion of the heart and brain as a result of a lowered pressure gradient through stenosed vessels.[15,16]

Management of Arrhythmia in Sleep Apnoea

Sleep apnoea remains a common clinical problem, with adverse cardiovascular implications, yet few treatment options.

Continuous Positive Airway Pressure

With contributing factors such as obesity and upper airway obstruction identified and ameliorated, the cornerstone of therapy for OSA is CPAP.

In a meta-analysis involving 1,718 subjects, CPAP showed significant improvements in symptoms of sleepiness, quality of life and cognitive function in people with moderate and severe OSA.[17] BPs were lower with CPAP compared with control. CPAP significantly reduced the AHI and improved sleep efficiency and minimum oxygen saturation

In the absence of structural heart abnormalities, bradyarrhythmias or heart block – both of which occur during apnoeic periods – may be treated effectively with CPAP.

Untreated OSA in patients after successful cardioversion for AF is associated with an 82% risk for recurrence of AF within 1 year, about double the risk seen in effectively treated OSA patients after cardioversion.[18]

CPAP resulted in a 58% reduction in the frequency of ventricular premature complexes during sleep, and a parallel reduction in nocturnal urinary norepinephrine concentrations.[19]

Patient education and improvement of hardware designs will improve response and tolerance to therapy. However, even with good compliance, CSA may be alleviated but not abolished.

Pacing in OSA

There has been some enthusiasm about atrial pacing in the management of sleep apnoea with and without documented daytime bradyarrhythmia. Atrial overdrive pacing was reported to significantly reduce the number of episodes of CSA or OSA and the number of arousals, and increase arterial oxyhaemoglobin saturation without reducing the total sleep time. These variables returned to baseline values when the pacemaker was turned off.[20] However, the finding has not been replicated in subsequent investigations.

In a meta-analysis of 10 studies, atrial overdrive pacing reduced the AHI and increased minimum SaO_2 significantly only in the subgroup of patients who presented predominantly with CSA syndrome.[21]

Drug Treatment in OSA

Pharmacological treatment of sleep apnoea has been evaluated. Small studies have reported positive effects of certain agents on short-term outcome. Drugs evaluated include fluticasone, mirtazapine, physostigmine and nasal lubricant. Certain agents have been shown to reduce the AHI in largely unselected populations with OSA of between 24% and 45%. There is insufficient evidence to recommend the use of drug therapy in the treatment of OSA.[22]

The efficacy and utilization of antiarrhythmic drugs in the setting of sleep-related or bradycardia-induced arrhythmia is usually limited by aggravation of bradyarrhythmia.

Conclusion

Sleep is associated with a broad spectrum of CVDs and arrhythmias. Awareness of symptoms and comorbidities, correct diagnosis and prompt treatment would improve clinical outcome.

A complete list of references can be downloaded from www.SOPHYSICIANSHK.org

A WORLD OF EXPERIENCE MAKES THE DIFFERENCE

Criteria	The world's First and Only FDA approved pneumococcal conjugate vaccine[1]	
Epidemiology	• Serotype coverage for invasive disease strains in Hong Kong is **89.7%**[2]	✓
Immunogenicity	• Antibody responses lead to documented effectiveness[3,4]	✓
Efficacy	• Proven efficacy against IPD, pneumonia, and acute otitis media in large-scale clinical trials[3,5-8]	✓
Effectiveness	• Documented real-world effectiveness in: Meningitis[9] Pneumonia[11] Sepsis[10] Acute otitis media[12] Bacteremia[10] Reduction in antibiotic resistance[13] • Herd effect—documented decrease in IPD in unvaccinated populations after routine childhood immunization programs[14-18] • Serotype coverage for nasopharyngeal strains in Hong Kong is **66.1%**[2]	✓
Safety	• Well-documented safety profile[4,19] • Post-licensure safety studies with more than 157,000 children[4] • More than 200 million doses distributed worldwide since 2000[20] • Established protein carrier - CRM_{197} used for more than 20 years in various vaccines[21]	✓

References: 1. User Fee Billable Biologic Products and Potencies Approved under Section 351 of the PHS Act available at http://www.fda.gov/AboutFDA/Centersoffices/CBER/ucm122936.htm accessed on Aug, 31 2009. **2.** Ho PL. Serotype distribution and antimicrobial resistance patterns of nasopharyngeal and invasive Streptococcus pneumoniae isolates in Hong Kong children. Vaccine. 2004;22:3334-3339. **3.** Black S, Shinefield H, Fireman B, et al; Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J. 2000;19:187-195. **4.** Black S, Shinefield H, Baxter R, et al. Postlicensure surveillance for pneumococcal invasive disease after use of heptavalent pneumococcal conjugate vaccine in Northern California Kaiser Permanente. Pediatr Infect Dis J. 2004;23:485-489. **5.** Eskola J, Kilpi T, Palmu A, et al; Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med. 2001;344:403-409. **6.** Cutts FT, Zaman SMA, Enwere G, et al; Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet. 2005;365:1139-1146. **7.** Black SB, Shinefield HR, Ling S, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. Pediatr Infect Dis J. 2002;21:810-815. **8.** Klugman KP, Madhi SA, Huebner RE, et al; A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med. 2003;349:1341-1348. **9.** Dubos F, Marechal I, Husson MO, et al; Decline in pneumococcal meningitis after the introduction of the heptavalent-pneumococcal conjugate vaccine in northern France. Arch Dis Child. 2007;92:1009-1012. **10.** Benito-Fernandez J. Pneumococcal Bacteremia among infants with fever without known source before and after introduction of pneumococcal conjugate vaccine in the Basque country of Spain. The Pediatric Infectious Disease Journal. 2007;26:667-671. **11.** Grijalva CG, Nuorti JP, Arbogast PG, et al. Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. Lancet. 2007;369:1179-1186. **12.** Zhou F, Shefer A, et al. Trends in Acute Otitis Media-Related Health Care Utilization by Privately Insured Young Children in the United States, Pediatrics. 2008;121:253-260. **13.** Kyaw MH, Lynfield R, Schaffner W, et al; Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant Streptococcus pneumoniae. N Engl J Med. 2006; 354:1455-1463. **14.** Kellner JD, Church DL, MacDonald J, et al. Progress in the prevention of pneumococcal infection. CMAJ. 2005;173:1149-1151. **15.** Poehling KA, Talbot TR, Griffin MR, et al. Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. JAMA. 2006;295:1668-1674. **16.** Centers for Disease Control and Prevention. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease—United States, 1998–2003. MMWR. 2005;54:893-897. **17.** Whitney CG, Farley MM, Hadler J, et al; Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med. 2003;348:1737-1746. **18.** Lexau CA, Lynfield R, Danila R, et al; Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. JAMA. 2005;294:2043-2051. **19.** Black S, Shinefield H. Safety and efficacy of the seven-valent pneumococcal conjugate vaccine: evidence from Northern California. Eur J Pediatr. 2002;161(suppl 2):S127-S131. **20.** World Health Organization. Worldwide progress in introducing pneumococcal conjugate vaccine, 2000-2008. Wkly Epidemiol Rec. 2008;83:388-392. **21.** Anderson P. Antibody Responses to Haemophilus influenzae Type b and Diphtheria Toxin Induced by Conjugates of Obligosaccharides of the Type b Capsule with the Nontoxic Protein CRM_{197}. Infection and Immunity. 1983;39:233-238.

Balancing Risk information: The decision to administer PREVENAR should be based on its efficacy in preventing invasive pneumococcal disease (IPD). PREVENAR does not provide 100% protection against vaccine serotypes or protect against nonvaccine serotypes. In clinical studies (n=18,168), the most frequently reported adverse events included injection site reactions, fever (≥38°C/100.4°F), irritability, drowsiness, restless sleep, decreased appetite, vomiting, diarrhea, and rash. Risks are associated with all vaccines, including PREVENAR. Hypersensitivity to any vaccine component, including diphtheria toxoid, is a contraindication to its use.

ABBREVIATED PRESCRIBING INFORMATION

Product Name: Pneumococcal conjugate vaccine, 7-valent

Composition: A sterile solution of saccharides of the capsular antigen of *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F individually conjugated to protein carrier CRM_{197}.

Indication: Indicated for active immunisation of infants and children from 6 weeks to 9 years of age against invasive disease, pneumonia and otitis media caused by *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F.

Dosage and Administration: For intramuscular use only. Do not mix with other vaccines or products in the same syringe.

Vaccination Schedule: For infants the primary vaccination schedule consists of three doses at least 4 weeks apart beginning at 6 to 8 weeks of age with an interval of at least 4 weeks between doses. A single booster injection should be given in the second year, at least 2 months after the primary series. (Table 1)

Table 1

Vaccination schedule for previously unvaccinated children ≥ 7 months of age	
Age at first dose	Total number of 0.5 mL doses
7-11 months of age	3
12-23 months of age	2
>24 months of age	1

Previously unvaccinated infants from 7 to 11 months of age should receive two doses approximately 1 month apart, followed by a third dose in their second year, at least 2 months after the second dose.

Previously unvaccinated children from 12 to 23 months of age should receive two doses at least 2 months apart.

Previously unvaccinated children who are 24 months of age or older should receive a single dose. (Table 2)

Table 2

Vaccination schedule for infants				
Dose:	Dose 1	Dose 2	Dose 3	Dose 4
Age at Dose:	2 months	4 months	6 months	12-15 months

Contraindications: Hypersensitivity to any component of the vaccine, including diphtheria toxoid. The occurrence of an allergic reaction, or anaphylactoid reaction following prior administration of Prevenar.

Precautions: The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their aetiology. Prevenar will not protect against *Streptococcus pneumoniae* serotypes other than those included in the vaccine, nor against other micro-organisms that cause invasive disease or otitis media. Prevenar, as with any intramuscular injection, should be given with caution to infants or children with thrombocytopenia or any coagulation disorder or to those receiving anticoagulant therapy. Appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic event following the administration of the vaccine. Immunisation with Prevenar does not substitute for routine diphtheria immunisation. Children with impaired immune responsiveness may have reduced antibody response to active immunisation. Prophylactic antipyretic medication is recommended for all children receiving Prevenar simultaneously with vaccines containing whole cell pertussis because of a higher rate of febrile reactions and for children with seizure disorders or with a prior history of febrile seizures. Antipyretic treatment should be initiated whenever warranted or when the temperature rises above 39°C. Prevenar is not recommended for use in adult populations. The use of Prevenar does not replace the use of 23-valent pneumococcal polysaccharide vaccine in children, 24 months of age or older, with conditions such as sickle cell disease, asplenia, HIV infection, chronic illness, or who are immunocompromised, and therefore at higher risk for invasive disease due to *S. pneumoniae*.

Drug Interactions: During clinical studies, Prevenar was administered simultaneously with diphtheria-tetanus-pertussis vaccine (DTP) or diphtheria-tetanus-acellular pertussis vaccine (DTPa), *Haemophilus Influenzae* type B vaccine (Hib), oral polio vaccine (OPV) or inactivated polio vaccine (IPV), hepatitis B vaccines, measles-mumps-rubella vaccine (MMR) and varicella vaccine. Thus, the safety experience with Prevenar reflects the use of this product as part of the routine immunisation schedule. In some studies, differences in antibody response to some of the antigens have been inconsistently found, however, this is not anticipated to be of any clinical relevance.

Side Effects: Injection site erythema, induration/swelling, pain/tenderness, diarrhea, vomiting, fever ≥ 38°C, decreased appetite, drowsiness, restless sleep, irritability and rash.

Supplied: 1 single dose pre-filled syringe. Prevenar should be stored at +2°C to +8°C. **DO NOT FREEZE.** Discard if the vaccine has been frozen.

API_Jun2009(P662011_1)

Full Prescribing Information available upon request.

Prevenar®
Pneumococcal Conjugate Vaccine, 7-valent

CONFIDENCE IN EXPERIENCE

Pfizer Corporation Hong Kong Limited
16/F, Stanhope House, 738 King's Road, North Point, Hong Kong
Tel: (852) 2811 9711 Fax: (852) 2579 0599 Website: www.pfizer.com.hk

PRV-PM-035B-AUG-09

The Use of Topical and Oral Drug Therapies in Acne Vulgaris

Dr Chan Pui Yiu, Nicola
(陳珮瑤醫生)

MBBChir (Cantab), MRCP (UK), FHKCP, FHKAM(Med)

Specialist in Dermatology

Honorary Clinical Assistant Professor, Department of Medicine, University of Hong Kong

Key words:
Acne vulgaris (痤瘡), retinoids (維生素A衍生物), antibiotics resistance (抗生素之抗藥性)

Acne vulgaris is a chronic inflammatory condition of the pilosebaceous unit of the skin, characterized by open and closed comedones and inflammatory lesions including papules, pustules and nodules. It is one of the commonest dermatological conditions encountered in clinical practice. In a local epidemiological study, the prevalence of active facial acne among teenagers aged 15 to 25 years was 91.3%.[1]

"An increasing number of acne patients who present to clinics are adults"

Acne is often wrongly dismissed as a self-limiting condition affecting mainly teenagers. The recently published update from the Global Alliance to Improve Outcomes in Acne Group redefined acne as a chronic disorder, often characterized by a prolonged course with recurrences, and a negative psychological and social impact that affects the patient's quality of life.[2] Indeed, an increasing number of acne patients who present to clinics are adults, especially females. Severe inflammatory acne can often lead to scarring. Thus, early intervention is paramount.

The pathogenesis of acne is multifactorial, which includes excessive sebum production due to an over response to androgens or excessive androgen secretion; hypercornification and blockage of pilosebaceous ducts; *Propionibacterium acnes (P acnes)* proliferation and cutaneous inflammatory response. Essentially, treatment of acne aims to target all these factors, and is tailored individually according to the type of acne, the severity of disease and its psychological impact. Although there has been much recent interest and research in the use of laser and light sources for the treatment of acne, topical and oral drug therapies remain the gold standard.

Topical Therapies

Topical therapies are the mainstay in the control of mild to moderate acne. They are used either alone or in combination with oral drugs to control acute lesions and as maintenance therapy to prevent recurrences. Topical agents commonly employed include benzoyl peroxide, azelaic acid, antibiotics and retinoids. Many are available in a variety of delivery systems. Gels and solutions are suited to oily skin, whereas creams and ointments are more suited to dry and easily irritated skin.

Benzoyl peroxide is an oxidizing agent which is bactericidal against *P acnes*. It is also mildly comedolytic and targets both inflammatory and noninflammatory lesions. It is available in concentrations of 2.5% to 10%. They are all effective, but irritation and dryness can be a problem with a higher concentration. An advantage of benzoyl peroxide is that drug resistance with *P acne* is not an issue because of its mechanism of action.

Azelaic acid is a naturally occurring chemical belonging to the class of dicarboxylic acids, which possesses comedolytic and antibacterial properties. It has an additional effect of lightening postinflammatory hyperpigmentation by reducing melanin production through the inhibition of tyrosinase.

Topical antibiotics, such as erythromycin, clindamycin and tetracycline, have been shown effective and well

tolerated in many trials. They reduce the number of *P acnes* as well as the inflammatory response. However, drug resistance is a concern, and the use of topical antibiotics as a single therapeutic agent should therefore not be encouraged.

The effectiveness of topical retinoids in the treatment of acne is well recognized. They target all pathogenic factors of acne without inducing bacterial drug resistance, and act on both non-inflammatory and inflammatory lesions. Current guidelines strongly advocate the use of topical retinoids as a first-line therapy for virtually all but the most severe forms of acne.[2] They are useful as monotherapy for mild comedonal acne. When used as initial therapy, topical retinoids significantly speed up the resolution of acne lesions. Since they target the formation of microcomedones, which is the initial step in comedogenesis and formation of subsequent acne lesions, they should be continued as maintenance therapy.[3] Different concentrations and preparations of topical retinoids are available. Common local adverse effects, including erythema, dryness, itchiness and stinging, can be minimized by choosing an appropriate formulation for each patient depending on his/her skin type and sensitivity. Among the different topical retinoids available, adapalene, a newer generation of topical retinoid derived from naphthoic acid, has been shown in comparative studies to be as effective as 0.025% tretinoin gel and 0.05% tretinoin cream but with less irritation.[4,5] It represents a reasonable choice especially for patients with sensitive skin. The maximum therapeutic response to topical retinoids occurs over about 12 weeks. It is therefore essential to emphasize to patients the need for their continuous use.

In recent years, an increasing number of fixed-dose combination products (eg, adapalene/benzoyl peroxide, benzoyl peroxide/clindamycin and tretinoin/clindamycin) have become available. Many of these agents have been shown to enhance the efficacy and speed of action. Since they target multiple pathogenic factors, they have a broader spectrum of action than a single topical drug. Overall, the combination of a topical retinoid and an antimicrobial agent (either benzoyl peroxide or an antibiotic) remains the preferred approach for almost all patients with mild to moderate acne. The superior efficacy of this combination has been shown in large clinical trials.[6,7] Fixed-dose combination products with a topical retinoid and an antimicrobial provide patient convenience and better adherence. The absence of an antibiotic in the formulation may minimize the development of bacterial resistance. Hence, on a theoretical basis, retinoid-benzoyl peroxide combination products may be the most desirable.

"Retinoid-benzoyl peroxide combination products may be the most desirable"

Oral Therapies

Moderate to severe acne warrants prompt treatment with oral therapies. Other indications for oral treatment include acne-excoriee, acne keloidalis, truncal acne, acne which resolved with significant postinflammatory hyperpigmentation, and any form of acne causing severe negative psychological impact. Three groups of oral therapies are available, which include: 1) oral antibiotics, 2) hormonal therapy, and 3) isotretinoin.

Oral antibiotics are often prescribed with topical retinoids and/or benzoyl peroxide to minimize drug resistance as well as to control microcomedone formation in moderate acne. They interfere with the growth and metabolism of *P acnes*, and also have an anti-inflammatory action by reducing and inhibiting cytokine production, affecting macrophage functions and inhibiting neutrophil chemotaxis. First- (tetracycline hydrochloride, oxytetracycline) and second-generation (doxycycline, lymecycline, minocycline) tetracyclines should be considered as first-line oral antibiotic therapy because of a lower incidence of drug resistance compared to macrolides. Second-generation tetracyclines have the advantage of improved gastrointestinal absorption, which is unaffected by food. Furthermore, the once-daily dosing also helps improve compliance. All oral tetracyclines have been shown to have similar efficacy. The choice depends on the cost, side effects profile, relative incidence of *P acnes* resistance and the dosing regimen. Macrolides (erythromycin, clarithromycin) should be reserved for cases where tetracyclines are not tolerated or contraindicated, as in the cases of pregnancy, breastfeeding and children below the age of 12 years. It is recommended to continue with oral antibiotic treatment for up to 3 months. If little response is seen after 6 weeks, a switch to an alternative oral antibiotic can be considered. Antibiotic resistance is a significant public health issue worldwide.[8] A large contributory factor has been their inappropriate use, including inadequate potency, inadequate duration of treatment and poor compliance. Guidelines for optimizing the use of antibiotics, both topical and oral, and for the limitation of drug resistance are detailed in Table 1.

Table 1. Recommendations to limit *P acnes* antibiotic resistance

- Limit the use of antibiotics to short periods. Discontinue their use when the improvement is only slight or when there is no further improvement.
- Co-prescribe an antibiotic (oral or topical) with a benzoyl peroxide-containing product to reduce the possibility of antibiotic resistance.
- Do not switch antibiotics without adequate justification. In the event of relapse, the same antibiotics should be given for subsequent courses when possible.
- Topical and oral antibiotics, especially those with chemically dissimilar properties, should not be used concurrently.
- Topical and oral antibiotics should not be used as monotherapy.
- Antibiotics should not be used as maintenance therapy. Topical retinoids are the first-line option for maintenance, and benzoyl peroxide can be added for an antimicrobial effect if required.
- Patients should be educated on the importance of adherence to the prescribed regimen.

Table 2. Side effects associated with isotretinoin therapy

Clinical side effects:

- Teratogenicity
- Xerosis, chelitis, itching, dermatitis, skin fragility, hair loss, bruising
- Dryness of nasal mucosa, epistaxis
- Irritation of eyes, conjunctivitis, diplopia
- Arthralgia, myalgia, skeletal changes
- Insomnia, change in appetite, abdominal pain, inflammatory bowel disease
- Ingrown nails, paronychia
- Intracranial hypertension, headache
- Mood change, depression

Laboratory side effects:

- Elevated total cholesterol, triglycerides
- Elevated aspartate aminotransferase or alanine aminotransferase level
- Elevated or decreased haemoglobin, white blood cells and platelets

Another class of oral treatment available for moderate acne is hormonal therapy, which includes oral contraceptives and antiandrogen drugs. Oestrogen-containing oral contraceptives first obtained approval by the Food and Drug Administration (FDA) for use in acne treatment more than 10 years ago. Several randomized controlled trials have since demonstrated their efficacy and safety in women of childbearing age. Hormonal therapy reduces acne lesions by increasing oestrogen levels and sex hormone-binding globulins, decreasing free testosterone and androgen levels, reducing sebum production and reducing proliferation of follicular keratinocytes. Females with adult-onset acne, hormonal disturbance, signs of hyperandrogenism, polycystic ovarian syndrome and those who also seek contraception are particularly suitable candidates for hormonal therapy. Among the different types of effective hormonal therapies available, a combination of cyproterone acetate and ethinyl oestradiol is commonly used for the treatment of acne because of its antiandrogen component. In general, hormonal therapy should be taken for at least 4 to 6 weeks for an improvement to be seen. Possible side effects should be explained to patients, and contraindications to hormonal therapy should be assessed through history and clinical examination before prescription.

Isotretinoin (13-*cis* retinoic acid) is a synthetic vitamin A derivative which is only approved by the FDA for use in patients >12 years of age with severe recalcitrant nodulocystic acne. Nevertheless, it is commonly used off-label for less severe refractory disease resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy. Isotretinoin is effective in acne as it comprehensively targets all four major factors involved in its pathogenesis. It is the only therapy that offers hope of permanent remission upon completion of a course of treatment. Nevertheless, it has a documented failure rate of 15% to 30%, and multiple courses may be required for some patients.[9] The recommended starting dose is 0.5 mg/kg/day, which is gradually increased to a maximum of 1 mg/kg/day according to side effects and clinical response.

Although effective, isotretinoin is associated with serious side effects, especially for pregnant women. (Table 2) Teratogenicity is by far the most significant untoward effect, which can cause craniofacial, cardiac, thymic and central nervous system defects in the developing fetus. It is therefore vital that women of childbearing age are not pregnant and do not become pregnant while on isotretinoin, as well as for 30 days after the completion of treatment. United States recommendations include simultaneous use of two reliable forms of contraception. The importance of teratogenicity of isotretinoin is highlighted by the implementation of the iPLEDGE programme in the United States in March 2006. In this mandatory distribution programme, patients, their doctors and pharmacists are required by the FDA to register in order to receive this medication. The intention is to prevent the use of isotretinoin during pregnancy. Other well-documented side effects of isotretinoin, as shown in Table 2, should also be explained to the patient prior to the commencement of treatment. Most of these are predictable and dose-related.[10] A signed consent form should be obtained for medical record. If used appropriately, the benefits of isotretinoin in the treatment of severe acne is unquestionable.

Conclusion

Acne should not be trivialized as a cosmetic problem affecting only teenagers. It should be treated as promptly and efficiently as possible to achieve the best possible patient outcomes and to limit the development of scarring. Topical retinoids form the foundation for the treatment of mild to moderate acne and as maintenance therapy. Antibiotic resistance of *P acnes* is a concern, and monotherapy with topical and oral antibiotics should be avoided. Finally, patient education is important to ensure compliance with and success of treatment.

References:

1. Yeung CK, Teo LH, Xiang LH, Chan HH. A community-based epidemiological study of acne vulgaris in Hong Kong adolescents. Acta Derm Venerol 2002;82:104-107.
2. Thiboutot D, Gollnick H, Bettoli V, et al. New insights into the management of acne: An update from the Global Alliance to Improve Outcome in Acne Group. J Am Acad Dermatol 2009;60:S1-S50.
3. Thielitz A, Sidou F, Gollnick H. Control of microcomedone formation throughout a maintenance treatment with adapalene gel, 0.1%. J Eur Acad Dermatol Venereol 2007;21:747-753.
4. Shalita A, Weiss JS, Chalker DK, et al. A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris: A multicenter trial. J Am Acad Dermatol 1996;34:482-485.
5. Ioannides D, Rigopoulous D, Katsambas A. Topical adapalene gel 0.1% vs. isotretinoin gel 0.05% in the treatment of acne vulgaris: A randomized open-label clinical trial. Br J Dermatol 2002;147:523-527.
6. Shalita AR, Rafal ES, Anderson DN, et al. Compared efficacy and safety of tretinoin 0.1% microsphere gel alone and in combination with benzoyl peroxide 6% cleanser for the treatment of acne vulgaris. Cutis 2003;72:167-172.
7. Wolf JE Jr, Kaplan D, Kraus SJ, et al. Efficacy and tolerability of combined topical treatment of acne vulgaris with adapalene and clindamycin: A multicenter, randomized, investigator-blinded study. J Am Acad Dermatol 2003;49:S211-S217.
8. Coates P, Vyakmams S, Eady EA, et al. Prevalence of antibiotic resistant proprionibacteria on the skin of acne patients: A ten year surveillance data and snapshot distribution and study. Br J Dermatol 2002;146:840-848.
9. Strauss JS, Rapini PR, Shalita AR, et al. Isotretinoin therapy for acne: Results of a multicenter dose-response study. J Am Acad Dermatol 1984;10:490-496.
10. McLane J. Analysis of common side effects of isotretinoin. J Am Acad Dermatol 2001;45:S188-S194.

PHYSIOGEL™ *Intensive Cream*

INTENSIVE HYDRATION

Intensive hydration for moderately dry to very dry skin

High level of natural lipids*

Unique DMS** base

Non-comedogenic

No preservatives

NEW

Just PHYSIOGEL™ *it!*

PHYSIOGEL™ Intensive Cream User Feedback[1]

100%	Satisfaction in the smoothness of feel on the skin
92%	Would continue to use
86%	Rated good in smell
72%	Ease in spread

N = 144

Application: Applied PHYSIOGEL Intensive Cream twice daily for 4 weeks

Reference: 1. Data on file. Stiefel 2007

** High level of natural lipids similar to the skin's physiologic lipids*

*** DMS = Derma Membrane Structure*

STIEFEL

Further information is available on request.
Stiefel, a GSK company Tel: (852) 3718 6666 Fax: (852) 3718 6600
™Physiogel is a trademark of Stiefel Laboratories.

N10SPH016/09022010

Infant Feeding in the First Year – Breastfeeding, Infant Formula, Nutritional Additives and Special Formula (Part I)

Dr Lam Cheung Cheung Barbara, JP
(藍章翔醫生、太平紳士)

MBBS, MRCP (UK), FRCP (Edin., Lond.), FRCPCH (UK), FHKAM (HK), FHKCPaed

Honorary Consultant, Queen Mary Hospital

Honorary Clinical Associate Professor, Department of Paediatrics and Adolescent Medicine, University of Hong Kong

Key words:
Infant feeding (嬰兒餵哺),
breastfeeding (母乳餵哺),
infant formula (嬰兒奶粉配方),
nutritional additives
(營養添加劑)

Introduction

The American Academy of Paediatrics (AAP) has recommended exclusive breastfeeding during the first 6 months of life, and continuation of breastfeeding with addition of solid foods as optimum nutrition for infants in the first year of life.[1] The World Health Organization (WHO) considers breastfeeding a key public health measure. Human milk provides complete nutrition for infants. Formula milk is just a food, whereas breast milk is a complex living nutritional fluid that contains antibodies, enzymes and hormones. Breast milk can synchronize with the infant's growing needs, and is specific to the mother-infant dyad. The WHO 2007 systemic reviews and meta-analysis on the benefits of breastfeeding showed that breastfeeding helps protect against certain childhood infections (eg, lower respiratory tract infection, acute otitis media, gastroenteritis) and possibly adult diseases (eg, obesity, type 2 diabetes and hypertension). Breastfeeding reduces the risk of breast and ovarian cancers in mothers.[2,3] Thus, it is the duty of all healthcare professionals to actively protect, promote and support breastfeeding.

Tips for primary care physicians to contribute to the promotion and support of breastfeeding:

1. Take every opportunity to inform pregnant women and breastfeeding mothers of the health benefits of breastfeeding their infants for 6 months.
2. Encourage mothers and enlist support from their family members to boost the mothers' confidence in their ability to breastfeed.
3. Provide early help and prompt referral to someone who does have the skill and time to deal with breastfeeding problems when these are encountered.
4. Avoid advising mothers to stop breastfeeding when medications are prescribed. Careful use of expert resources and careful evaluation of the benefit and risk to individual infants and mothers can usually enable breastfeeding to continue. In general, if a drug is licensed for infants, the small amounts present in breast milk are likely to be safe.

Although breastfeeding is the best way to feed infants in their first year of life, the breastfeeding rate in Hong Kong remained low. According to a breastfeeding survey conducted at the Maternal and Child Health Centre of the Department of Health, in 2006, only about 70% of mothers had ever breastfed at the time of discharge from hospital, and only about 12% exclusively breastfed their infants in the first 4 months after birth. For infants whose mothers do not or cannot provide breast milk, infant formula has to be used as a breast milk substitute or supplement.

Standard Infant Formula vs Breast Milk

Standard infant formula is an artificial formula, usually cow milk-based, manufactured for infants less than 1 year of age. With increased understanding of the

content and composition of breast milk, most infant formulas are modified using breast milk as a reference. (Table)

The major modifications made include:

1. A lower protein concentration (protein content in unmodified cow milk is approximately 40% greater than that in human milk).
2. The butterfat of cow milk is replaced with vegetable oils that enhance digestibility and absorption.
3. The fat utilized varies between different formulas and brands, Generally, it contains a mixture of short-chain fatty acids (coconut oil), long-chain polyunsaturated fatty acids (palm oils) and polyunsaturated fatty acids (soy, corn, and safflower oils).
4. A lower calcium and phosphorus content to achieve a better calcium to phosphorus ratio, which is close to that of human milk.
5. The bioavailability of iron in cow milk is lower than that in breast milk. Most infant formulas are fortified with iron based on the recommendation from the AAP.[3] The iron content varies between different brands, and is generally lower for formulas for infants less than 6 months of age. It is a general perception that higher iron content may be associated with constipation and other feeding difficulties in young infants.

The Codex Alimentarius Commission sets food standards, and is one of the international professional bodies that sets the standard for infant formula. Most international brand infant formulas that are registered in Hong Kong have to comply with the standard criteria recommended.

Choice of Infant Formula: Who Makes the Decision?

A survey was conducted on 100 consecutive newborn babies under the care of the author to investigate how mothers choose infant formula as complete or partial breast milk substitute. Most mothers (59%) made their choice based on information from friends, self-reading, advertisements and other public media. Only 41% of mothers made the choice after consultation with their obstetricians, paediatricians or other healthcare workers. Among those who chose their own formula, 15% of mothers requested to start their babies on "nonstandard" infant formula (eg, soy formula, lactose-free formula, hypoallergenic formula, goat milk). Another study investigating the frequency and reasons for formula changes in young infants revealed that 9% of infants were started on "nonstandard" formulas at birth. More than 1/3 of infants were changed from standard to "nonstandard" formulas for various reasons, such as colic, splitting up, bloody stools, diarrhoea, constipation, somebody's preference, and suspected 'allergy'. Forty-seven percent of the decisions were made by the mothers, and 44% were made by doctors or paediatricians.[4]

Currently, more than 40 different brands of infant formula are available in the market. There is an influx of more infant formulas into the market each year. The influx of Japanese brands in recent years makes the competition particularly keen. Each company describes each of its products as having a particular unique and desirable feature for optimal infant growth and development. It is not surprising that healthcare professionals, not to mention parents, are confused about which formula to use and what the differences are between the various formulas. Doctors who take care of pregnant women and infants should keep updated on the differences between the formulas, the impact of these differences on the growth and development of the infants, and the implication of these differences for different clinical conditions or those with special requirement.

International vs Japanese Infant Formulas

Both infant formulas are modified from cow's milk using breast milk as a reference. The Japanese formulas follow the standard set by the Japan Health Authority, while the international brands registered in Hong Kong comply with the standard set by the Codex Alimentarius. Like other international brands, there are minor differences in the type of fat, the iron content and the use of various nutritional additives between Japanese and international brands. Most Japanese formulas have added prebiotics and probiotics. The prebiotics are natural or synthetic oligosaccharides such as fructo-oligosaccharides and galacto-oligosaccharides. The addition of these oligosaccharides was associated in a dose-dependent manner with increased stool frequency, reduction of stool pH and softer stool consistency. Similar additives have been recently included in some locally marketed international formulas. The addition of prebiotics might be beneficial to infants suffering from constipation; however, prolonged exposure might potentially increase the risk for

Table. Comparison of content of breast milk vs cow milk and infant formulas

Per 100 mL	Energy (Kcal)	Protein (g)	Carbohydrate (g)	Calcium (g)	Phosphorus (mg)	Iron (mg)	Magnesium (mg)
Human milk	65	1.3	7.4	30	13	0.1	32
Cow milk	60	3.1	5.1	114	87	0.1	19
Formula I (0–6 months)	67	1.4	7.3	42	24	0.8	5
Formula 2 (6–12 months)	67	2.2	8.2	115	65	1.2	8.5
Formula 3 (1–3 years)	100	3.2	14	100	80	1.3	10

dehydration during the first few months when the kidney has poor ability to concentrate urine, especially during times of stress such as fever or infectious diarrhoea. Another difference of clinical importance is the different methods of preparation of the formulas. International brands use 30 cc (1 oz) as a unit, whereas all Japanese brands use 20 cc as a unit. It is important to remind parents to read the instructions of preparation carefully. Unfortunately, some Japanese formulas do not have English or Chinese instructions, and there are situations where babies suffer as a result of being fed with milk with the wrong concentration over a period of time.

Modified Infant Formulas

These infant formulas are modified by changes in the forms and sources of protein, fat, carbohydrates and additives:

1. Instead of cow protein, modified infant formulas may contain soy protein (eg, soy-based formula), goat protein, or partially hydrolyzed protein (eg, hypoallergenic formula).
2. For carbohydrates, these formulas may be lactose free, lactose free and sucrose free, or have thickening agents added (eg, antireflux formula).
3. For the fat components, instead of predominantly long-chain fatty acids, modified infant formulas contain predominantly medium-chain fatty acids.
4. Modified infant formulas may contain various additives, such as nucleotides, long-chain polyunsaturated fatty acids, prebiotics and probiotics, taurine, lutein, phospholipids and others.

"Nonstandard" Infant Formula

Soy-based Formula

The protein component of the soy formula is based on soybean protein. Most soy formulas are also lactose free, and may contain sucrose, corn syrup solids and maltodextrin. Soy-based formulas have been used for secondary lactase deficiency following small intestinal injury, such as gastroenteritis and galactosaemia. Soy formulas can provide adequate nutrients for normal growth for young infants. However, for healthy infants, soy-based formulas offer no specific advantage over cow milk-based formula. In addition, there are potential adverse effects associated with prolonged use of soy formulas due to their higher amounts of aluminum and phyto-oestrogens. The relatively high aluminum content may compete with calcium absorption. The phytate in soy formulas, in addition to the absence of lactose, could also diminish calcium absorption. To compensate for this, recent soy formulas have improved on mineral supplementation and have shown no significant difference in bone mineralization compared with standard infant formula.

Other potential adverse effects of soy formulas include decreased bioavailability of phosphorus, zinc, manganese, copper and iron. Soy formulas containing fructose may induce fructose intolerance. There is no evidence to suggest that prophylactic use of soy formulas can reduce allergies or food intolerance in healthy or high-risk infants. Moreover, there is no proven value of soy formulas in the prevention or management of infantile colic. The AAP cautions against the use of soy protein-based formulas for low-birth weight infants (ie, birth weight <1,800 g).[5] Soy formulas are not recommended for the treatment of documented cow milk protein intolerance, especially those with documented cow milk protein-induced enteropathy because of high cross reactivity (soy protein is also antigenic; approximately 10% to 50% of those with cow milk protein allergy have concomitant soy protein allergy).[6] However, for those with immunoglobulin E-medicated allergy to cow's milk, soy formulas may be used after 6 months of age to replace the extensively hydrolyzed formula.

Goat Milk-based Infant Formula

Unlike pasteurized fresh goat milk, which is very low in vitamin A, D, B2, B6 and folic acid, modified goat milk-based infant formula is safe for feeding infants. However, there is no evidence to suggest that the use of goat milk formula can prevent or reduce allergy. There are no nutritional or medical indications to select goat milk-based infant formula over cow milk-based infant formula. Goat milk, like other mammalian milk such as sheep, buffalo, horse and camel milk, presents an equally high risk of cross-reactivity and is not recommended for the prevention or treatment of cow milk allergy in infants.

Lactose-free Formula

Lactose is the major carbohydrate in breast milk and standard infant formula. There is a growing market for non-lactose containing formulas for infants with nonspecific symptoms of bloating, gaseous distension, vomiting and loose stool. Indeed, primary lactose intolerance is uncommon in the first year of life; though lactose-free formulas can support normal growth of term infants through the first year, there are very few indications for the use of lactose-free formulas except galactosaemia and secondary lactase deficiency following small intestinal injury (eg, post-gastroenteritis). Lactose-free formulas have not been shown to improve symptoms such as reflux or colic. Some undigested lactose that enters and ferments in the distal small bowel is beneficial by permitting proliferation of predominantly acidophilic bacterial flora (lactobacilli). These bacteria produce an acid medium that suppresses growth of the more pathogenic organisms and promotes absorption of calcium and phosphorus. Besides, lactase is a substrate-dependent enzyme, and prolonged use of lactose-free formulas will result in a loss of lactase activity and subsequent intolerance to lactose-containing food. Prolonged use of lactose-free formulas for otherwise healthy infants is generally not recommended.

Hypoallergenic Formula (Partially Hydrolyzed Formula)

The cow's milk protein in hypoallergenic formulas is broken down, usually by enzymatic hydrolysis, into smaller protein molecules that are said to be potentially less allergenic. There is, however, no evidence to suggest that prophylactic use of these partially hydrolyzed formulas as opposed to cow milk-based formulas can reduce the incidence and severity of allergic disease such as asthma, atopic

eczema or rhinitis in the general population or in otherwise healthy infants.[7] The evidence on the protective effect against allergic disease in high-risk infants with very strong family history of allergy is conflicting. A longitudinal prospective study conducted locally on a group of infants at high risk of allergy showed that prophylactic use of hypoallergenic formulas is associated with a lower cumulative incidence of allergic manifestations compared with cow milk-based formulas in the first 3 years of life. However, the differences disappeared when the cohort was followed up to 7 years of age, suggesting that other environmental factors in addition to infant feeding may also influence the development of allergic disease.[8] Hypoallergenic formulas are not to be used for the treatment of documented cow milk protein allergy. The AAP recommends only extensively hydrolyzed and amino acid-based formulas for infants with documented cow milk protein allergy.

Follow-up Formulas

The 'follow-up formulas' have been marketed for infants aged 6 to 12 months. In general, these formulas have higher protein concentration and higher levels of some minerals such as iron and calcium and electrolytes. (Table) The iron fortification is an advantage for infants receiving inadequate intake of solid food. However, other compositional changes in protein, fat, carbohydrates, sodium and calcium have no clearly established superiority over infant formula. Parents are frequently misled by the term 'follow-on formula' because it implies that these formulas automatically follow the infant formula. Indeed, for infants who continued to consume milk as their major source of food intake after 6 months of age, the high protein intake may contribute to increased renal solute load and increased risk of constipation and obesity. Thus, follow-up formulas, although nutritionally adequate, offer no clear advantage for infants receiving sufficient amounts of iron- and vitamin-containing solid food.[9] Family doctors and paediatricians should encourage parents to introduce a variety of solid food to provide additional nutrients. Change to the follow-up infant formula can be used after the child reaches 12 months of age.

References:

1. American Academy of Pediatrics. Work Group on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics 1997;100:1035-1039.
2. Ip S, Cheung M, Raman G, et al. Breastfeeding and maternal and infant health outcomes in developed countries. Evidence report/technology assessment. Report 153. Rockville, USA: Agency for Healthcare Research and Quality, 2007.
3. Horta BL, Bahl R, Martines JC, Victoria CG. Evidences of the long term effects of breastfeeding. Geneva: WHO, 2007. Available at: http://whqlibdoc.who.int/publications/2007/9789241595230_eng.pdf Accessed May 2009.
4. Polack FP, Khan N, Maisels MJ. Changing partners: The dance of infant formula changes. Clinical Pediatrics 1999;38:703-798.
5. Klish WJ, Baker SS, Cochran WJ, et al. Soy protein-based formulas: Recommendations for use in infant feeding. Pediatrics 1998;101:148-153.
6. Osborn DA, Sinn J. Soy formula for prevention of allergy and food intolerance in infants. Cochrane Database Syst Rev 2006;(4):CD003741.
7. Osborn DA, Sinn J. Formulas containing hydrolysed protein for the prevention of allergy and food intolerance in infants. Cochrane Database Syst Rev 2006;(4):CD003664.
8. Lam, BCC. Early infant feeding and allergic manifestations – a 7 year follow up of high risk infants. Proceedings of Symposium on Infant Nutrition and Growth. November 1999; Hong Kong.
9. American Academy of Pediatrics Committee on Nutrition: Follow-up or weaning formulas. Pediatrics 1989;83:1067.

Protection is Never Premature

Synagis® is Indicated for Prevention of Serious LRTI* Caused by RSV** in Pediatric Patients at High Risk of RSV**

Synagis® is Safe and Effective in[1]

- Infants with bronchopulmonary dysplasia (BPD)
- Infants with a history of prematurity (≤ 35 weeks GA***)
- Children with hemodynamically significant congenital heart disease (CHD)

For further information, please see full Synagis® prescribing information

1. Synagis® Prescribing Infomation
* LRTI : Lower Respiratory Tract Infection
** RSV: Respiratory Syncytial Virus
*** GA : Gestational Age

℞ SYNAGIS®
PALIVIZUMAB

www.synagis.com

Abbott Laboratories Limited
20/F., AIA Tower, 183 Electric Road, North Point, Hong Kong. Tel: 2566 8711 Fax: 2219 8066

AI-A494-L-0171 Sept 2009

Abbott
A Promise for Life

JOURNAL OF THE SOCIETY OF PHYSICIANS OF HONG KONG
March 2010 • Vol. 2 • No. 2

Sleep Apnoea and Arrhythmias

Author: Dr Lam Tse Fan, Cathy (林紫芬醫生)
MBBS (HK), FHKCP, FHKAM (Med), FRCP (Edinburgh, London)
Specialist in Cardiology
Honorary Clinical Assistant Professor, Department of Medicine & Therapeutics, Chinese University of Hong Kong

References

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230-1235.

2. Brodsky M, Wu D, Denes P, et al. Arrhythmias documented by 24 hour continuous electrocardiographic monitoring in 50 male medical students without apparent heart disease. Am J Cardiol 1977;39:390-395.

3. Smith I, Lasserson TJ, Wright J. Drug therapy for obstructive sleep apnoea in adults. Cochrane Database Syst Rev 2002;(2):CD003002.

4. Javaheri S, Parker TJ, Liming JD, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure : Types and their prevalences, consequences, and presentations. Circulation 1998;97:2154-2159.

5. Mehra R, Benjamin EJ, Shahar E, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. Am J Respir Crit Care Med 2006;173:910-916.

6. Gami AS, Pressman G, Caples SM, et al. Association of atrial fibrillation and obstructive sleep apnea. Circulation 2004;110:364-367.

7. Porthan KM, Melin JH, Kupila JT, Kalervo Venho KK, Partinen MM. Prevalence of sleep apnea syndrome in lone atrial fibrillation. Chest 2004;125;879-885.

8. Gami AS, Hodge DO, Herges RM, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. J Am Coll Cardiol 2007;49:565-571.

9. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. Am J Cardiol1983;52:490-494.

10. Hoffstein V, Mateika S. Cardiac arrhythmias, snoring, and sleep apnea. Chest 1994;106:466-471.

11. Ryan CM, Juvet S, Leung R, Bradley TD. Timing of nocturnal ventricular ectopy in heart failure patients with sleep apnea. Chest 2008;133:934-940.

12. Watanabe MA, Bhalodia R, Lundequam EJ, et al. Increased ventricular premature contraction frequency during REM sleep in patients with coronary artery disease and obstructive sleep apnea. Indian Pacing Electrophysiol J 2008;8:258-267,

13. Rosenberg J, Pedersen MH, Ramsing T, Kehlet H. Circadian variation in unexpected postoperative death. Br J Surg.1992;79:1300-1302.

14. Lavery CE, Mittleman MA, Cohen MC, Muller JE, Verrier RL. Nonuniform nighttime distribution of acute cardiac events. A possible effect of sleep states. Circulation 1997;96:3321-3327.

15. Somers VK, Dyken ME, Mark AL, et al. Sympathetic nerve activity during sleep in normal subjects. N Engl J Med 1993;328:303-307.

16. Mancia G. Autonomic modulation of the cardiovascular system during sleep. N Engl J Med 1993;328:347-349.

17. Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. Cochrane Database Syst Rev 2006;(1):CD001106.

18. Kanagala R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation 2003;107;2589-2594.

19. Ryan CM, Usui K, Floras JS, Bradley TD. Effect of continuous positive airway pressure on ventricular ectopy in heart failure patients with obstructive sleep apnoea. Thorax 2005;60:781-785.

20. Garrigue S, Bordier P, Jais P, et al. Benefit of atrial pacing in sleep apnea syndrome. N Engl J Med 2002;346:4404-4412.

21. Weng C, Chen Q, Ma Y, He Q. A meta-analysis of the effects of atrial overdrive pacing on sleep apnea syndrome. Pacing Clin Electrophysiol 2009;32:1434-1443.

22. Smith I, Lasserson TJ, Wright J. Drug therapy for obstructive sleep apnoea in adults. Cochrane Database Syst Rev 2002;(2):CD003002.