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Editorial

The World Health Organization recommends exclusive breastfeeding during the first 6 months of life as a way to improve the health and nutrition of infants and young children. Although breastfeeding is the best way to feed infants, the overall rate of exclusive breastfeeding in Hong Kong has remained unacceptably low. This is partly attributable to the overwhelming advertisements on various claimed benefits of infant and follow-on formulas. Currently, more than 40 different brands of infant formula are available in the market. 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 parents and even some healthcare professionals could be misled to believe that these modifications can make infant formulas comparable to or even better than human breast milk. The health authority should develop policies to support, promote and protect breastfeeding by regulating inappropriate sales promotion of infant food that can be used to replace breast milk.

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Infant Feeding in the First Year (Part II) – Nutritional Additives, Special Formulas and Introduction of Solids

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Key words:
Infant feeding (嬰兒餵哺), nutritional additives (營養添加劑), special formula (特別配方奶粉), weaning and introduction of solid (戒奶及引入固體食物)

Introduction

Nutrition in the first year influences a child's growth and future health. It is the duty of healthcare professionals to take every opportunity and to give priority in educating parents about good nutrition for their children during consultations. All mothers must be made aware of the nutritional benefits of breastfeeding and be provided with appropriate support for breastfeeding when needed. Most babies receive formula at some stage during the first year of life. A balanced view of the nutritional benefits of breast milk and infant formulas allows healthcare professionals to share sound advice with mothers. Healthcare professionals also have a responsibility to be aware of current developments in infant formulas, and the benefits and potential harms of the ever-growing new additives in infant formula (eg, long-chain polyunsaturated fatty acids, nucleotides, prebiotics, etc). Special infant formula should only be used under specific medical indications and under continuous medical supervision.

Weaning is an important nutritional milestone as lifelong eating behaviour begins during this period. A good weaning practice can help avoid several nutritional problems such as picky eating, faltering growth, constipation, iron deficiency anaemia and obesity. However, advice on weaning is often lacking or conflicting, and needs to be more structured with good quality practical information and leaflets. Since all babies are different and reach developmental milestones at different ages, a flexible approach regarding the age and type of the weaning food introduced is more physiological. Eating is an important social development; infants should be encouraged to have meals with the family from an early age, for both social and nutritional reasons.

Nutritional Additives

Human milk is recognized as the ultimate functional food for infants because of its biological compatibility, nutritional value and the added value of its health-promoting qualities. Intensive research has recently evolved in a quest to identify and define the components of human milk that might confer disease-preventing and health-enhancing properties. The outcome of the research provided a rationale for advocating the supplementation of commercial infant formulas with such substances.

It must be emphasized that human milk contains human protein, hormones, immune factors, growth factors, enzymes, viable cells, and many other components yet to be identified, most of which cannot practically be added to infant formulas. Besides, the complex interaction and synergistic effect of these bioactive substances could not possibly be copied by simple addition of these substances to the formula. The nutritional additives might make the infant formula's composition closer to that of human milk, but one can never "humanize" infant formula. This review is intended to provide an overview of the new nutritional additives that have been introduced to infant formulas. The Table summarizes the rationale, potential specific benefits, possible disadvantages and issues that still remain unresolved for each of the additives.[1-4]

As a result of keen commercial competition among manufacturers, changes will continue to be made to "perfect" infant formula. These changes generally result in products with compositions closer to that of human milk. It is clear that none of the modified formulas can match up with mother's breast milk, which is designed for each specific mother-baby dyad. The composition of infant formula is constant while the content of breast milk is adjusted to the changing demand of the infant. Maximal benefits can only be obtained through the complex interplay and synergistic effect of the various nutritional and immunologic factors. These

Table. Nutritional additives in infant formula

	Rationale	Potential specific benefits	Unresolved issues	Potential disadvantages
1. Long-chain poly-unsaturated fatty acids (LCPUFA – ARA & DHA)	• Unmodified formula contains only the pre-cursors, but not ARA and DHA • Present in large quantities in brain and retina	• Potential visual and neurodevelopmental benefits • Little evidence from RCT to support benefit for neurodevelopment of term infants, but may be beneficial to preterm infants who have a greater demand	• No gold standard for ideal amount and ratio of DHA/ ARA • Insufficient evidence to determine true functional benefit and safety profile	• Possible adverse effect due to imbalance in intake of DHA and ARA • Theoretical risks of increased infection and susceptibility to oxidant injury
2. Nucleotides and nucleic acid	• Semiessential nutrient; de novo synthesis from non-essential precursors demands a metabolically costly pathway • Dietary nucleotides may be important in tissues with rapid turnover (eg, bone marrow, leucocytes and intestinal mucosa [neonatal gut has complete replacement of enteric epi-thelium in around 5 days])	• Enhance growth and differentiation of gastrointestinal tract (eg, speed up recovery from intestinal illnesses such as necrotizing enterocolitis, diarrhoea, state of malnutrition) • Upregulate cellular and humoral im-munity, decrease incidence of diarrhoea, fewer URTI in malnourished children, higher antibody response to immuni-zation • Promote growth: RCT on term SGA infants showed better catch-up (height, body weight and head circumference) in supplemented group in the first 6 months	• Very few studies on actual reduction of infection with fortification of nucleotides in infant formula • Benefits of nucleotide supplementation remains controversial in term infants	• No adverse effects have been reported • Nucleotide-supplemented infant formulas are currently considered safe
3. Taurine	• Most abundant free amino acid in human milk; low in cow's milk and absent in unsupplemented soy milk • High concentration in brain – several times higher in newborns than adults	• Taurine deficiency in cats associated with retinal degeneration • Prolonged taurine-free parenteral nutrition resulted in retinal degeneration, which was reversed with taurine supple-mentation • Premature infants on taurine-supplemented formula has more mature auditory brainstem evoked potential • Lower plasma taurine in preterm infants was associated with lower scores on the Bayley Mental Development Index at 18 months and the WISC-R arithmetic subtest at 7 years	• Cochrane systematic reviews of 9 small RCT showed no significant effects on growth and development with taurine supplementation in preterm or low birth weight infants	• No adverse effects demon-strated • Taurine is currently added to all infant formulas and soy protein-based formulas worldwide

ARA = arachidonic acid; DHA = docosahexaenoic acid; RCT = randomized controlled trials; SGA = small for gestational age; URTI = upper respiratory tract infections; WISC-R = Wechsler Intelligence Scale for Children revised edition

effects are unlikely to be mimicked by simple addition of isolated factors to the cow's milk formula. Furthermore, there are issues of bioavailability, loss through processing, shelf-life, and the added cost associated with these modifications. Infant formula should aim at providing the best alternative to breast milk for infants by adapting its content so that the physiological and functional outcomes of formula-fed infants are closer to those of breast-fed infants in terms of growth and development.

Special Formulas

Protein Hydrolysate Formulas

Protein hydrolysate formulas or extensively hydrolyzed formulas (eHF) refer to formulas with the protein component consisting of extensively hydrolyzed proteins derived from cow's milk, in which most of the nitrogen is in the form of free amino acids and peptides <1,500 kDa. To meet the standard for hypoallergenicity, these formulas, after appropriate pre-clinical testing, must demonstrate that they do not provoke reactions in 90% of infants with confirmed cow's milk allergy (95% confidence interval) in prospective, randomized, double-blind, placebo-controlled clinical trials.[5]

Commercially available eHF are made up of hydrolyzed proteins (oligopeptides) with the addition of free amino acids (eg, cysteine, tyrosine, oligopeptides). Examples are casein hydrolysates (eg, Pregestimil) or whey hydrolysates (eg Pepti-Junior). These eHF contain carbohydrate in the form of polycose polymers, and is usually lactose free, sucrose free and fructose free. The fat is predominantly medium-chain triglycerides (MCT oil) so that absorption can take place in the absence of bile salts. Apart from treatment of infants with documented allergy to cow's milk or other milk protein, eHF is frequently used as an elemental diet for infants with compromised enteric digestion (eg, short gut syndrome, autoimmune enteropathy, cystic fibrosis, human immunodeficiency virus-associated enteropathy and hepatobiliary disorders [biliary atresia]). Although most studies showed no major differences in the anthropometric and biochemical parameters in infants fed with eHF vs infants fed with adapted cow's milk or human milk,[6] the process

Table. Nutritional additives in infant formula

	Rationale	Potential specific benefits	Unresolved issues	Potential disadvantages
4. Lutein	• An antioxidant that may have anti-inflammatory, photo-protective and anticarcinogenic properties • High concentration in the retina • Lutein and zeaxanthin are major components of the human retina that are derived solely from the diet – macular pigment • Protects the eye from degenerative eye diseases (eg, macular degeneration and cataract) • May also be critical for the proper development of the central retina and retinal pigment epithelium	• Dietary deprivation in primates causes pathological changes in the macular • Sufficient dietary intake of lutein and zeaxanthin may support optimal infant retinal development and may protect the infant retina from damage • No good evidence or RCT to support that supplementation improves long-term visual outcome or prevents macular degeneration in vulnerable subjects	• Lutein concentrations in human milk varied at different times of lactation, and were affected by maternal diet • No good standard about the optimal level of supplementation • Too early for recommending lutein supplements as a means of reducing the risk of eye disease	• No reported adverse effects in clinical trials on supplementation of up to 30 mg daily for up to 1 year • Lutein concentrations vary widely in different supplemented formulas • Generally recognized as safe
5. Prebiotics and probiotics	• Prebiotic is a nondigestible food ingredient that affects the growth/activity of one bacterium or a limited number of bacteria in the colon (eg, lactulose, oligosaccharides) • Probiotic is a live, nonpathogenic microbial food that is normally part of the human intestinal microflora which enhance intestinal microbial balance (eg, *Bifidobacterium bifidum, Lactobacillus*)	• Some small positive studies of probiotics ingestion for prevention or treatment of gastroenteritis • Prebiotics (mixture of galacto-oligosaccharide and fruto-oligo-saccahrdies) significantly increase *Bifidobacteria* population and reduce the number of pathogens to levels similar to those in breast-fed infants • Might be beneficial to infants suffering from constipation by increasing stool frequency, reducing stool pH and softening stool consistency; effect only exists during period of ingestion	• No well-designed RCT to demonstrate the efficacy; limited data on long-term efficacy and safety • Optimal quality and strains of probiotics are uncertain • Very limited data on use of prebiotics; thus, general recommendations cannot be given	• Theoretical risk of developing resistance against antibiotics; might become risky if the resistance is transferred to other enteric pathogens • Caution in immunocompromised individuals (eg, premature infants) • Prebiotics might increase the risk of dehydration in young infants during time of stress (eg, fever, infectious diarrhoea)
6. Selenium	• An antioxidant and a component of a group of enzymes that remove toxic peroxidase and protect cell membrane from oxidative injuries • Severe deficiency in young infants is associated with skeletal and cardiac myopathy	• Important in preterm infants because of the rapid postnatal growth, lower plasma concentration, less fetal accretion, and higher risk of oxidative stress • Poor selenium intake in preterm infants increases risk of chronic lung disease	• Doubtful benefit in term infants • Need more studies to show the direct causal relationship in preterm infants	• Oversupplementation might increase the risk of infection

ARA = arachidonic acid; DHA = docosahexaenoic acid; RCT = randomized controlled trials; SGA = small for gestational age; URTI = upper respiratory tract infections; WISC-R = Wechsler Intelligence Scale for Children revised edition

of extensive hydrolysis frequently comprised the taste of the milk, and might compromise protein and nitrogen utilization. Therefore, regular assessment of growth, blood urea and (where feasible) blood amino acid values (compared with reliable local reference values from breastfed infants) is recommended for infants on prolonged treatment with casein or whey eHF.[7] Although there are claims that infants at high risk for developing allergy, as identified by a strong family history (biparental, parent or sibling) of allergy, may benefit from feeding with a hypoallergenic formula, conclusive studies are not yet available to permit definitive recommendations. A Cochrane review showed no evidence to support feeding with eHF for prevention of allergy in preference to exclusive breastfeeding.[8] Therefore, the use of these eHP infant formulas, which cost as much as three times more than standard formulas, should be limited to infants with well-defined clinical indications as listed above.

Free Amino Acid Formulas

Amino acid-based formulas, also known as elemental formulas, are a type of hypoallergenic infant formula whose protein is broken down into individual amino acids. The amino acids are in the simplest form, making it easy for the body to process and digest. Commercially available amino acid-based formulas for infants 0–1 year of age include Neocate and Nutramigen AA.

Amino acid-based formulas are classified as medical foods and should be prescribed by doctors under specific indications. These formulas are most commonly indicated for children with multiple food protein intolerance, cow's milk protein allergy-induced eosinophilic oesophagitis and intractable gastro-oesophageal reflux disease unresponsive to eHF. Other medical conditions requiring an amino acid-based diet are severe enteropathy or short bowel syndrome to facilitate transition from parenteral to enteral nutrition. Amino acid-based formulas usually have a higher osmolarity and poor taste. Flavouring can be added to improve its acceptability.

Premature Infant Formulas

Premature infants in general have a higher energy requirement of 120 kcal/kg/day. The requirement may be as high

as 150 kcal/kg/day for those with heart failure or chronic lung disease. Premature infant formulas are designed to meet the higher nutritional requirement of the rapidly growing low birth weight (LBW) infants. Compared with formulas for term infants or human milk, premature infant formulas contain a higher amount of calorie (24 kcal vs 20 kcal per ounce). The protein content is also higher (1.4 g vs 1.1 g per 100 mL), with the protein being predominantly whey protein. The carbohydrates are mixtures of lactose, glucose polymers and maltodextrins. The fat component has a higher proportion of MCT oil. To cater for the rapid growth and rapid tissue turnover in premature infants, there is a higher mineral content including increased calcium to phosphorus ratio and higher iron content. Most premature infant formulas are also fortified with DHA, ARA, taurine and other nucleotides.

Therefore, premature infant formulas are generally recommended for premature infants born earlier than 34 weeks or whose body weight is less than 1,800 g, and when breast milk is not available. Breast milk, if available, is still the preferred source of nutrient over infant formula for premature infants for its immunological and other health benefits. The calorie and nutrients of breast milk can be enhanced with the addition of a breast milk fortifier, or supplemented with a premature infant formula or parenteral nutrition. Studies showed that development of LBW infants fed with human milk is comparable to that of infants fed with nutrient-enriched formulas despite a slower early growth rate. Exploratory analysis have suggested that some subgroups of LBW infants fed with human milk may have enhanced development.[9]

Premature infant formulas are not available for sale in the market, and most of the premature infants will either switch to breast milk, ordinary formulas or other nutrient-enriched formulas (eg, Neosure) after hospital discharge.

Weaning and Introduction of Solids

For most infants, breast milk and/or iron-fortified formulas provide all required nutrients during the first 6 months of life. After 6 months, milk is still important and mothers should be advised to continue breastfeeding if possible. If no human milk is available, fortified infant formulas continue to be the optimal choice. It is not necessary to change to a follow-on formula. The amount of milk calories consumed should gradually reduce to <65% of the total calories; the rest should be consumed from solid foods, which are rich in vitamin and iron. Parents should be aware of and respond to their infants' developmental skills and appetite cues so that they can provide appropriate foods in a positive, safe and healthy feeding environment. Parents should not overdominate the time, amount, type and pace of food to be given to a young infant.

When to Introduce Solids?

Introduction of solid foods begins when the baby is at the appropriate stage of development, which may vary between individuals. In general, babies about 6 months of age are physiologically (better functioning gut and kidney) and developmentally (better head control, with ability to sit upright) ready for solid foods. Late introduction of solid foods may lead to problems in accepting solid foods later as it takes time for babies to learn chewing and swallowing, as well as tasting foods of different textures.

Starting Solid Foods: A Step by Step Process

Introduction of solid foods is best started with a small amount (about one teaspoonful) of rice cereal prepared in a thin and smooth texture. The amount and texture can be increased gradually from thin, smooth, creamy and puree consistency to a thickened and coarse texture, depending on the acceptance of the baby.

It is best to start solids and try new foods when the baby is hungry and wants to eat, but one should work towards a regular feeding schedule. During feeding, it is best to wait for the infant to pay attention and open her mouth before trying to feed her. Some parents find it easier to feed the baby by distracting her with television or toys. However, to develop a good eating habit, it is best to avoid making the baby too excited during feeding. The baby should be allowed to eat at her own pace. Parents should let her eat as much as she wants and stop feeding as soon as she shows you that she is done.

The Order of Introducing Complementary Foods

For otherwise well infants with a low risk of allergy, the order of introduction of various kinds of food is not critical. One can first start with foods that are generally less allergenic. It is recommended to give single-ingredient food as the first solid food (usually rice cereal), and to start one solid food at a time at 2- to 7-day intervals. Combination foods may be given to older infants after tolerance to the individual components has been established.

Schedule of Introducing Solids

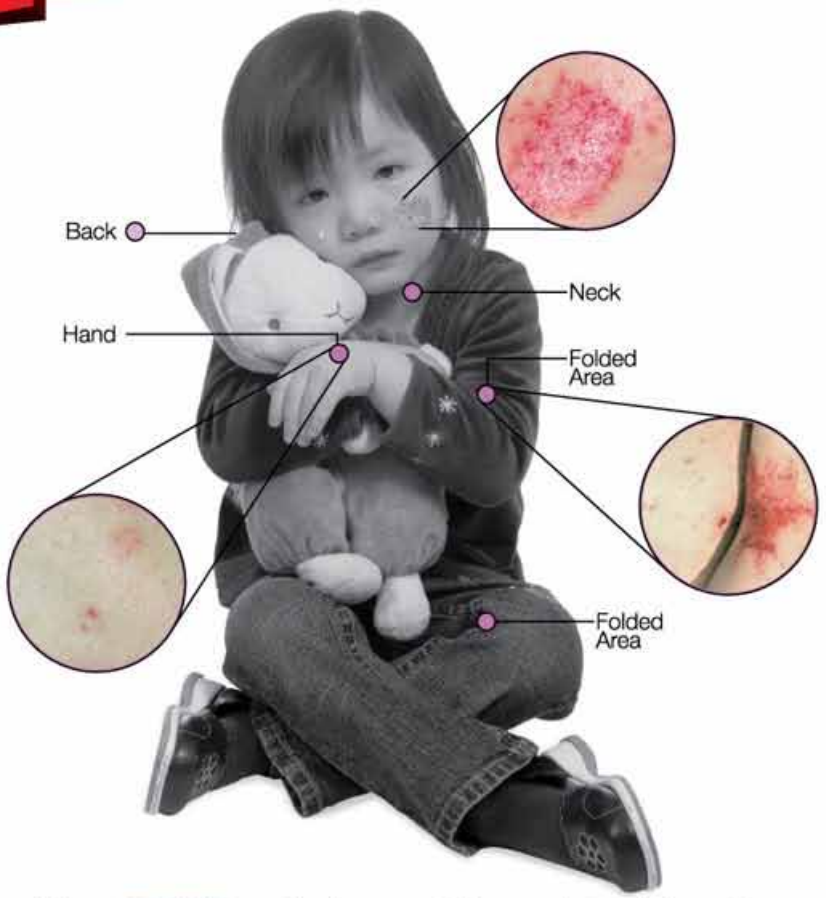
Infants should be encouraged to have meals with the family from an early age, for both social and nutritional reasons. There is no hard rule for scheduling solid food. Parents can take the following feeding pattern as reference:

- 6 to 9 months of age: Three to four milk feeds, with solid food twice a day
- 9 to 12 months of age: Two to three milk feeds, with 2–3 times of solid food a day
- 1 to 2 years of age: One to two milk feeds, with 3 times of solid food plus a snack a day
- About 2 years of age: Three meals a day, with two additional snacks in between

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

Atopic Dermatitis

A Rising Problem...



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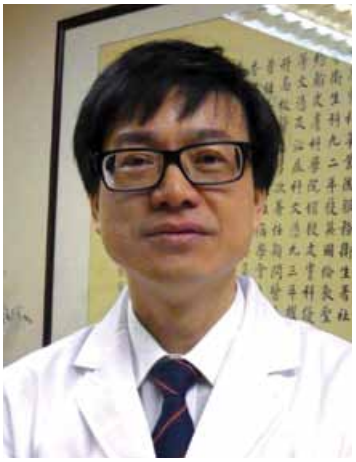
Case Quizzes in Dermatology



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Key words: Rash (皮疹), macule (斑疹), reticulated pattern (網狀), tetracyclines (四環素)

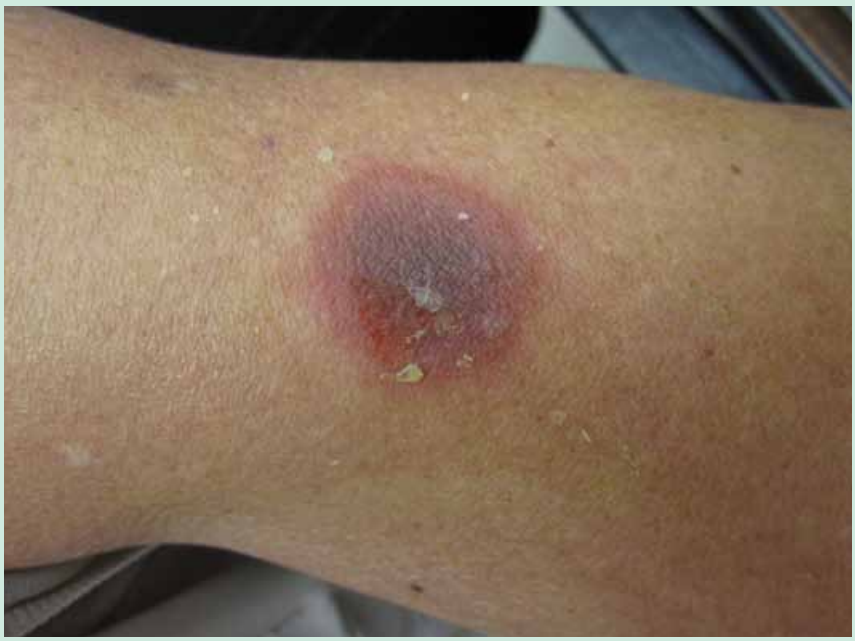
Case 1: Recurrent Rash on the Limbs of an Elderly Man

A 70-year-old patient reported 1-month history of recurrent, itchy and burning skin rash affecting his face and limbs. He denied preceding trauma or insect bite, and had no fever or systemic upset. He enjoyed good past health with no history of diabetes mellitus, hypertension or cardiac disease. He was not on long-term medication except for irregular intake of "anti-inflammatory" drugs for degenerative arthritis of his knee.

Physical examination revealed a few round macules over the neck, and upper and lower limbs. Each lesion measured about 1 to 2.5 cm in diameter. A central dusky red area was noted in the more recently erupted lesions. Central blistering and erosion were noted in a few. Several hyperpigmented macules were noted on the body suggestive of resolving old lesions. Further examination showed an erythematous macule on the glans penis. The eyes and oral mucosa were not affected.

Questions

1. What is the clinical diagnosis?
2. What is the typical presentation of this condition?
3. What are the commonly affected anatomical sites in this condition?
4. What are the medications implicated in this condition?
5. What are the treatments?



Answers on page 92

Case 2: Net-like Rash on the Back of a Young Lady

A 30-year-old Chinese lady presented with 1-year history of recurrent itchy skin rash on the shoulders and back. She was not able to recall any provoking factors. The rash could last for days, after which the itch lessened. However, the rash and itch did not totally resolve, and a second wave of itchy eruption occurred.

The patient enjoyed good past health with no history of skin, food, drug or contact allergy. Treatment with topical steroid failed to give significant improvement. On examination, there were multiple erythematous papules on the back. Some papules were excoriated. Red papules were intermingled with pigmented macules and papules. The shoulders and upper and mid back were involved, exhibiting symmetry and a net-like pattern. Examination of skin elsewhere and mucous membranes were unremarkable.

Questions

1. What is the clinical diagnosis?
2. What are the differential diagnoses?
3. What are the factors associated with this disease?
4. What are the treatments?

Answers on page 92

Case Study – A Patient with Paresthesia of Both Hands

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A 63-year-old male working as an accountant started to experience vague tingling of both palms in early April 2010. The sensation was quite mild, but in about 2–3 weeks' time it seemed evident that this was something out of the ordinary. There was no pain, weakness or clumsiness. Apart from feeling a little tired, he was otherwise well, and continued with his usual busy schedule at work. He did not have any history of diabetes, hypertension or other chronic diseases. There was no exposure to toxic chemicals, side effects of drugs or the suspicion of a deficiency state. He was a non-drinker and non-smoker. Physical examination was normal. Routine screening blood tests including vitamin B levels were normal. There was no evidence of collagen vascular disorders or monoclonal gammopathies. A nerve conduction test performed in June was insignificant. There was no evidence of carpal tunnel syndrome or nerve entrapment at other sites. Magnetic resonance imaging (MRI) of the cervical spine was normal.

Questions:

1. What was the clinical syndrome?
2. Which specific blood test was indicated?

Continued on page 89

Treatment of *Helicobacter pylori* in Practice

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Key words:
Helicobacter pylori (幽門螺旋菌), resistance (抗藥性), triple therapy (三合療法)

Introduction

Helicobacter pylori was first discovered by two Australian clinicians, Warren and Marshall, in early 1980s.[1] This discovery has dramatically changed our understanding of the pathogenesis of peptic ulcer disease and gastric cancer, which led to the award of the Nobel Prize in Medicine and Biology in 2005. *H pylori* is a Gram-negative bacterium that lives in the mucus layer of the stomach. It can easily be eradicated by a combination of antibiotics. Eradication of *H pylori* leads to improvement of chronic gastritis and healing of peptic ulcer. However, it remains to be proven whether *H pylori* clearance could prevent gastric cancer development, although findings of a recent meta-analysis favour this speculation.[2]

One important emerging issue related to treatment of *H pylori* infection is the ever-rising failure rate of recommended first-line treatments. Standard triple therapy for *H pylori* includes a proton pump inhibitor (PPI), amoxicillin, and clarithromycin or metronidazole. Although this triple therapy regime is recommended by various international and local gastroenterology societies,[3-5] the previously reported high eradication rate (>90%) is not encountered anymore in daily practice due to increasing antibiotic resistance.

Indications for Treatment

Before we prescribe our patients with anti-*H pylori* therapy, the most important question to ask is whether treatment is indicated and necessary. Despite the causal relationship between *H pylori* and peptic ulcer or gastric cancer, it remains controversial whether *H pylori* should be eradicated in all infected individuals. In particular, there is concern that eradication of *H pylori* may increase the risk of proximal gastric cancer related to gastro-oesophageal reflux disease, especially in Western countries. The currently recommended indications for *H pylori* treatment are listed in Table 1.[3-5] Patients with peptic ulcer disease or dyspepsia would benefit most from *H pylori* eradication therapy.[6,7] It is also believed that *H pylori* should be eradicated in patients who require nonsteroidal anti-inflammatory drugs or aspirin, and in first-degree relatives of gastric cancer patients.

"Patients with peptic ulcer disease or dyspepsia would benefit most from* H pylori *eradication therapy"

With the global decline in *H pylori* prevalence, empirical therapy is not generally recommended. Hence, pre-treatment testing for confirmation of *H pylori* infection is considered necessary under most circumstances. C-13 urea breath test and *H pylori* stool antigen test are two reliable noninvasive tests in diagnosing current *H pylori*

Table 1. Indications for *H pylori* treatment

Recommended	Peptic ulcer disease
	Gastric MALToma
	After endoscopic resection of early gastric cancer
	H pylori-infected nonulcer dyspepsia
	To reduce the risk of peptic ulcer and upper gastrointestinal bleeding in patients naïve to nonsteroidal anti-inflammatory drugs
Controversial	Gastric cancer prevention in high-risk populations
	Patients with first-degree relatives who have gastric cancer
	Before starting long-term aspirin therapy for patients at high risk of ulcers and ulcer-related complications
	Gastro-oesophageal reflux disease patients requiring long-term PPI therapy

MALT = mucosa-associated lymphoid tissue; PPI = proton pump inhibitor
Adapted from references 3-5.

Table 2. Current treatments for *H pylori* infection		
	Regime	**Duration**
First-line		
Concomitant	PPI (standard dose) bid Clarithromycin 500 mg bid Amoxicillin 1,000 mg bid or metronidazole 400 bid or tds	7–14 days
	PPI (standard dose) bid Bismuth 120 mg qid Metronidazole 400 mg tds or qid Tetracycline 500 mg qid	7–14 days
Sequential	PPI bid Amoxicillin 1,000 mg bid Metronidazole 400 mg tds Clarithromycin 500 mg bid	10 days Day 1–5 Day 6–10 Day 6–10
Retreatment		
	PPI bid Levofloxacin 250 mg bid Amoxicillin 1,000 mg bid	10–14 days
	PPI bid Bismuth 120 mg qid Metronidazole 400 mg tds or qid Tetracycline 500 mg qid	10–14 days
	PPI bid Amoxicillin 1,000 mg bid Metronidazole 400 mg tds or qid Clarithromycin 500 mg bid	10–14 days

PPI = proton pump inhibitor; bid = twice daily; tds = three times per day; qid = four times per day

infection. They are also useful in monitoring treatment success. Previous experience with *H pylori* serology tests found that they have poor accuracy in diagnosing infection in our population. Serology tests also have a very limited role in monitoring treatment success due to the persistence of immunoglobulin G antibody in the body. Endoscopic biopsy is the only way to obtain tissue for *H pylori* culture and hence sensitivity testing. It could be considered in patients with refractory or difficult-to-cure *H pylori* infection such that antimicrobial sensitivity can be determined.

Therapy for *H pylori*

Bismuth-containing triple therapy (bismuth, tetracycline and metronidazole) was the classical therapy for *H pylori* infection in the 1980s and early 1990s. Due to its poor tolerance by patients, it was rapidly replaced by the PPI-based triple therapy. PPI-based triple therapy, which consists of 1–2 weeks of a PPI, clarithromycin, and amoxicillin or metronidazole, has been shown to have a very high eradication rate (>90%) in clinical trials.[8] It remains the recommended treatment for *H pylori* infection according to guidelines of various societies,[3-5] although the recommended duration of therapy is 7 days in Europe and 10–14 days in America. A longer duration of therapy is associated with a slightly higher (<5%) eradication rate.

"With the global decline in H pylori prevalence, empirical therapy is not generally recommended"

However, the high success rate is no longer encountered in current practice due to the rapid emergence of antibiotic resistance, particularly to clarithromycin. The current success rate of standard triple therapy is far less than 80% in most countries.[9] Hence, post-treatment testing to confirm *H pylori* eradication appears to be necessary, particularly in patients with peptic ulcer disease. There is a genuine need to search for a better and more effective regime for *H pylori* infection to replace the currently recommended triple therapy.

Whilst conventional triple therapy consists of concomitant therapy with a PPI and two antibiotics, recent studies showed that the eradication rate can be improved by using three different antibiotics given sequentially over two 5-day intervals (sequential therapy).[10] Together with 10 days of PPI, the sequential therapy consists of 5 days of amoxicillin and another 5 days of metronidazole and clarithromycin. This regime has been shown superior to standard triple therapy in clinical trials. Preliminary data also support the use of sequential therapy in Asia.[11] It is however suggested that the efficacy of sequential therapy drops in the presence of dual resistance to clarithromycin and metronidazole. Concomitant, rather than sequential, use of three different antibiotics has been proposed to overcome this dual resistance issue,[9] and further data are needed to address the problem.

Treatment Failure

With the widespread use of antibiotics for respiratory and urinary tract infections in the community, *H pylori* resistance to clarithromycin are not uncommon. Patients previously exposed to these antibiotics are therefore at higher risk of treatment failure. Resistance to other antibiotics (eg, amoxicillin) is less common and can sometimes be overcome by increasing the dose and duration of antibiotics (eg, metronidazole).

When patients failed first-line triple therapy, one has to consider alternatives. Resistance to previous antibiotics should be assumed to be the case, and simply repeating or prolonging the previous regime is unlikely to be successful. In the absence of pretreatment antibiotic resistance profiles, different regimes have to be applied. Moreover, a longer duration of therapy (10–14 days) is considered necessary in patients with

previous treatment failure. Whilst resistance to clarithromycin is likely to be the contributing factor for treatment failure in patients receiving standard triple therapy, substituting clarithromycin with levofloxacin is a viable option. (Table 2) However, levofloxacin resistance is also rising, which may limit the use of this rescue regime. Another approach would be to use the classical bismuth-containing triple regime (bismuth, tetracycline and metronidazole) and PPI (bismuth-based quadruple therapy) to overcome antibiotic resistance. In particular, high-dose metronidazole can possibly overcome metronidazole resistance. However, the bismuth-containing regime is associated with considerable side effects, and a significant proportion of patients cannot complete the whole course of therapy. As described above, the use of sequential or concomitant quadruple therapy with a PPI, amoxicillin, clarithromycin and metronidazole has also been suggested in patients with previous treatment failure. Other less commonly used regimes include the use of rifabutin or furazolidone to substitute for clarithromycin or metronidazole. The risk and benefits of using these drugs for the treatment of *H pylori* infection should be carefully balanced, and their use should be reserved for specialists.

Conclusion

Despite the initial success in treatment of *H pylori* infection in the past, antibiotic resistance has led to a rapid decline in treatment success rate. Previously recommended standard therapy for *H pylori* may no longer be effective in daily practice. A longer treatment duration and the addition of a third antibiotic may partly overcome this issue. Local resistance profiles should be monitored closely, and new clinical trials on treatment of resistant *H pylori* should be conducted. Whilst new antibiotics for *H pylori* are unlikely to be available in the near future, cautious use of existing antibiotics in the community should be reinforced.

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Case Study

The more common conditions to be ruled out included nerve entrapment syndromes such as carpal tunnel syndrome, peripheral neuropathy and cervical lesions, which were reasonably excluded by the tests already mentioned. Peripheral neuropathies usually affect the lower limbs first, and with greater severity. It is also associated with muscle wasting and motor weakness. Selective disturbance of sensory function, especially affecting the upper limbs initially, would suggest a **sensory neuronopathy**. In this condition, the dorsal root ganglion is selectively damaged, sparing the function of motor nerves. In patients suffering from sensory neuronopathy of unexplained causes, more than one-third may develop an associated cancer.[1] The symptom therefore points to a paraneoplastic neurological syndrome. In this syndrome, a cancer, recognized by the host immune mechanism as a foreign body, triggers the secretion by T cells of certain antibodies, which in turn attacks parts of the normal nervous system. One of these antibodies, anti-Hu (also known as ANNA 1 or antineuronal nuclear antibody 1), is particularly associated with the syndrome of sensory neuronopathy.

The patient's serum tested positive for anti-Hu.

Question:

3. If you are allowed to do one more laboratory test, which would you choose?

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Colon Cancer – The Rising Star

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Key words:
Colon cancer (結腸癌), chemotherapy (化療), targeted therapy (標靶治療)

Introduction

Colon cancer is gradually emerging as the most common cancer in Hong Kong in both male and female.[1] It is a typical example of how the environment can influence our genes and lead to a fatal outcome. This paper intends to highlight the aetiology, diagnosis, treatment, early detection and possibly prevention of colon cancer.

Aetiology

About 10% to 15% of colon cancer are hereditary and strongly associated with mutation or dysfunction of protective genes, such as *adenomatous polyposis coli (APC)* or the 'mismatch repair' gene for hereditary non-polyposis colorectal cancer (HNPCC). Carriers tend to develop cancer at an earlier age (usually before 40), and a detailed family history may reveal the pedigree of disease.

Environmental factors account for 80% of the cases, and the peak incidence is around 45 to 55 years of age. According to epidemiological studies, excess intake of fat and calorie and low fibre intake is the major culprit.

Clinical Features

Most colon cancer patients present with alteration of bowel habit such as frequent passage of mucous or bloody stool. Unlike the blood-stained stool in haemorrhoids, the blood content usually intermingles with stool in patients with colon cancer. In severe cases, the tumour may obstruct faecal passage. This leads to complete large bowel obstruction, and the patients may present initially at the emergency room. In the past, they were treated with initial defunctioning colostomy and then definite resection, followed by re-anastomosis at a later stage. Nowadays, colonic stent for initial decompression followed by surgery is a preferred method.

Hereditary cancer tends to occur frequently on the right side of the colon. The presentation is subtle because stool materials are relatively slippery due to higher water content. Moreover, hereditary colon cancer seldom causes obstructive symptoms, but there is a tendency for prolonged insidious bleeding. Not uncommonly, the patients present with symptoms and signs of anaemia especially in young male. Therefore, it is imperative to search for underlying gastrointestinal cancer in young anaemic patients. Patients with ulcerative colitis should be followed up closely for cancer development.

Investigation

Anyone presenting with suspicious symptoms or signs of colon cancer needs full investigation using colonoscopy and biopsy under sedation, usually at an outpatient setting. If colonoscopy is difficult, one can use computed tomography (CT) virtual colonoscopy to detect the lesion. Once the diagnosis of colon cancer is established, whole-body positron emission tomography-CT (PET-CT) is most valuable for staging.

Treatment

Surgery is the mainstay of treatment for stage I to stage III disease. For mucosal lesion, the state-of-the-art therapy is endoscopic resection. The rest are treated by en-bloc resection of the primary tumor together with the regional lymph nodes.[2]

Rectal cancer should be evaluated with magnetic resonance imaging (MRI) or endoscopic ultrasound to evaluate the depth of invasion. If the fat plane is involved, preoperative radiotherapy plus chemotherapy are necessary to reduce the chance of local relapse. If the fat plane is intact, mesorectal excision is enough. Conventional anterior resection is usually feasible for tumours 7 cm above the anal edge. With the help of anastomotic gun, one can reduce the margin to 4–5 cm. Abdominal-perineum resection is reserved for those with a margin of less than 4 cm.

The recent trend of colon cancer resection is laparoscopic resection through the port hole. The relapse rate and survival are comparable with the traditional approach, but the hospital stay is shorter and postoperative complications are reduced.

Adjuvant chemotherapy with 5-fluorouracil (5-FU) and leucovorin (also known as folinic acid) for a period of 6 months is offered to patients with stage III disease. Evidence suggests that this regimen reduces 5-year mortality by 5% to 10 %.[3]

Patients with stage IV disease with liver involvement were deemed inoperable in the past. However, recent data showed that targeted therapy with

cetuximab (also known as C225) in combination with FOLFOX (oxaliplatin, leucovorin and 5-FU) or FOLFIRI (irinotecan, 5-FU and leucovorin) chemotherapy can shrink the liver metastases to a resectable size, with 5-year survival of 30%.[4]

Tumour gene analysis for *KRAS* mutation helps determine whether the patient is likely to respond to cetuximab therapy.

For patients with metastatic disease, the gold-standard treatment is combination chemotherapy using 5-FU plus oxaliplatin, or 5-FU plus irinotecan. The response rate is around 40%.[5] The addition of bevacizumab or cetuximab to these chemotherapy regimens may increase the response rate further to 70%, as well as the overall survival.[6]

Early Detection

The natural history of colon cancer is that it often starts as a polyp and gradually develops into a malignant lesion over a period of 5 to 7 years. This provides us with an ample opportunity to detect the cancer over that period.

Different countries adopt different screening tools for early detection. In Britain, faecal occult blood test and flexible sigmoidoscopy are used, but in the USA colonoscopy is used instead. The availability of resources dictates the pattern of screening in different parts of the world. For individuals with a family history of colon cancer, it is suggested to start screening at the age of 30. For the ordinary public, the appropriate age for commencement of screening is 50.

Prevention

Since the majority of colon cancer is environmentally related, it is imperative to reduce the risk factors in our diet. A randomized controlled study of individuals taking supplementary diets high in fruits and vegetables showed an improvement of gene repair function and reduced risk of developing cancer.[7] However, the supplementary food content is high. We need to consume 2–3 lbs of fruits and vegetables daily. That is roughly equivalent to 2 bowls of fruits and vegetables.

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Answers to Case Quizzes in Dermatology

Answers to Case 1

1. The clinical diagnosis is fixed drug eruption (FDE).
2. FDE is a relatively common and distinctive form of drug reaction. It develops in the same site with each exposure to a particular medication. The lesions are well-demarcated, round or oval patches with erythema and swelling, sometimes developing into blisters. Local symptoms include pain and pruritus. Postinflammatory hyperpigmentation is common.
3. FDE commonly occurs in the oral and genital mucosa, face and acral areas, although anywhere of the body may be involved.
4. Many medications have been implicated. These include non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen and mefenamic acid, sulphonamides, tetracyclines, barbiturates, salicylates, paracetamol and phenolphthalein. On further questioning, the patient said he noted the occurrence of eruption upon taking NSAID for his arthritis.
5. The offending drug should be identified and avoided, as repeated challenge may cause worsening of subsequent eruption. For mild disease, topical steroid improves symptoms. For an extensive eruption, systemic corticosteroid may be required to hasten recovery.

Answers to Case 2

1. Prurigo pigmentosa (PP).
2. The history of chronic, recurrent pruritic erythematous papules (sometimes with vesicles) with hyperpigmentation, coalescing into a reticulated pattern and found over the back, sacral areas, chest and abdomen is characteristic of PP. Differential diagnoses include dermatitis herpetiformis, pigmented contact dermatitis, linear immunoglobulin A disease, and confluent and reticulate papillomatosis. These can be distinguished by careful clinical history and histopathological changes from skin biopsy.
3. The aetiology of PP is unknown, and pathogenesis is not certain. Many cases were reported in Japan, suggesting that ethnicity or environment may play a role. Friction with clothes has been implicated. Systemic diseases such as diabetes mellitus and ketosis, as well as pregnancy, fasting or dieting have been associated with PP.
4. Topical and/or systemic corticosteroids are not effective for PP. Dapsone, sulfamethoxazole and tetracyclines have been shown effective in prompting resolution, but the postinflammatory hyperpigmentation remains. For some cases not responsive to minocycline, macrolide antibiotics may be effective.

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Discussion of Case Study

Now that the patient was confirmed to suffer from a paraneoplastic neurological syndrome, a thorough search for cancer was indicated. In a series of 200 patients positive for anti-Hu, 83.5% were detected to have a cancer, 90% of which were small cell lung cancer.[2] The one test that was most likely to be productive is therefore a low-dose computed tomography (CT) of the lung. In this patient, this was negative. Other tests performed included bronchoscopy, gastroscopy, colonoscopy, total body MRI and CT upper abdomen with contrast. These all proved to be negative.

In such patients, a positron emission tomography-computed tomography (PET-CT) would be in order. An abnormal scan can be expected in 20%–40% of cases. Since the rate of false positive scans is high, only 10%–20% of cases will eventually be found to have a cancer.[3] PET-CT on this patient, performed on 7 July 2010, turned out to be normal. In the mean time, the patient's symptoms subsided. Repeated blood test for anti-Hu was negative on two occasions. The patient was well in November 2010.

Paraneoplastic neurological disorders are normally severe, disabling and rapidly progressive. If the search for cancer is negative, usually a repeat work-up is indicated in about 6 months. Since the symptoms were mild and had regressed in this patient, and the antibody had disappeared from the body, a longer interval for repeat investigation seemed to be justified.

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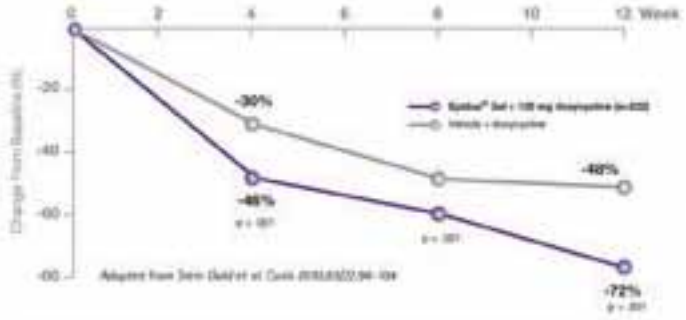
Epiduo™ New clinical data

Effective in combination with doxycycline in patients with severe acne[1]

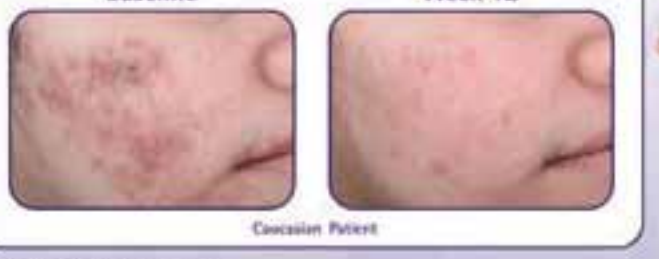
Effective and Safe Combination Therapy for Severe Acne Vulgaris: A Randomized, Vehicle-Controlled, Double-blind Study of Adapalene 0.1%–Benzoyl Peroxide 2.5% Fixed-Dose Combination Gel With Doxycycline Hyclate 100 mg

A randomized, vehicle-controlled, double-blind study of Epiduo® Gel with doxycycline 100 mg (N=459).

Median reduction in inflammatory lesions over 12 weeks (N=459)



Patients with inflammatory and comedonal lesions[1]



Cutaneous tolerability results

- Mean tolerability scores for both arms at each visit were all less than mild (<1)
- Few local cutaneous dermatologic adverse events were reported in the Epiduo® Gel + 100 mg doxycycline arm (1.7%)
- Most reported adverse events were GI disorders, which were primarily associated with doxycycline use (9.6%)

At week 4

- 46% median reduction in inflammatory lesions at week 4 (P< .001)[1]

At week 12

- Patients treated with Epiduo® Gel + 100 mg doxycycline experienced a 64% median reduction in total lesions at week 12 (P< .001)[1]
  - 72% median reduction in inflammatory lesions at week 12 (P< .001)[1]
  - 61% median reduction in noninflammatory lesions at week 12 (P< .001)[1]

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Before prescribing the product, the complete prescribing information should be consulted. For prescribing information is available on request.

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Infant Feeding in the First Year (Part II) – Nutritional Additives, Special Formulas and Introduction of Solids

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