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JOURNAL OF PAEDIATRICS, OBSTETRICS & GYNAECOLOGY

JPOG

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IN PRACTICE

JOURNAL WATCH

PAEDIATRICS

Type 1 Diabetes Mellitus in Childhood

Atopic Dermatitis in Children: A Practical Approach

GYNAECOLOGY

Bacterial Vaginosis

CME ARTICLE

1 Point

Ovarian Cancer Screening—An Update

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MAR/APR 2012
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Journal Watch

Review Articles

Paediatrics

Friso® gold

Family of Products

Brand Name	Frisomum Gold	Frisolac Comfort	Frisolac Gold 1	Frisolac Gold 2	Friso Gold 3	Friso Gold 4
Product Descriptor	Maternal Formula	Special Infant Formula	Infant Formula	Follow-up Formula	Growing Up Milk	Growing Up Milk
Age Descriptor	For Pregnant & Breast-feeding mothers	From birth onwards	From birth to 12 months	From 6 months onwards	1 - 3 years	3 - 9 years
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Breast Milk Is the Best For Babies

Mother's milk is the best for baby because it uniquely fulfills of the baby's needs. Mothers should start breast-feeding as soon as possible within the first hour after delivery. Breast milk has several benefits – it provides the best nutrition for babies; strengthens immunity; prevents various allergic disorders; contain nutrients critical to brain development and has a reduced in chance of contamination which can occur with other forms of feeding. Breast milk contains several strains of beneficial bacteria. It contains oligosaccharides so breast fed babies are rarely constipated. To prevent a diminishing supply of breast milk, supplementary feeding or bottle feeding should not be given too early. Once a decision is made to stop breast-feeding, it is difficult to reverse. Working mothers can also continue breast-feeding. We at Dutch Lady Milk Industries Berhad support breast-feeding. Not only it is good for the baby's health, but it is also strengthens the bond between mother and baby - a bond that lasts a lifetime.

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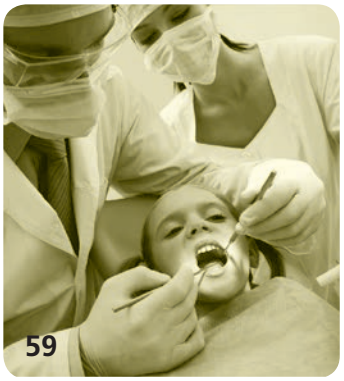

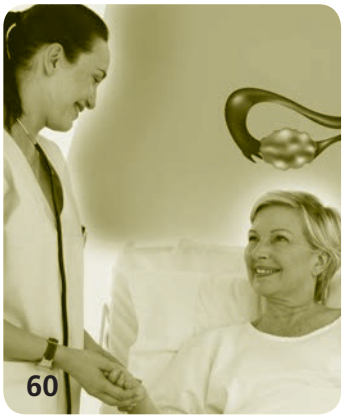

In Practice

Review Articles

Gynaecology

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UBM Medica

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Milk-based from EU formulated in accordance with Malaysian Food Act 1983 and Food Regulations 1985. Besides 25 vitamins and minerals, all contain Omega 3 & 6 from vegetable oils, pre-cursors for DHA & AA to meet the nutritional needs.

Adapted formula

for infants with mild gastrointestinal disorders (MGD)

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(0-12 months old)

Novalac IT Grow
(1-3 years old)

For constipation
The key nutrient mix :
- Modified level of lactose and magnesium
- Ca/P ratio of 2
- Medium-chain triglycerides (MCT)
- Whey/Casein ratio of 60/40

Novalac AC
(0-12 months old)

For colic
The key nutrient mix :
- Reduced lactose load
- Maltodextrins enriched with amylopectin

Novalac AR
(0-12 months old)

For regurgitation and reflux
The key nutrient mix :
- Corn starch enriched with amylopectin that thickens only in the low pH (stomach)
- Medium-chain triglycerides (MCT)

Novalac AD
(from birth onwards for temporary use as per advice of health professional)

For acute mild-to-moderate diarrhoea
The key nutrient mix :
- Lactose-free, replaced with maltodextrins and monosaccharides
- Modified electrolytes levels with low osmolarity
- Fruit pectin and cream of rice

Standard formula

Novalac 1
(0-6 months old)
Infant formula

Novalac 2
(6-12 months old)
Follow-up formula

Novalac 3
(1-3 years old)
Growing-up milk with light vanilla taste

The key nutrient mix :
- Reduced lactose load
- Maltodextrins enriched with amylopectin
- Sucrose-free

The benefits and superiority of breastfeeding :

Breast milk is the best food for infants as it provides the best nutrition, immune defence and protection from diarrhea, colic, regurgitation and constipation for infants. Good maternal nutrition is essential to prepare and maintain breast-feeding. Mothers should be reminded the benefits of breast milk, and also it is the most economical food for infants.

However, if mothers decide to supplement with an infant formula or not to breastfeed at all, they should seek advice from their health professionals before starting the use of infant formula. Mothers should be professionally instructed on the importance of infant feeding methods, including the cost of infant formula and the health hazards of inappropriate foods or feeding methods. Working mothers should also be encouraged to continue breastfeeding even after they resume their full time jobs. Mothers who are unable to breastfeed should seek professional advice. It is important to warn mothers of the difficulty of reversing a decision not to breastfeed.

When Healthy and Happy, 1Family Rejoices

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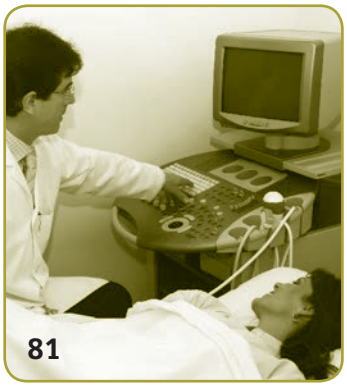

Review Articles

Paediatrics

The Cover:
'Atopic Dermatitis in Children'

Rowena Sim, Art Director
Connie Lim, Illustrator

This material is for medical professionals only.

Nestlé Start Well Stay Well

"I can't see you, but I can already protect you."

From pregnancy through breastfeeding, the baby's good development relies on essential nutrients that can be provided day by day through balanced nutrition.

New **Nestlé MOM&ME®** is a nutritional supplement especially designed for both mother and baby:

- With **BL® BIFIDUS** active cultures to help establish friendly bacteria in the intestine
- Added with **DHA**, which is found in abundance in the brain
- Added with **20 vitamins** and **minerals**, including **folic acid**, **iron** and **calcium** to support the baby's overall growth and development

Nestlé MOM&ME® every day to start a happy motherhood journey.

Dedicated to protection from day 1

Colonisation by gut microflora is essential

Bacterial colonisation of the gut can be significantly delayed in Caesarean-born infants,[1,2] potentially delaying maturation of the immune response.[3,6] NAN® Pro™ contains BL BIFIDUS®, a probiotic shown to help all infants – even those delivered by caesarean section – build a healthy intestinal microbiota.[7,8] It has been shown that infants fed NAN® Pro™ may have a lower incidence of rotavirus infection[9] and diarrhoea[10] than infants fed a non-probiotic formula.

NAN® Pro range, distributed and imported by Nestlé Malaysia is certified Halal and has passed the stringent inspection of the Department of Islamic Development, Malaysia (JAKIM). Muslim consumers are completely assured that Nestlé Malaysia provides only Halal products.

Important Notice:

The Ministry of Health Malaysia[1] and the World Health Organisation (WHO)[2] have recommended that pregnant women and new mothers be informed of the benefits and superiority of breast-feeding – in particular the fact that it provides the best nutrition and protection from illness for babies. Breastfed infants have a healthy intestinal microbiota and reduced risk of infections and diarrhoea. Mothers should be given guidance on the preparation for, and maintenance of, breast-feeding, with special emphasis on the importance of a well-balanced diet both during pregnancy and after delivery. To stimulate better lactation, baby should be put to the breast within the first hour after birth. Working mothers can breast-feed before leaving home in the morning and again when they return home in the evening. While at work, babies may be fed with breast milk, which has been expressed and stored hygienically. Unnecessary introduction of bottle-feeding or other foods and drinks should be discouraged since it will have a negative effect on breast-feeding. Similarly, mothers should be warned of the difficulty of reversing a decision not to breast-feed. Before advising a mother to use an infant formula, she should be advised of the social and financial implications of her decision: for example, if a baby is exclusively bottle-fed, more than one can (400g) per week will be needed, so the family circumstances and costs should be kept in mind. Mothers should be reminded that breast milk is not only the best, but also the most economical food for babies. If a decision to use an infant formula is taken, it is important to give instructions on correct preparation methods, emphasizing that unboiled water, unboiled bottles or incorrect dilution can all lead to illness. The source of the infant formula product is of cow's milk origin.

Refer to:

1. Code of Ethics for the Marketing of Infant Foods and Related Products, 4th edition, Ministry of Health Malaysia, August 2008.
2. International Code of Marketing of Breast Milk Substitutes, adopted by the World Health Assembly in Resolution WHA 34.22, May 1981.

References:

1. Gronlund MM, Lehtonen OP, Eerola E, Kero P. *J Pediatr Gastroenterol Nutr* 1999; 28: 19-25. 2. Penders J, Thijs C, Vink C *et al. Pediatrics* 2006; 118: 511-21. 3. Saavedra JM. *Nutr Clin Pract* 2007; 22: 351-365. 4. Walker WA. *J Pediatr Gastroenterol Nutr* 2000; 30 (Suppl. 2): S2-S7. 5. Gronlund MM, Arvilommi H, Kero P *et al. Arch Dis Child Fetal Neonatal Ed* 2000; 83: F186-F192. 6. Thilaganathan B, Meher-Homji N. Nicolaides KH. *Am J Obstet Gynecol* 1994; 171: 1271-1272. 7. Langhendries JP, Detry J, Van Hees J *et al. J Pediatr Gastroenterol Nutr* 1995; 21: 177-81. 8. Mohan R, Koebnick C, Schildt J *et al. J Clin Microbiol* 2006; 44(11): 4025-4031. 9. Saavedra JM. Bauman NA, Oung I *et al. Lancet* 1994; 344: 1046-1049. 10. Chouraqui JP, Van Egroo L-D, Fichot M-C. *J Pediatr Gastroenterol Nutr* 2004; 38: 288-292.

Product Symbol: NWB023/LEB032/LEB047/LNFB003
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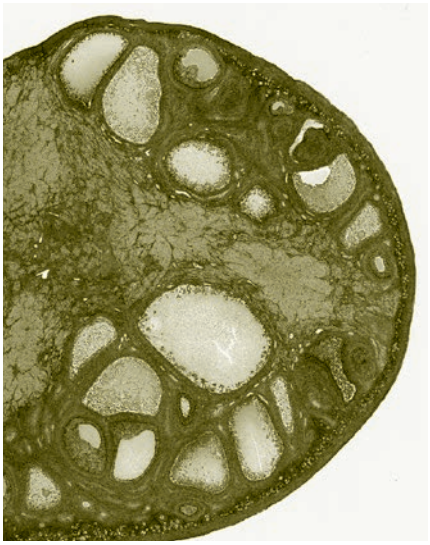
GYNAECOLOGY

Bevacizumab for ovarian cancer



Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), and VEGF is implicated as a promoter of ovarian cancer. Two trials, one in the USA, Canada, South Korea and Japan, and one in eight European countries, Canada, Australia and New Zealand, have assessed the benefits of bevacizumab for women with ovarian cancer.

In the first of the trials, a total of 1,873 women with newly diagnosed stage III or IV ovarian cancer had debulking surgery and were then randomized at 336 centres to 22 × 3-week cycles of chemotherapy (paclitaxel plus carboplatin) plus either bevacizumab in cycles 2–22 (bevacizumab throughout, BT), or bevacizumab in cycles 2–6, and placebo in cycles 7–22 (bevacizumab-initiation, BI), or placebo in cycles 2–22 (controls). Median progression-free survival was 10.3 months (controls), 11.2 months (BI), and 14.1 months (BT). BT was associated with a significant 28% reduction in progression or death compared with control treatment, but there was no significant difference between the BI and control groups. At the time of analysis, overall survival was 76% with no differences in survival between the three groups. Hypertension was more common in the bevacizumab groups (BT, 23%; BI, 17%) than in the control group (7%). Gastrointestinal wall disruption needing treatment occurred in 2.6%, 2.8%, and 1.2%, respectively.

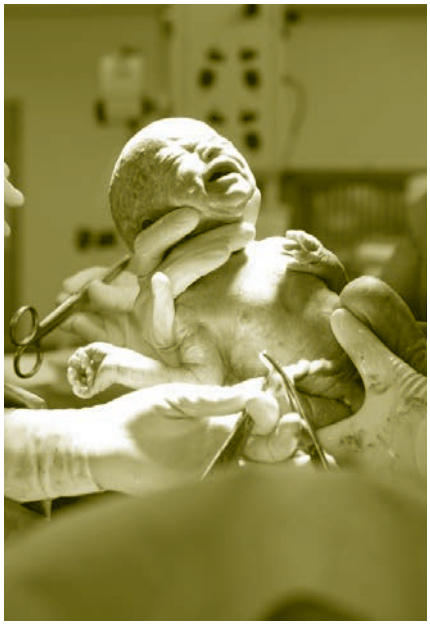
In the second of these trials, a total of 1,528 women with stage I, IIa, and IIB-IV ovarian cancer, peritoneal cancer, or Fallopian tube cancer were randomized at 263 centres to chemotherapy with (CB) or without (C) bevacizumab. Median mean progression-free survival at 36 months was 21.8 months (CB) vs 20.3 months (C). There was a significant 19% reduction in risk of progression or death with bevacizumab. The maximum effect of bevacizumab was at 12 months, at the end of planned bevacizumab treatment, and it had diminished by 24 months. Hypertension occurred in 18% of patients on bevacizumab. At 42 months, progression-free survival was 22.4 months (C) vs 24.1 months (CB). Among high-risk patients, the corresponding figures were 14.5 months vs 18.1 months and overall survival 28.8 vs 36.6 months.

In both of these trials, the addition of bevacizumab to chemotherapy improved survival with greater benefit for high-risk patients.

Burger RA et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. NEJM 2011; 365: 2473–2483; Perren TJ et al. A phase 3 trial of bevacizumab in ovarian cancer. Ibid: 2484–2496.

OBSTETRICS

Induction of labour at term: Transcervical Foley catheter vs vaginal prostaglandin E2 gel



Worldwide, some 20–30% of deliveries follow induction of labour. Cervical ripening may be promoted by mechanical or pharmacological means. Investigators in the Netherlands have compared transvaginal Foley catheter inflation with use of a prostaglandin E2 vaginal gel.

The study, at 12 centres, included a total of 824 women with a singleton, term pregnancy in cephalic presentation with intact membranes, an unfavourable cervix, no history of caesarean section, and an indication for induction of labour. Randomization was to transcervical Foley catheter (inflated with 30 mL of saline or water) or use of prostaglandin E2 vaginal gel. Amniotomy was performed, and oxytocin infusion started at least 6 hours after the last dose of vaginal gel and with a Bishop score of 6 or more.

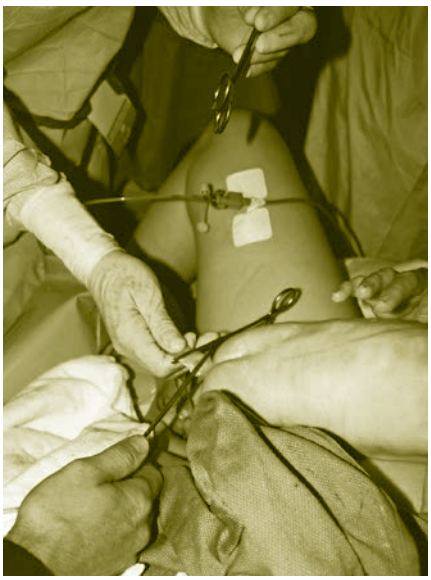
The rate of caesarean section was 23% (Foley catheter) vs 20% (prostaglandin gel), a non-significant difference. There were two serious adverse events, one uterine perforation and one uterine rupture, both in the vaginal prostaglandin group. The time from the start of induction to birth of the infant was significantly longer with the Foley catheter method (29 hours vs 18 hours) probably because of a longer time to the onset of labour. Sig-

nificantly more women in the prostaglandin group (3% vs 1%) were treated for suspected intrapartum infection. A meta-analysis including this and two other studies showed that the Foley catheter method was associated with significantly less risk of hyperstimulation or postpartum haemorrhage.

These researchers conclude that the two methods are similarly effective, but the Foley catheter method is associated with less maternal and neonatal risk.

Jozwiak M et al. Foley catheter versus vaginal prostaglandin E2 gel for induction of labour at term (PROBAAT trial): an open-label, randomised controlled trial. Lancet 2011; 378: 2095–2103; Norman JE, Stock S. Intracervical Foley catheter for induction of labour: Ibid: 2054–2055 (comment).

Early versus delayed clamping of the umbilical cord



The benefits of delaying clamping of the umbilical cord have been promoted for many years, but in developed countries early clamping remains the rule. A study in Sweden has re-emphasized the benefits.

A total of 400 term infants born after a low-risk pregnancy were randomized to early (within 10 seconds of birth) or delayed (at least 3 minutes after birth) cord clamping. Mean serum ferritin levels at 4 months of age were significantly 45% higher with delayed clamping (117 vs 81 µg/L). The prevalence of iron deficiency was reduced by 90% with delayed rather than early clamping. Delayed clamping would prevent one case of iron deficiency for every 20 children born. The two groups had similar haemoglobin levels at age 4 months, but the rates of anaemia at age 2 days were 1.2% vs 6.3%, a significant difference in favour of delayed clamping. The rates of neonatal respiratory problems, polycythaemia, and hyperbilirubinaemia were similar in the two groups.

Delayed cord clamping reduced the rate of early neonatal anaemia and reduced the rate of iron deficiency, but not of anaemia, at the age of 4 months. A *BMJ* editorialist calls for more units to practice delayed clamping.

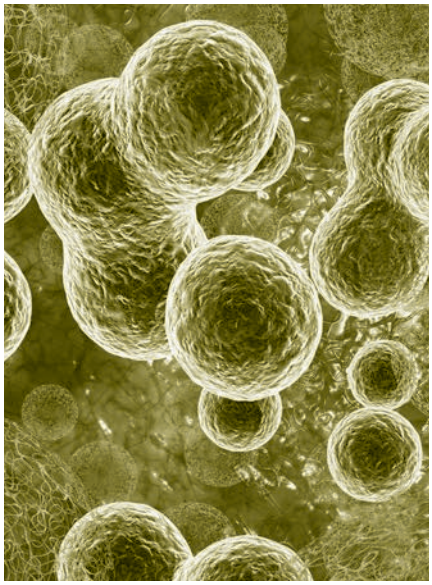
Anderson O et al. Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4 months: a randomised controlled trial. BMJ 2011; 343: 1244 (d7157); Van Rheenan P. Delayed cord clamping and improved infant outcomes. Ibid: 1233–1234 (d7127) (editorial).

PAEDIATRICS

Malaria and bacteraemia in children

Bacteraemia is common in children in sub-Saharan Africa. HIV infection, malnutrition, and sickle-cell disease all contribute to the susceptibility. Malaria is also thought to make children susceptible to invasive bacterial infections. Sickle-cell trait (HbAs), however, provides protection against malaria, and researchers in Kenya have taken advantage of this to perform a mendelian randomization study.

First, they studied 292 children aged 3 months to 13 years with bacteraemia and 528 control children. Bacteraemia was associated with sickle-cell disease, HIV infection, undernutrition, and leukocyte haemozoin pigment. Sickle-cell trait was associated with a 64% reduction in risk of bacteraemia. Next, they performed a longitudinal case-control study with 1,454 cases (children with bacteraemia) and 10,749 controls. Between 1999 and 2007, the rate of hospital admission for malaria fell from 28.5 to 3.45 admissions per 1,000 child-years because of more effective malaria control. At the same time, the protection provided by sickle-cell trait against bacteraemia fell, and hospital admissions for bacteraemia, largely Gram-negative



bacteraemia including cases due to non-typhoidal salmonella, decreased in parallel with those for malaria, from 2.59 to 1.45 per 1,000 child-years. Malaria parasitaemia increased the risk of bacteraemia 6.7-fold. In 1999, the prevalence of parasitaemia in the community was 29%, and 62% of cases of bacteraemia were attributed to malaria.

Malaria control should reduce the prevalence of bacteraemia.

Scott JAG et al. Relation between falciparum malaria and bacteraemia in Kenyan children: a population-based, case-control study and a longitudinal study. Lancet 2011; 378: 1316–1323; Obaro S, Greenwood B. Malaria and bacteraemia in African children. Ibid: 1281–1282 (comment).

Friso gold

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Friso gold

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Influenza in children worldwide

Acute lower respiratory infections (ALRI) were the cause of 1.56 million deaths in young children in 2008. The most common pathogen is respiratory syncytial virus, accounting for 22% of ALRI episodes in young children. It has been suspected that seasonal influenza viruses cause many childhood episodes of ALRI but, until now, there have been no estimates of the global burden of disease from this cause. Now, the available data have been analysed in a systematic review and meta-analysis of 43 studies.

Data were obtained from studies published between Jan 1, 1995 and Oct 31, 2010, and 16 unpublished population-based studies. The 43 studies included about 8 million children younger than 5 years. It was estimated that in 2008, about 13% of all cases of ALRI and 7% of cases of severe ALRI

in young children were caused by influenza viruses. Around the world, there were 90 million new cases of influenza in this age group, 20 million cases of ALRI due to influenza, and 1 million cases of severe ALRI from this cause. The estimated number of deaths from ALRI due to influenza viruses in children < 5 years old in 2008 was between 28,000 and 111,500, with almost all (99%) of these deaths occurring in developing countries.

Influenza is a common cause of ALRI in young children worldwide.

Nair H et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet 2011; 378: 1917–1930; Zambon M. Assessment of the burden of influenza in children. Ibid: 1897–1898 (comment).

Speed of intravenous rehydration for children

A recent trial in sub-Saharan Africa showed that

rapid bolus intravenous fluid administration was potentially lethal for children with dehydration, fever, and poor peripheral perfusion. Now, a study in Toronto, Canada, has shown no advantage from rapid rehydration compared with standard rehydration.

A total of 226 children > 90 days old (weight, 5–33 kg) presenting with gastroenteritis and mild to moderate dehydration to the emergency department of a children's hospital were treated initially with oral rehydration. When oral rehydration had failed, they were randomized to rapid intravenous rehydration (0.9% saline 60 mL/kg over 1 hour) or standard intravenous rehydration (20 mL/kg over 1 hour). Clinical rehydration at 2 hours was achieved in 36% (rapid) vs 30% (standard), a non-significant difference. Prolonged treatment was needed by 52% vs 43% (non-significant difference), but the time to hospital discharge was significantly longer in the rapid rehydration group (6.3 vs 5.0 hours).

Rapid rehydration did not give better results than standard rehydration. The writer of a largely critical editorial insists that currently available evidence points, overall, to rapid rehydration being effective and safe.

Freedman SB et al. Rapid versus standard intravenous rehydration in paediatric gastroenteritis: pragmatic blinded randomised clinical trial. BMJ 2011; 343: 1190 (d6976); Nager AL. Rapid intravenous rehydration in paediatric gastroenteritis. Ibid: 1183 (d7083) (editorial).

Hospital-acquired bacteraemia in children in a Kenyan hospital

Although community-acquired bacteraemia is common in children in sub-Saharan Africa, there are few data about hospital-acquired bacteraemia. A 7-year survey in a single hospital has been reported.

In the Kilifi District Hospital in Kenya between 16 April 2002 and 30 September 2009, there were 33,188 admissions of children up to the age of 15 years (14% aged 0–28 days, 3% 29–59 days, 25% 60 days to 1 year, and 58% over 1 year). The rate of hospital-acquired bacteraemia (> 48 hours after admission) was 5.9 per 1,000 admissions overall, rising during the study period by 27% per year. These researchers suspect that the increase is related to increased hospital stays because of an increasing proportion of neonates and fewer short stays with malaria. The incidence was 1.0 per 1,000 days in hospital, about 40 times the local rate of community-acquired bacteraemia. Mortality was 53% for hospital-acquired bacteraemia and 24% for community-acquired bacteraemia. Survivors of hospital-acquired bacteraemia spent an extra 10 days in hospital compared with patients who did not become bacteraemic. The main infecting organisms were *Escherichia coli* and *Klebsiella pneumoniae*, each accounting for around 20% of cases. *Acinetobacter* species, *Staphylococcus aureus*, group D streptococci, and *Pseudomonas aeruginosa* each accounted for slightly less than 10% of cases and, in all, 18 bacterial pathogens were isolated. Yeasts were isolated in 5% of cases. The main pathogen in community-acquired bacteraemia was *Streptococcus pneumoniae* (29%), followed by *Staphylococcus aureus* (13%), *Acinetobacter* species (10%), and non-typhi *Salmonella* species (9%). Factors associated with hospital-acquired bacteraemia included severe malnutrition and blood transfusion in the absence of severe anaemia.

Hospital-acquired bacteraemia was uncommon in this study but carried a high mortality. The main pathogens differed from those of community-acquired bacteraemia, and severe malnutrition and unnecessary blood transfusion were contributory factors.

Aiken AM et al. Risk and causes of paediatric hospital-acquired bacteraemia in Kilifi District Hospital, Kenya: a prospective cohort study. Lancet 2011; 378: 2021–2027; Feasy N, Molyneux E. Keep it clean: hospital-acquired infections in children. Ibid: 1982–1983 (comment).

Type 1 Diabetes Mellitus in Childhood

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) is the most common chronic metabolic condition in children and adolescents. Diabetes mellitus (DM) comprises a group of heterogeneous conditions involving defects in insulin secretion or action, or both, resulting in hyperglycaemia and associated abnormalities in carbohydrate, protein and fat metabolism. The classification of DM is described by the American Diabetes Association.[1] T1DM is by far the most common type seen in childhood. The incidence of type 2 diabetes (T2DM) is increasing most notably in the adolescent age group, in parallel with the rise in obesity throughout the world.[2]

EPIDEMIOLOGY

Worldwide, there are approximately 480,000 children with T1DM, and 76,000 new cases are diagnosed each year.[3] Incidence rates of T1DM in children and adolescents under 15 years of age vary greatly by geographical region, from the highest in Finland (57.4/100,000/year) and Canada (21.7/100,000/year) to the lowest reported in China (0.6/100,000/year) and Venezuela (0.1/100,000/year).[3] The overall annual incidence is increasing at a rate of about 3%[4] with the greatest increase in the youngest age group.[5] Several hypotheses to explain this changing incidence have been proposed, such as rapid growth in early childhood, environmental exposures, and reduced early exposure to pathogens, but none is widely accepted.[6] Data are lacking about the incidence of T1DM in some developing countries in sub-Saharan Africa and South and East Asia, in which the diagnosis may be being missed.[3] T1DM affects children of all ages, both sexes, and all ethnic groups.

Table 1. American Diabetes Association criteria for the diagnosis of diabetes

1) HbA_{1c} ≥ 6.5%
OR
2) Fasting plasma glucose 7.0 mmol/L (fasting is defined as no caloric intake for at least 8 hours[a])
OR
3) 2-hour plasma glucose ≥ 200 mg/dL (≥ 11.1 mmol/L) during an oral glucose tolerance test. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water[a]
OR
4) In a patient with classic symptoms of hyperglycaemia or a hyperglycaemic crisis, a random plasma glucose ≥ 200 mg/dL (≥ 11.1 mmol/L)

[a]In the absence of unequivocal hyperglycaemia, criteria 1–3 should be confirmed by repeat testing.

PATHOPHYSIOLOGY

T1DM is the result of a combination of genetic and environmental influences. It most commonly results from autoimmune destruction of insulin-producing β-cells in the pancreas. Devendra *et al* proposed that one or more environmental factors, such as enteroviruses, dietary factors or toxins, might trigger the development of T-cell-dependent autoimmunity in genetically susceptible individuals.[7] Autoimmunity is manifest by detectable antibodies to ICA512/IA-2, insulin autoantibody and glutamic acid decarboxylase. Insulitis with gradual β-cell destruction leads to pre-diabetes and finally to overt DM. These patients are susceptible to other autoimmune diseases, such as Hashimoto's thyroiditis, coeliac disease, Addison's disease, and myasthenia gravis.

Forty genetic loci have been associated with T1DM by a genome-wide association study and meta-analysis.[8] A number of genetic loci in the major histocompatibility region are associated with increased susceptibility to developing T1DM, including the alleles DR3/4, DQ 0201/0302, DR 4/4, and DQ 0300/0302. The risk of T1DM is approximately 5% if there is an affected first-degree relative and slightly higher if the affected parent is the father rather than the mother. To date, interventional trials have failed to delay the onset or prevent T1DM in those genetically at risk. Ongoing research by international networks is exploring ways to prevent, delay or reverse the progression of T1DM (eg, TrialNet, TRIGR).[9]

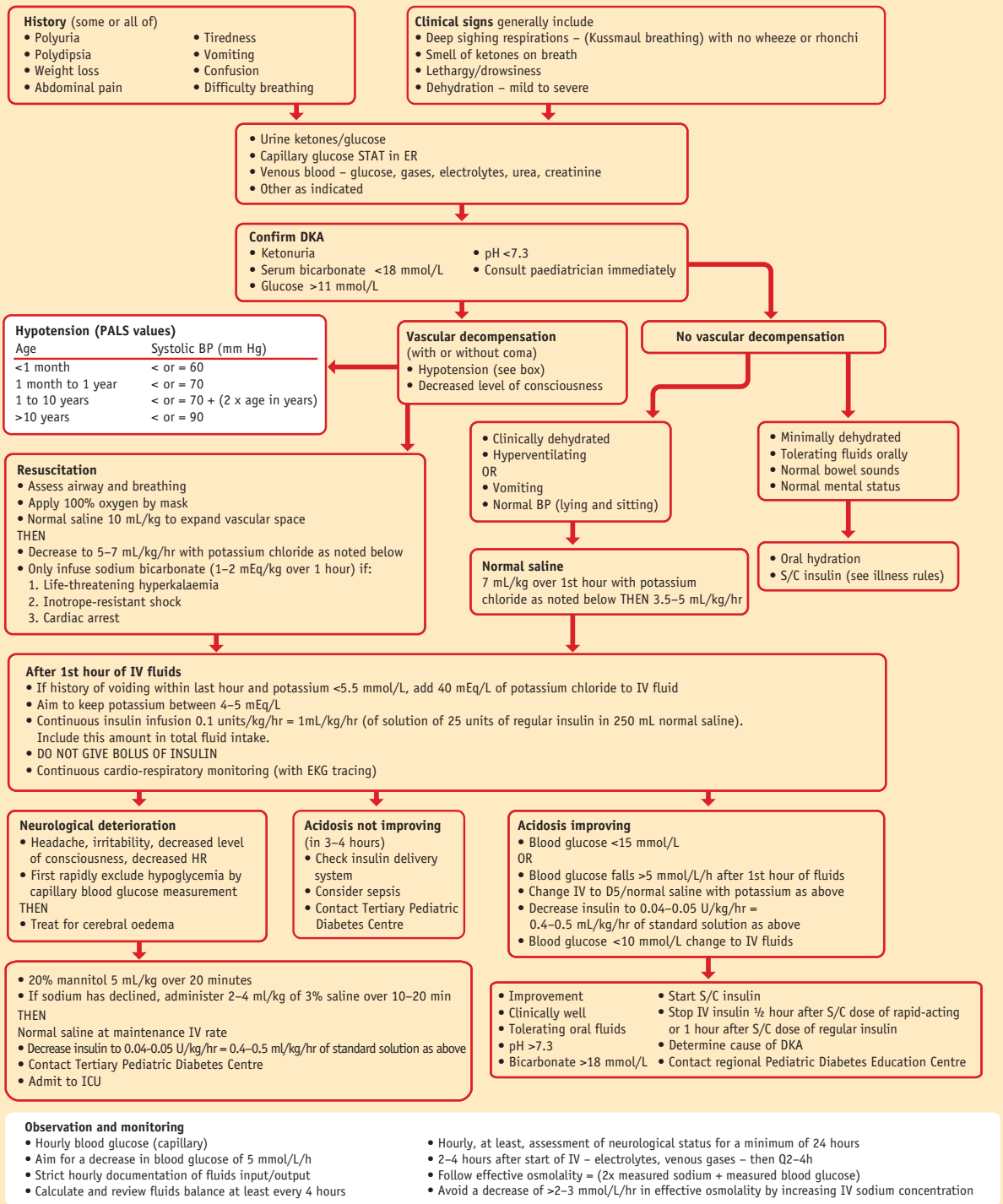
CLINICAL PRESENTATION AND DIAGNOSIS

The presentation of T1DM can range from a clinically stable child with symptoms of polyuria, polydipsia, enuresis and weight loss to a severely dehydrated child with diabetic ketoacidosis (DKA). In the presence of these classical symptoms of hyperglycaemia, a single blood glucose measurement > 11.1 mmol/L is sufficient to make the diagnosis of DM. In such situations, the diagnosis should not be delayed; treatment should be initiated urgently to prevent or reverse DKA. Only rarely are repeated blood glucose measurements and/or an oral glucose tolerance test required to make the diagnosis of T1DM in children (Table 1).[1]

Type 2 Diabetes (T2DM)

In the pubertal age group, T1DM must be differentiated from T2DM. A Canadian population-based surveillance study of non-type 1 diabetes in children under 18 years of age found an incidence rate of 1.55/100,000/year.[10] The aetiology of T2DM is multifactorial, but key factors include genetic predisposition (> 80% have a positive family history), ethnicity (more common in African-American, Asian, Hispanic and Native North Americans), obesity, intrauterine environment, sex, and insulin resistance. Both secretion and action of insulin are usually dis-

Figure 1. Emergency room (ER) management guidelines for the child with type 1 diabetes in diabetic ketoacidosis (DKA)



Adapted from: Ontario Ministry of Health and Long-term Care. Emergency Room Management for the Child with Type 1 Diabetes. © Queen's Printer for Ontario, 2009. Reproduced and adapted with permission. Available at: www.health.gov.on.ca/english/providers/pub/diabetes/child_poster.pdf.
BP = blood pressure; D5 = 5% dextrose; EKG = electrocardiography; HR = heart rate; ICU = intensive care unit; IV = intravenous; PALS = Pediatric Advanced Life Support; Q2–4h = every 2–4 hours; S/C = subcutaneous; STAT = statim.

Table 2. Glycaemic and HbA_{1c} targets according to the 2008 Clinical Practice Guidelines of the Canadian Diabetes Association

Age (y)	HbA_{1c} (%)	Plasma glucose (mmol/L)	2-hour postprandial plasma glucose (mmol/L)	Considerations
< 6	≤ 8.5	6.0–12.0	–	Careful avoidance of hypoglycaemia in this age group owing to risk of cognitive impairment
6–12	≤ 8.0	4.0–10.0	–	Adapt targets to patient's age
13–18	≤ 7.0	4.0–7.0	5.0–10.0	Appropriate for most patients[a]

Source: Canadian Diabetes Association 2008 Clinical Practice Guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2008;32(suppl 1).
[a]In adolescents in whom it can be safely achieved, consider aiming toward normal PG range (ie, HbA_{1c} ≥ 6.0%, fasting/preprandial plasma glucose 4.0–6.0 mmol/L, and 2-hour postprandial plasma glucose 5.0–8.0 mmol/L).

ordered at clinical presentation, although one feature may predominate. Insulin resistance may manifest clinically with acanthosis nigricans (a velvety thickening of the dermis found especially on the posterior neck and axillae), features of polycystic ovarian syndrome (hyperandrogenism, menstrual irregularity), and features of metabolic syndrome (hypertension, dyslipidaemia, and obesity).

Monogenic Diabetes

Occasionally, T1DM must be differentiated from monogenic diabetes, formerly known as maturity-onset diabetes of the young. Monogenic forms of diabetes result from single gene mutations that cause impaired β-cell function or, rarely, severe insulin resistance. Identifying this diagnosis is important to predict the course of disease, explain associated clinical features, guide management, and aid in diagnosis and management of similarly affected family members.[11] Monogenic diabetes should be considered in the following clinical scenarios[11]:

- Neonatal diabetes and diabetes diagnosed within the first 6 months of life
- Familial diabetes with an affected parent
- Mild (5.5–8.5 mmol/L) fasting hyperglycaemia, especially if young or familial
- Diabetes associated with extra-pancreatic features

Specific genetic defects are listed in Table 1, and genetic testing is available for all of the identified mutations.

DIABETIC KETOACIDOSIS

Diabetic keoacidosis results from absolute insulin insufficiency, leading to metabolic acidosis (pH < 7.3 or bicarbonate < 15 mmol/L), hyperglycaemia (blood glucose > 11 mmol/L), ketonaemia, and ketonuria.[12] DKA is present at T1DM presentation in 15–67% of children, its frequency being inversely related to the incidence of T1DM in that area.[13] In those with established T1DM in the United States, the incidence of DKA has been reported to be 8 episodes per 100 patient-years. Risk factors that predict DKA include female sex, longer duration of diabetes, higher mean HbA_{1c}, higher reported insulin dose, the presence of psychiatric disorders,[14] insulin omission or insulin pump failure. DKA may also be present in up to 25% of young people presenting with T2DM.

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DKA should be treated as a medical emergency by an experienced medical team. The treatment algorithm used at our centre is outlined in Figure 1. Treatment of DKA in children differs in several respects from that in adults: first, both fluids and insulin are calculated on a per kilogram rather than an empirical basis. Fluid repletion should occur gradually with sodium chloride 0.9%. Boluses of fluid and insulin should be avoided. Bicarbonate should be given only in the setting of life-threatening hyperkalaemia, inotrope-resistant shock, or cardiac arrest.

DKA is the major cause of hospitalization, morbidity and mortality in young people with T1DM. The most serious complication is cerebral oedema, which occurs in 0.5–1.0% of DKA episodes, with 25% mortality. Demographic risk factors associated with increased risk for cerebral oedema include younger age, new-onset diabetes, and longer duration of symptoms. Risk factors that are present at the time of diagnosis or during treatment are increased serum urea, severe acidosis, greater hypocapnia after adjusting for the degree of acidosis, administration of sodium bicarbonate, and an attenuated rise in the measured serum sodium during treatment.[12]

MANAGEMENT OF T1DM IN CHILDHOOD

The diagnosis of T1DM is a pivotal moment for the child as well as for his/her family. T1DM is a lifelong condition with serious short- and long-term implications. It is essential that from the moment of diagnosis, these families receive expert care from a team of health professionals experienced in childhood diabetes, including a physician, diabetes nurse, dietitian and social worker.

At onset, children presenting without DKA can be safely managed on an ambulatory basis provided that support services are available and that no other medical or social conditions exist that would place the child in danger. A meta-analysis of home-based management at DM onset suggests that in comparison to routine hospital admission, outpatient care is not associated with worse metabolic control, acute diabetic complications or psychosocial outcomes, or greater costs.[15] Early 'survival skills' to be mastered include insulin injections, blood glucose monitoring, basic nutrition planning, and detection and treatment of hypoglycaemia. In the subsequent weeks, more detailed information is provided about diabetes management (pathophysiology, insulin dose adjustment, effects of exercise, and sick days).

Families need to be forewarned of the natural history of T1DM so that they do not develop false hope that their child's diabetes is 'going away'

Insulin initiation varies greatly among different centres but generally consists of two to four injections per day. The starting total daily dose is 0.4–0.6 units/kg body weight/day, usually lower in younger children, and is adjusted on a daily basis until target blood glucose is achieved (Table 2). Families of children with T1DM should have a clear understanding of the rationale for blood glucose and HbA_{1c} targets for their child.

After initial stabilization and education, children and their families enter the long-term follow-up phase of their diabetes. This includes regular

Table 3. Onset, peak, and duration of action of commonly used insulin preparations

Generic name	Onset	Peak	Duration
Rapid-acting Lispro Aspart	10–30 min	30 min–3 h	3–5 h
Short-acting Regular human insulin	30–60 min	2–5 h	Up to 12 h
Intermediate-acting (NPH) NPH human insulin	90 min–4 h	4–12 h	Up to 24 h
Basal insulin Glargine Detemir	45 min–4 h	Minimal peak action	Up to 24 h

Source: Insulin action. 2010 Joslin Diabetes Center. Available from: www.joslin.org/info/insulin_action.html.

follow-up visits with their diabetes team with surveillance for psychosocial problems, associated conditions (hypothyroidism, coeliac disease), and microvascular and macrovascular complications. Special attention must be paid to those children and their families, most frequently the youngest children and adolescents, who have the greatest difficulty meeting the considerable demands of their diabetes regimen.

Soon after initial presentation, most patients enter a transient remission or 'honeymoon' phase when exogenous insulin requirements decrease as a result of residual β-cell secretion. The duration of the honeymoon phase is proportional to the age of the child. Families need to be forewarned of the natural history of T1DM so that they do not develop false hope that their child's diabetes is 'going away'.

GLYCAEMIC AND HbA_{1C} TARGETS

The Diabetes Control and Complications Trial (DCCT) demonstrated conclusively that intensive glycaemic control delays and prevents the microvascular and macrovascular complications of T1DM.[16,17] Intensification of therapy is associated with an increased risk of hypoglycaemia that can be a limiting factor in achieving good metabolic control. Severe hypoglycaemia in young children has been associated with mild cognitive deficits later in life, although the cause-and-effect relationship remains controversial. This demands that age-appropriate targets be set and that progressively tighter control be sought as the child grows older. Table 2 summarizes the glycaemic goals published in the 2008 Clinical Practice Guidelines of the Canadian Diabetes Association.[18] Multiple studies attest to the difficulties in achieving these goals in all children with T1DM.[19,20]

INSULIN REGIMENS

Approaches to insulin therapeutics vary from one centre to another. Most children and teenagers now start their treatment with a combination of intermediate-acting insulin or basal insulin analogue (insulin glargine or insulin detemir), combined with rapid-acting insulin analogues (insulin lispro or insulin aspart) given two or more times daily, with insulin doses calculated to match carbohydrate intake and ambient blood sugar. The choice of regimen should be tailored to the child's age, duration of diabetes, daily routines, targets of metabolic control, and individual and family preferences.[21] When rigorously applied, this basal-bolus approach can help to achieve and maintain near-normal glycaemia. See Table 3 for the onset, peak, and duration of action of commonly used insulin preparations.

Increasingly, children and teenagers with T1DM are using continuous subcutaneous insulin infusion (CSII) pumps.[22] CSII is a more sophisticated form of basal-bolus regimen whereby fast-acting insulin analogue is administered by continuous in-

fusion (basal rate) with intermittent boluses given before carbohydrate ingestion or to correct hyperglycaemia. A systematic review and meta-analysis of randomized controlled trials comparing CSII to multiple daily injection in children with T1DM found a modest improvement (0.24%) in HbA_{1c} in the CSII group and found no differences in DKA or severe hypoglycaemia between groups.[5] Quality of life and patient satisfaction have been reported to be at least equal or improved with CSII.[6] The cost of CSII is considerable and cannot be accommodated by many families and health-care systems.

BLOOD GLUCOSE MONITORING

Children and adolescents with T1DM are encouraged to monitor blood glucose at least four times per day (before each meal and at bedtime). Maintenance of a blood glucose logbook is essential to follow patterns and to make appropriate dose adjustments. Continuous glucose monitoring technologies have been developed and are increasingly being used in clinical care as an adjunct to intermittent monitoring.[23]

HbA_{1c} is a measure of glycaemic control over the previous 4–12 weeks, weighted more heavily toward the most recent 4 weeks. Lower HbA_{1c} values have been associated with fewer and delayed microvascular and macrovascular complications.[16,17] The goal of diabetes management should be to maintain the lowest possible HbA_{1c} without severe or prolonged hypoglycaemia or hyperglycaemia.

NUTRITION

Recommendations for nutritional intake in young people with T1DM should aim to support optimal glycaemic control, blood pressure, and lipid profiles, and fit with the insulin regimen.[24] If carbohydrate counting is used, insulin doses can be calculated based on the number of grams of carbohydrates consumed and on deviation from the target blood glucose. Nutritional requirements for children with T1DM do not differ from those of healthy children and adolescents.[25]

PHYSICAL ACTIVITY

Physical activity in general leads to increased glucose utilization, although in some cases rigorous exercise may induce a stress response leading to hyperglycaemia. For children and teenagers involved in exercise activities, more frequent monitoring with either insulin dose adjustment or appropriate food intake are needed to avoid the extreme hypoglycaemia that can occur with activity. Diabetes should not limit the ability of a child to participate in sport. Methods for adjusting insulin and carbohydrate intake to accommodate exercise have been proposed.[26,27]

HYPOGLYCAEMIA

Hypoglycaemia (blood glucose < 3.9 mmol/L or 70 mg/dL) is a common unwanted effect in people treated with insulin and occurs when there is an imbalance in insulin dose, food consumed and activity. Symptoms include autonomic (adrenergic) activation and/or neurological dysfunction (neuroglycopenia).[28] Recognition of symptoms of hypoglycaemia can be difficult in young children with T1DM, and therefore increased monitoring of blood glucose when hypoglycaemia might be expected (overnight, after insulin dose adjustment, strenuous exercise, or illness) is recommended. Families should have injectable glucagon at home to treat severe hypoglycaemia (coma, seizure, or severe confusion). Hypoglycaemia has been associated with reduced cognitive functioning and can, rarely, be a cause of death in young people with T1DM. Co-morbidities

such as coeliac disease and Addison's disease can increase the risk of hypoglycaemia.

SICK-DAY MANAGEMENT

Diabetes control may deteriorate during periods of intercurrent illness. Illnesses associated with decreased oral intake may predispose to hypoglycaemia. Alternatively, the stress of some illnesses may lead to a vigorous counter-regulatory hormone response, leading to hyperglycaemia and ketosis. Frequent monitoring of blood glucose and ketones, continuation of insulin therapy with appropriate dose adjustment, and timely emergency department attendance for those with repeated vomiting should help to prevent metabolic deterioration.

ADOLESCENTS WITH T1DM

Given the association of smoking with both microvascular and macrovascular complications of DM, adolescents should be counselled in smoking prevention and cessation. It is important to address the risk of severe hypoglycaemia associated with an unpredictable daily activity schedule, intensification of the insulin regimen, and the effect of alcohol and illicit drugs on blood glucose. Adolescents who plan to or hold a driver's licence should always check their blood glucose before driving. Unstable glycaemic control and severe hypoglycaemic events may limit their ability legally to obtain or maintain a driver's licence.

Adolescents should be offered regular sexual health and contraception counselling. Poorly controlled T1DM is a risk factor for maternal and fetal complications. Diabetes is not an absolute contraindication to using oral contraception. Depression, body image concerns, and higher body mass index percentile in teenage girls with T1DM have been shown to predict the onset of eating disturbances and disorders[29] and should therefore be assessed in the routine diabetes care in this population. Insulin omission may be one method by which the teenager may attempt to control his/her weight.

TRANSITION TO ADULT CARE

The transition period from paediatric to adult DM care can be a daunting time for the patient and family. In anticipation of this, adolescents with DM should be encouraged to take an increasingly active role in their diabetes care from an early stage. Teenagers should also have private time with the members of the diabetes care team as this promotes independence and responsibility. In the context of universal health-care funding, there is an increased rate of DM-related hospitalizations in the 2 years after transition to adult care, although the risk is less for youth who transfer to a new allied health team but maintain physician continuity.[30] Formal transition programmes may facilitate transfer to adult care and prevent the high rates of drop-out reported in some centres.

COMPLICATION SURVEILLANCE

Chronic hyperglycaemia is associated with subsequent development of microvascular complications (retinopathy, neuropathy and nephropathy). Tight metabolic control delays and slows the progression of these complications. Suboptimal metabolic control has been shown to have an enduring negative effect on the development and progression of microvascular complications even if glycaemic control is subsequently ameliorated, a phenomenon termed metabolic memory.[31] Other risk factors for long-term complications include younger age of DM onset, longer duration of disease, smoking, hypertension, dyslipidaemia, and family history.

DM is also a major risk factor for macrovas-

cular complications (coronary artery, peripheral artery, and cerebrovascular disease). Cardiovascular disease is the most important cause of the excess mortality associated with diabetes. Preventive measures include maintaining normal blood pressure, correcting dyslipidaemia, avoiding smoking, and participating in regular exercise.

Recommendations for screening for complications are summarized by the Canadian Diabetes Association 2008 Clinical Practice Guidelines.[18] Trials are ongoing to determine whether, in addition to optimizing glycaemic control, pharmacological interventions for high-risk young people with T1DM will provide cardio-renal protection.[32] Patient and family education about complications should begin early and be ongoing, emphasizing the proven benefit of excellent glycaemic control.

FUTURE DEVELOPMENTS

Pancreatic and islet-cell transplantation has been performed in adults with T1DM for end-stage renal disease or persistent metabolic instability. These procedures carry significant risks related to the procedures themselves and the need for chronic immunosuppression. Furthermore, only 10% of patients were insulin-independent at 5 years after islet-cell transplantation.[18]

Research to develop an effective extracorporeal artificial pancreas is ongoing. This system involves an insulin pump to deliver insulin, a continuous glucose sensor, and an effective algorithm to alter insulin delivery based on real-time glucose sensor inputs.[33]

Other strategies to improve the effectiveness of subcutaneous insulin action in T1DM have been proposed, including insulin-sensitizing therapies such as recombinant human insulin-like growth factor 1, growth hormone suppressors or antagonists, and direct insulin-sensitizing agents (metformin, thiazolidinediones). Other agents that may improve postprandial blood glucose, such as amylin analogues (pramlintide), alpha glucosidase inhibitors (acarbose), and glucagon-like peptide 1 analogues have also been studied. The long-term safety and effectiveness of these agents for the management of T1DM in young people remain uncertain.

CONCLUSION

T1DM in young people remains a common and challenging condition. Advances continue in the understanding of the pathogenesis of DM, especially in the area of genetic susceptibility. Significant improvements have been made in the development of glucose monitors, insulin formulations and delivery systems, and the organization of health services. These substantial advances should be made known to young people and their families as reason for hope, and as an impetus to maintain the best possible metabolic control. A multidisciplinary approach to the care of young people with T1DM should

What's new?

- The incidence of type 1 diabetes mellitus (T1DM) is increasing worldwide at a rate of approximately 3% per year with the greatest increase in the youngest age group
- Genetic loci associated with T1DM are being discovered by genome-wide association studies
- In the management of diabetic ketoacidosis, bicarbonate should be given only in the setting of life-threatening hyperkalaemia, inotrope-resistant shock, or cardiac arrest
- Despite advances in monitoring devices, insulin preparations and delivery mechanisms, many children and adolescents (especially) with T1DM fail to achieve their age-appropriate glycaemic targets
- Ongoing research in the area of islet-cell transplantation, closed-loop insulin delivery systems, and insulin-sensitizing and other adjunctive agents may lead to improved therapies for the management of T1DM in the future

emphasize optimal metabolic control with minimal hypoglycaemia, in the context of a healthy and supportive physical and psychosocial environment.

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Rayzel M Shulman is currently pursuing a PhD at the University of Toronto, Ontario, Canada. Competing interests: Rayzel Shulman received the 2009/10 Canadian Pediatric Endocrine Group (CPEG) Fellowship sponsored by Novo Nordisk Canada. Denis Daneman is Paediatrician-in-Chief at SickKids and Chair of the Department of Pediatrics at the University of Toronto, Ontario, Canada. Competing interests: Denis Daneman has been a member of the Hvidøre International Study Group for Childhood Diabetes sponsored by Novo Nordisk Inc.

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Clinical Case
Rotting Teeth in a Young Girl

Simon Wooley, BDS, MPHC; Kaye Roberts-Thomson, BDSc, MPH

Figure 1

CASE SCENARIO

Tracey, aged 5 years old, was brought in to my clinic from an outlying rural community to receive her immunizations before starting school. An opportunistic health check revealed that three of her top front teeth had rotted away to below the gum line. She also had several carious teeth towards the back of her mouth. Her mother denied that Tracey excessively consumed sweets or sweet drinks, confirmed that Tracey brushed her teeth and rather defensively asserted that Tracey had been born with 'soft teeth'.

How should the current situation be handled? Will the secondary dentition suffer?

(Answers on p. 79)

Bacterial Vaginosis

Phillip Hay, MBBS, FRCP

Bacterial vaginosis is the most common cause of abnormal vaginal discharge in women of childbearing age. It is a syndrome of unknown cause characterized by depletion of the normal *Lactobacillus* population and an overgrowth of vaginal anaerobes, accompanied by loss of the usual vaginal acidity. In 1983, the term 'bacterial vaginosis' replaced the older term '*Gardnerella* vaginitis'. This recognized the fact that many anaerobic or facultative anaerobic bacteria are present and that classical signs of inflammation are absent.[1]

Women with symptomatic bacterial vaginosis report an offensive, fishy-smelling discharge that is most noticeable after unprotected intercourse or at the time of menstruation. The diagnosis can be confirmed by microscopy ± additional tests. About 50% of cases are asymptomatic. Bacterial vaginosis is associated with infective complications in pregnancy and following gynaecological surgery, and is a risk factor for the acquisition of sexually transmitted infections (STIs) including human immunodeficiency virus (HIV).

EPIDEMIOLOGY

In unselected populations in the UK, the prevalence of bacterial vaginosis is 10–20%, but it may be as high as 36% in women attending STI clinics and 28% in those seeking elective termination of pregnancy.[2] A prevalence of more than 50% was reported in rural Uganda.[3] The debate about whether bacterial vaginosis is an STI or merely sexually associated continues. A meta-analysis has concluded that bacterial vaginosis has the characteristics of an STI: being associated with partner change and other STIs.[4] The strongest evidence against it being an STI has come from studies reporting similar rates in self-reported virgin and non-virgin women.[5–7] This has been chal-

lenged by a detailed study that reported no bacterial vaginosis in women denying any oral or digital genital contact.[8] In many studies, it is associated with black race and intrauterine device use. The condition often arises spontaneously around the time of menstruation and may resolve spontaneously in mid-cycle. It is not known how often bacterial vaginosis occurs in post-menopausal women.

AETIOLOGY AND PATHOGENESIS

Lactobacilli dominate the normal vaginal flora, although other organisms may be present in small numbers. When bacterial vaginosis develops, the lactobacilli reduce in concentration and may disappear whilst there is an increased concentration of anaerobic and facultative anaerobic organisms. Lactobacilli produce inhibitory mediators including lactic acid, H_2O_2, defensins, and bacteriocins. The triggers for bacterial vaginosis are probably multiple. An increase in vaginal pH from the normal 3.5–4.5 to as high as 7.0 is observed, which reduces the inhibitory effect of H_2O_2 on anaerobic growth. Hormonal changes and inoculation with organisms from a partner might also be important.

The organisms classically associated with bacterial vaginosis using culture and those more recently identified using molecular techniques[9,10] are shown in Table 1. The description of the biofilm that develops in bacterial vaginosis by Swidsinski and colleagues places *Gardnerella vaginalis* once again at the centre of pathogenesis of bacterial vaginosis.[11] In some women, the biofilm covered the entire biopsy; in others, it was more patchy. *Gardnerella* accounted for 90% of bacteria seen in the biofilm, with *Atopobium vaginae* the only other numerically important organism. Lactobacilli predominated in women with normal flora but did not form a biofilm.

Table 1. The organisms classically associated with bacterial vaginosis using culture are shown in the first column and those more recently identified through molecular techniques in the second

Gardnerella vaginalis	*Atopobium vaginae*
Bacteroides (*Prevotella*)	BVAB1-3 (*Clostridiales*)
Mycoplasma hominis	*Megasphaera*
Mobiluncus species	*Sneathia*
	Leptotrichia

Table 2. Composite (Amsel) criteria for the diagnosis of bacterial vaginosis

- Vaginal pH > 4.5
- Release of a fishy smell on addition of alkali (10% potassium hydroxide)
- Characteristic discharge on examination
- Presence of 'clue cells' on microscopy of vaginal fluid mixed with normal saline

At least three of the four criteria must be fulfilled to make a diagnosis of bacterial vaginosis.

DIAGNOSIS

Bacterial vaginosis should be suspected in any woman presenting with an offensive, typically fishy-smelling vaginal discharge. Speculum examination shows a thin, homogeneous, white or yellow discharge adherent to the walls of the vagina. Amsel criteria (Table 2) have been the mainstay of diagnosis in settings such as genitourinary medicine clinics where microscopy can be performed. Epithelial cells covered with so many small bacteria that the border is fuzzy are termed 'clue cells' because their presence is a clue to the diagnosis.[12]

Any of the Amsel criteria can, however, be misleading:

- The appearance of vaginal secretions may be

Figure 1. Gram-stained vaginal smear from a woman with normal flora. Epithelial cells and their nuclei can be seen clearly. Gram-positive rods are typical of lactobacilli.

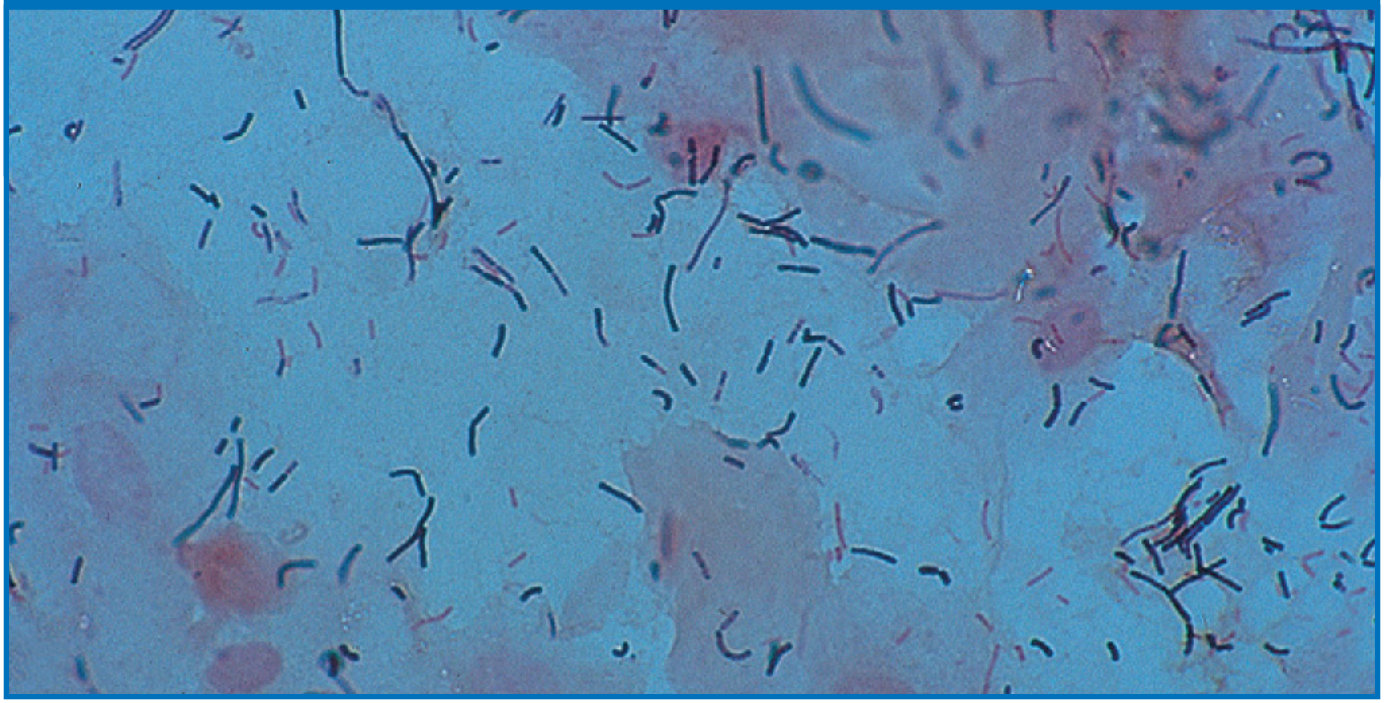
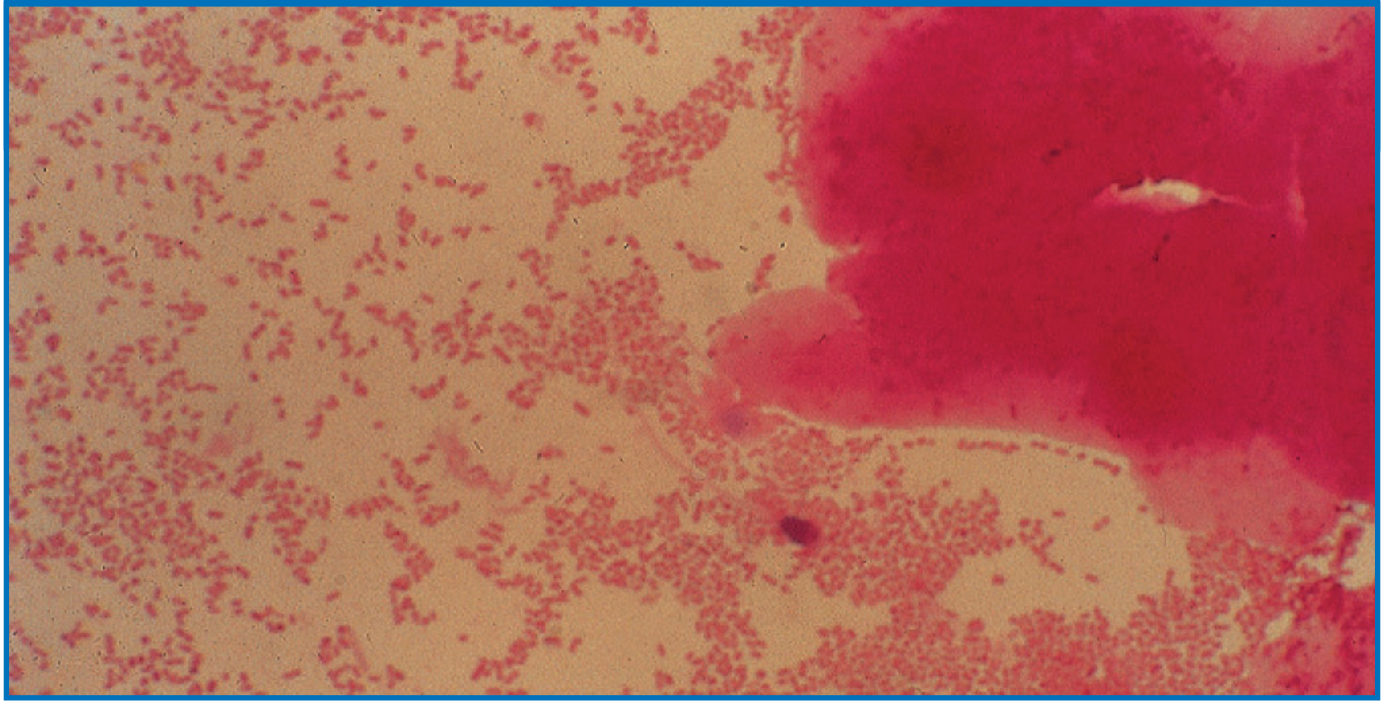


Figure 2 Gram-stained vaginal smear from a woman with bacterial vaginosis. There are many small bacteria present, some Gram-positive and some Gram-negative. Large, curved rods, typical of *Mobiluncus mulieris*, are present. Clue cells are not part of most scoring systems for bacterial vaginosis, and none are seen in this field.



altered by factors such as recent intercourse and douching.
- Both *Candida* and trichomoniasis can give a similar clinical appearance.
- A positive potassium hydroxide test may be found in the presence of semen.
- Vaginal pH may be elevated during menstruation or by the presence of semen.
- Detection of clue cells is the single most sensitive and specific criterion, but the interpretation of microscopy is subjective. Debris or degenerate cells can be mistaken for clue cells, and lactobacilli sometimes adhere to epithelial cells in low numbers.

Recent studies have concluded that there is a continuum from normal *Lactobacillus*-dominated flora to 'severe bacterial vaginosis'. This is recognized in Gram-stain scoring systems but not with Amsel criteria. When the history is highly suggestive of the condition but the tests are negative, offer further testing if symptoms return.

Gram Staining

Examination of a Gram-stained vaginal smear is a quick and relatively simple means of diagnosis. It enables recognition of intermediate flora, and stored slides can be subsequently evaluated independently in research studies.

Typical lactobacilli are large, Gram-positive rods with blunt ends. *Gardnerella* is usually a Gram-negative coccus. The normal flora includes plentiful lactobacilli (Figure 1), whereas in bacterial vaginosis there are large numbers of Gram-negative cocci and small rods (Figure 2). Curved rods (*Mobiluncus* species) may be present. Recognition of intermediate categories can be more difficult and entails subjective assessment of the morphotypes. Scoring systems (eg, the Nugent) have attempted to reduce interobserver variability.[13] A simplified scoring system (Hay–Ison criteria) has been recommended for use in genitourinary medicine clinics in preference to the Amsel criteria.[14]

Other Tests

Commercially available tests detect biochemical changes in vaginal fluid associated with bacterial vaginosis. However, the relatively high cost of the currently available tests compared with use of the Gram stain or Amsel criteria has limited their uptake. In routine practice, vaginal pH can be measured using pH-sensitive paper. A pH of less than 4.5 almost excludes bacterial vaginosis. If the pH is high, a high vaginal swab can be sent to the microbiology laboratory for examination by wet mount or Gram staining.

Recent studies have concluded that there is a continuum from normal *Lactobacillus*-dominated flora to 'severe bacterial vaginosis'

DIFFERENTIAL DIAGNOSIS (TABLE 3)

Other common causes of vaginal discharge are cervicitis caused by *Chlamydia* or gonorrhoea, candidiasis and trichomoniasis, all of which can also coexist with bacterial vaginosis. In cervicitis, there may be contact bleeding, and purulent discharge may be visible in the external os. *Candida* typically causes a curd-like discharge and is associated

Table 3. Differential diagnosis of vaginal discharge

Symptoms and signs	Candidiasis	Bacterial vaginosis	Trichomoniasis	Cervicitis
Itching or soreness	++	–	+++	–
Smell	May be 'yeasty'	Offensive, fishy	May be offensive	–
Colour	White	White or yellow	Yellow or green	Clear or coloured
Consistency	Curdy	Thin, homogeneous	Thin, homogeneous	Mucoid
Other signs				Purulent mucus at cervical os
Potassium hydroxide test	–	++	±	–
pH	< 4.5	4.5–7.0	4.5–7.0	< 4.5
Confirmation	Microscopy and culture	Microscopy	Microscopy and culture	Microscopy, tests for *Chlamydia* and gonorrhoea

with itching. *Trichomonas* causes a more purulent discharge and is associated with soreness and erythema. These organisms can be sought using specific diagnostic tests.

MANAGEMENT

Bacterial vaginosis is sometimes distressing and must be managed with sensitivity. Because it has a relapsing–remitting course in many women, the value of treating asymptomatic bacterial vaginosis has not been established. There is also no evidence that treatment reduces the prevalence in the community. Treatment should therefore be prescribed for control of symptoms and in situations in which it might prevent complications of a procedure (eg, termination of pregnancy) or in pregnancy.

Antibiotics

Antibiotics targeting anaerobic organisms should be effective in bacterial vaginosis. Metronidazole and clindamycin are obvious choices. The standard treatment for bacterial vaginosis is metronidazole, 400 mg orally 12-hourly for 5–7 days.[15,16] An alternative is a 2-g single dose, or tinidazole 2 g which is more expensive. The cure rate immediately after treatment with metronidazole is up to 95%, but after 4 weeks this declines to 80% in open-label studies and less than 70% in blinded studies.[17]

Topical treatments with intravaginal 2% clindamycin cream or 0.75% metronidazole gels are licensed for the treatment of bacterial vaginosis. They are more expensive than oral metronidazole but have similar efficacy and can be useful when systemic treatment is not desirable.

Adverse Effects of Treatment

Oral metronidazole is associated with nausea, a metallic taste, and alcohol intolerance. Allergic rashes occur occasionally. Initial concerns about potential teratogenicity have not been substantiated, and metronidazole can be used in pregnancy.[18] Oral clindamycin can induce rashes and occasionally pseudomembranous colitis. About 10% of women develop symptomatic candidiasis following

treatment of bacterial vaginosis.

Male Partners

Four double-blind, placebo-controlled trials have failed to show any difference in bacterial vaginosis relapse rates following treatment of male partners with metronidazole, tinidazole or clindamycin. Many physicians advocate screening for STIs in the partners of women with recurrent bacterial vaginosis, but this is not based on prospective studies.

Alternative Treatments

Probiotics and prebiotics have been studied as a treatment for gastrointestinal conditions. Vaginal lactobacilli differ from those considered optimal for the gut, but several vaginal strains are now available. Another approach is to use lactic acid gel to acidify the vagina. Both approaches have been evaluated in small studies of variable quality, so there is insufficient evidence to support their routine use in current guidelines.[19,20]

Relapses

In some women, bacterial vaginosis recurs frequently following treatment. Management of such cases is difficult. It is reasonable to screen the sex partner for infections. If available, the probiotics or lactic acid gel may help to prevent relapse, otherwise regular antibiotic treatment is the only option. One study showed that use of metronidazole gel twice weekly reduced the rate of relapse, although it was associated with increased rates of candidiasis.[21] The author usually prescribes metronidazole in the dosage and preparation preferred by the woman to self-treat at the first sign of relapse, accompanied by an antifungal agent if there is a history of candidiasis.

Patient Advice and Self-help

Vaginal douching and the use of shower gel and bubble bath should be avoided. If the woman washes her hair in the shower, she should avoid contact between the shampoo and the vulval area. It is sensible to use condoms with new sex partners to protect against infections, possibly including bacterial vaginosis.

Bacterial vaginosis is sometimes distressing and must be managed with sensitivity.

COMPLICATIONS

Pregnancy

Bacterial vaginosis is associated with second-trimester miscarriage and preterm birth. The reported odds ratio is 1.4–7.0. It is thought that women with bacterial vaginosis are at increased risk of chorioamnionitis, which can stimulate preterm birth through the release of proinflammatory cytokines.[22] Several studies have assessed the value of screening for and treatment of bacterial vaginosis in preventing adverse outcomes in pregnancy. The results have been variable; some studies showed a benefit with treatment in terms of reducing preterm birth

What's new?

- Molecular techniques have identified several new organisms in bacterial vaginosis, including *Atopobium vaginae*
- The description of a vaginal biofilm containing predominantly *Gardnerella vaginalis* places the organism as central in pathogenesis again
- The biofilm also offers the opportunity to study potential new treatments for bacterial vaginosis
- Probiotics and lactic acid gels need further study as alternative treatments to antibiotics

Practice points

- Metronidazole 400 mg twice daily for 5–7 days remains the first-line treatment for bacterial vaginosis
- The frequency of recurrence can be reduced by regular application of 0.75% metronidazole gel
- Routine screening and treatment in pregnancy to prevent preterm birth are not recommended, but symptomatic women should be treated

Because the aetiology of bacterial vaginosis is not fully understood, it is not known how to prevent it

rates, but the largest study to date showed no benefit from treatment with short courses of metronidazole.[23] On the basis of these studies, it cannot be concluded that antibiotic treatment of bacterial vaginosis in pregnancy will universally reduce the incidence of preterm birth. This was confirmed by the most recent Cochrane review.[24]

Termination of Pregnancy

Women infected with *Chlamydia trachomatis* who undergo elective termination of pregnancy are at high risk of endometritis and pelvic inflammatory disease. Bacterial vaginosis also confers an increased risk and may be present in almost 30% of such women. A double-blind, placebo-controlled trial in Sweden showed that the risk of endometritis in women without *Chlamydia* was 12.2% in a placebo-treated group and 3.8% in those prescribed oral metronidazole before termination.[25] A more recent randomized controlled trial in Sweden found a fourfold reduction in infective complications with clindamycin cream compared with placebo.[26]

Other Gynaecological Surgery

Bacterial vaginosis has been associated with vaginal cuff cellulitis, wound infection and abscess formation after hysterectomy. No randomized trials have been performed to investigate the value of screening and treatment before such surgery. The potential role of bacterial vaginosis in infections following intrauterine device insertion, hysteroscopy, and dilatation and curettage has not been systematically studied.

HIV and STIs

HIV has spread rapidly through sub-Saharan Africa

and South East Asia in the last two decades. Initial reports identified genital ulcer STIs as co-factors for transmission. Bacterial vaginosis emerged as a cofactor for HIV acquisition in the Rakai study in rural Uganda.[3] A study of pregnant women in Malawi reported bacterial vaginosis to be associated with HIV acquisition during pregnancy and the postnatal period.[27] Potential mechanisms by which bacterial vaginosis might increase HIV transmission include effects on local immune mediators. Additionally, hydrogen peroxide produced by lactobacilli can inhibit HIV *in vitro* and is absent in most women with bacterial vaginosis. If bacterial vaginosis is established as an important risk factor for HIV spread, its control will become an important public health issue in many countries.

Bacterial vaginosis has also been associated with an increased incidence of non-gonococcal urethritis in male partners.

PREVENTION

Because the aetiology of bacterial vaginosis is not fully understood, it is not known how to prevent it. Antibiotics inhibit growth of the anaerobes but do not necessarily eliminate the factors that led to the development of bacterial vaginosis; therefore, relapse is relatively common. In the Rakai study, intermittent 'mass treatment', which included a course of metronidazole, did not reduce the prevalence of bacterial vaginosis, except in pregnant women.[3]

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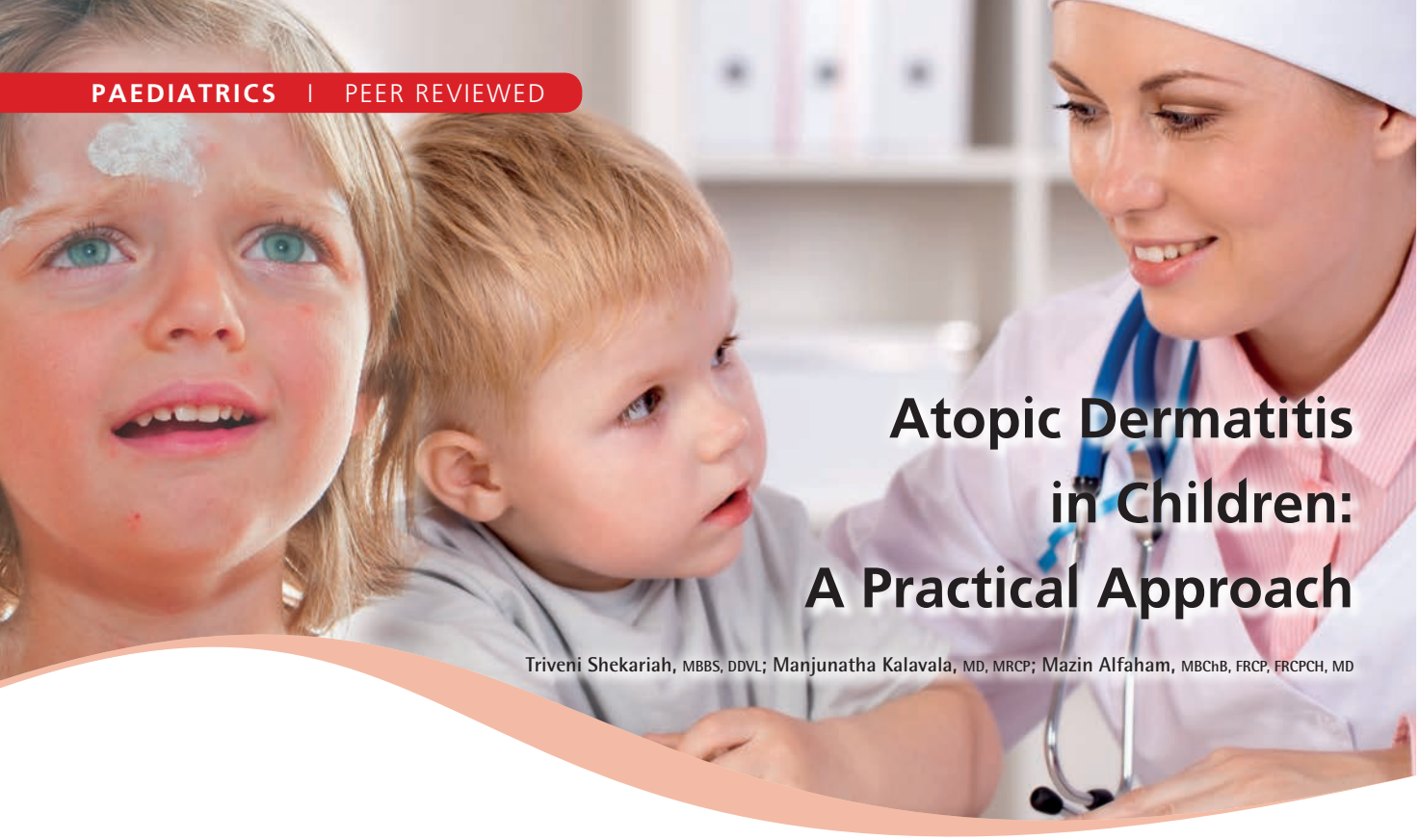


Atopic Dermatitis in Children: A Practical Approach

Triveni Shekariah, MBBS, DDVL; Manjunatha Kalavala, MD, MRCP; Mazin Alfaham, MBChB, FRCP, FRCPCH, MD

EPIDEMIOLOGY

Atopic dermatitis (AD) is a chronic pruritic, inflammatory, skin disease that typically begins in early childhood. AD is one of the most common skin disorders in children. Prevalence in children in UK is up to 20%. Disease onset typically occurs by 6 months of age in 45%, by 1 year of age in 60%, and by 5 years of age in 85% of affected infants and children. Up to 70% of children have a spontaneous remission before adolescence.

The prevalence of AD in children has increased steadily over the last three decades of the 20th century. This is paralleled by increases in the prevalence of asthma, allergic rhinoconjunctivitis, eosinophilic oesophagitis, and gastroenteritis.

However, recent data suggests that AD and hay fever prevalence might have levelled off or decreased over the last 10 years in those aged 12 years or older, whereas it continues to increase in younger children. Migrant studies reveal that AD prevalence increases in populations that move from an area of low to high prevalence, supporting the role of environmental factors in the expression of AD.

AD, asthma and allergic rhinitis are known as the 'atopic triad'. The concept of 'atopic march' evolved from clustering of these conditions in the same individuals and families. AD is frequently the first disorder of the atopic triad. It is possible that epicutaneous sensitization to allergens predisposes to development of asthma and allergic rhinitis. In a large multicentre study, by 5 years of age, 50% of children with early AD and a strong family history of allergy had allergic airway disease or asthma compared with 12% in patients without AD or a family history of atopy.

IMPACT ON THE CHILD AND FAMILY

AD has the potential to be a major handicap with considerable personal, social and financial consequences. In children with AD, quality of life is impaired owing to pruritus, sleep disturbance, pain, irritability, restricted activities, and adverse social interactions. Severe AD may result in poor school performance, behavioural problems, low self-esteem, and decreased participation in sport and other social activities. Parents of children with moderate to severe AD experience sleep disturbance, exhaustion, frustration, and worry owing to their child's disease. The family stress related to the care of children with moderate or severe AD is significantly greater than that of the care of children with type 1 diabetes mellitus.

AETIOLOGY

The pathophysiology of AD is not completely understood. Complex interaction of defects in skin barrier function, host immune response, environmental factors and infectious agents in a genetically susceptible individual are thought to result in AD.

The concordance rate for AD is higher among monozygotic twins (77%) than among dizygotic twins (15%). Parental atopy, in particular AD, is significantly associated with the manifestation and severity of early AD in children.

Defective epidermal barrier function is a hallmark of AD. This results in increased trans-epidermal water loss and dry skin. It will also allow increased trans-epidermal penetration of environmental allergens and triggers inflammation. Mutations in the genes coding for filaggrin, a key protein in barrier function, might play an important part in early-onset AD and asthma. Filaggrin mutations are identified in 30% of European patients with AD. Reduced ceramide levels, and genetic varia-

Figure 1. Erythematous papules and plaques with background oedema typical of infantile atopic dermatitis.

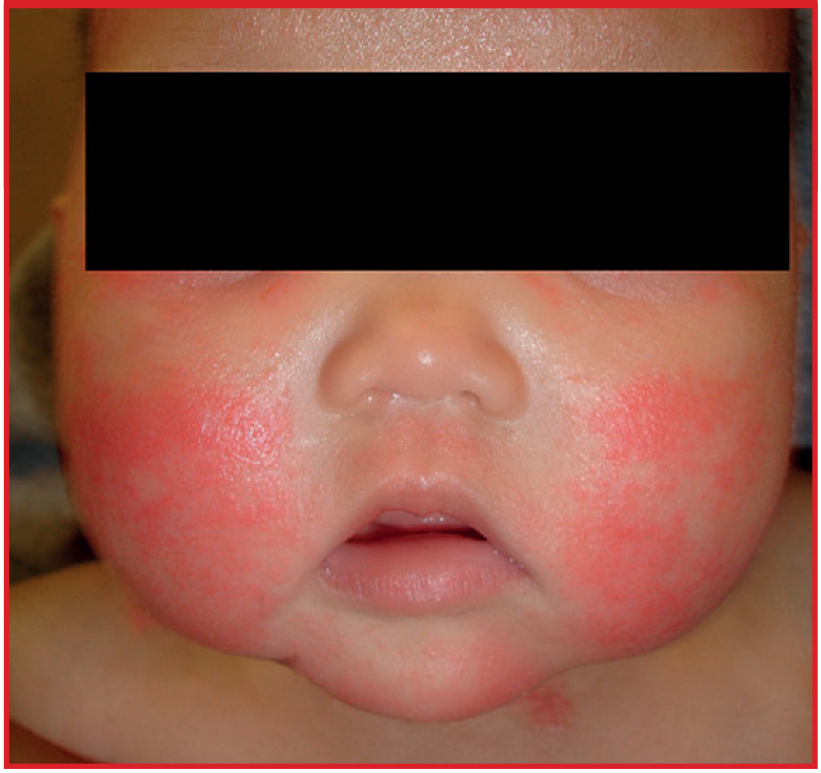


Figure 2. Dry scaly lesions on the scalp. May overlap with seborrhoeic dermatitis.

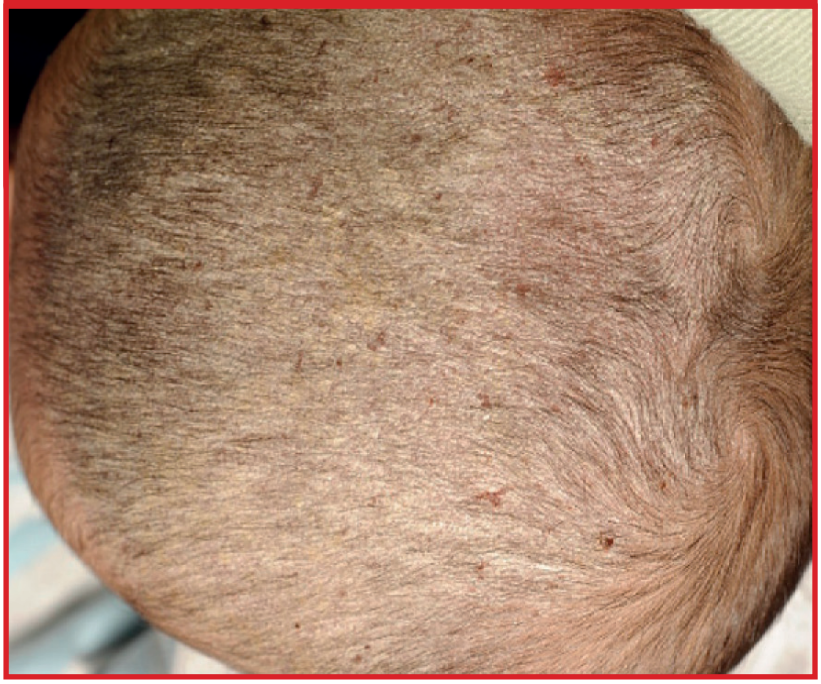


Figure 3. Atopic dermatitis on extensor surface of extremities.

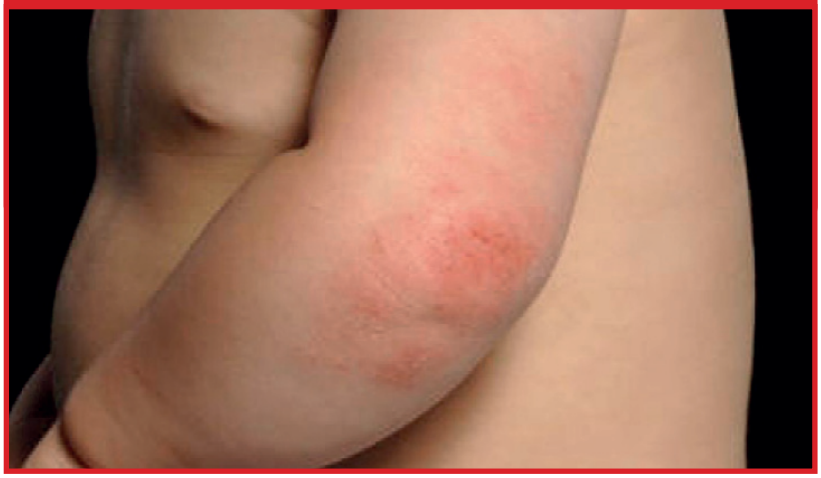


Figure 4. Lichenified plaques on cubital fossae.

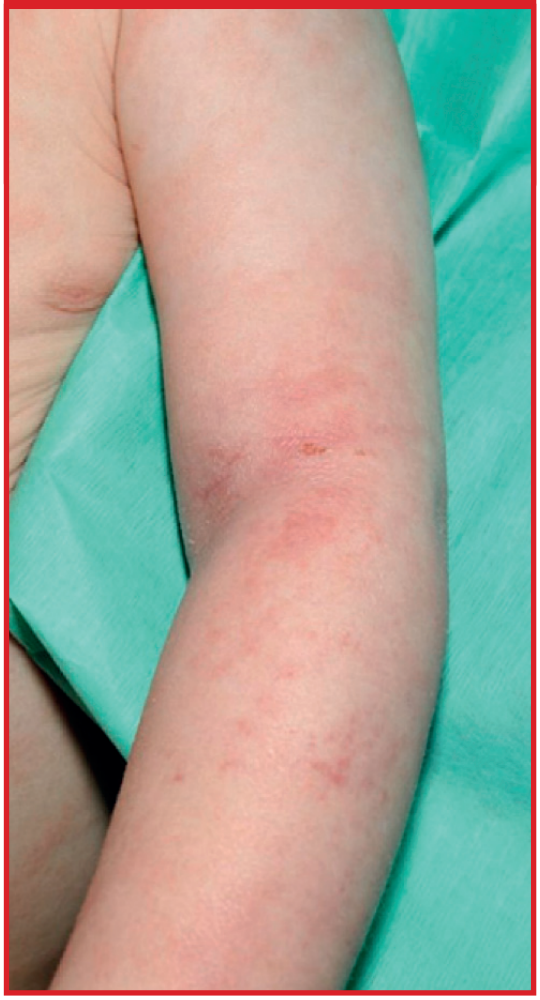


Figure 5. Discrete lichenified papules on the dorsum of hands.

tion in stratum corneum tryptic enzyme and epidermal collagen may also play a role. Exogenous proteases from *Staphylococcus aureus* and house dust mites, and the use of soaps and detergents further damage the barrier function.

Defective barrier function allows penetration of high-molecular-weight allergens in pollens, house dust mite products, microbes, and food. Early-onset AD usually emerges in the absence of detectable IgE-mediated allergic sensitization. IgE-mediated sensitization occurs several weeks or months later. Antigen-specific IgE is the major recognition structure for allergens on basophils and mast cells. Keratinocytes in atopic skin produce cytokines that signal dendritic cells to drive helper T-cell (Th)2 polarization. Inflammation in AD is biphasic; an initial Th2 phase precedes a chronic phase in which Th0 cells and Th1 cells are predominant.

S aureus colonization with or without clinical signs of infection occurs in more than 90% of patients with AD and contributes to the severity of inflammation. Scratching increases the binding of *S aureus* to skin. *S aureus* enterotoxins increase the inflammation in AD and provoke the generation of enterotoxin-specific IgE, which correlates with the severity of disease. Enterotoxins also contrib-

Figure 6. Nummular lesions on the trunk.

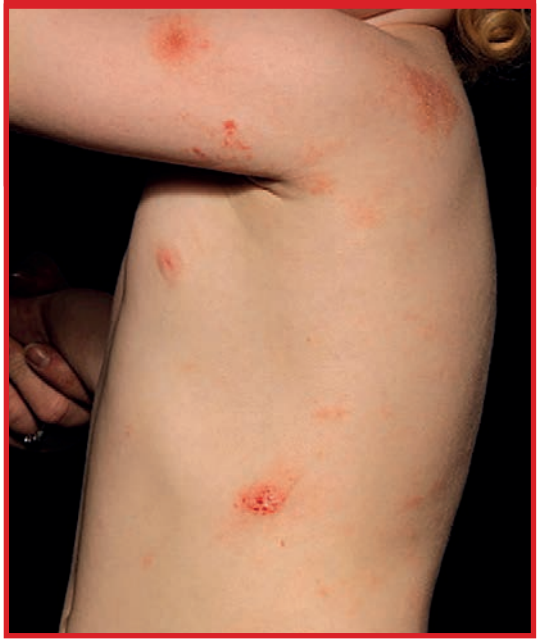
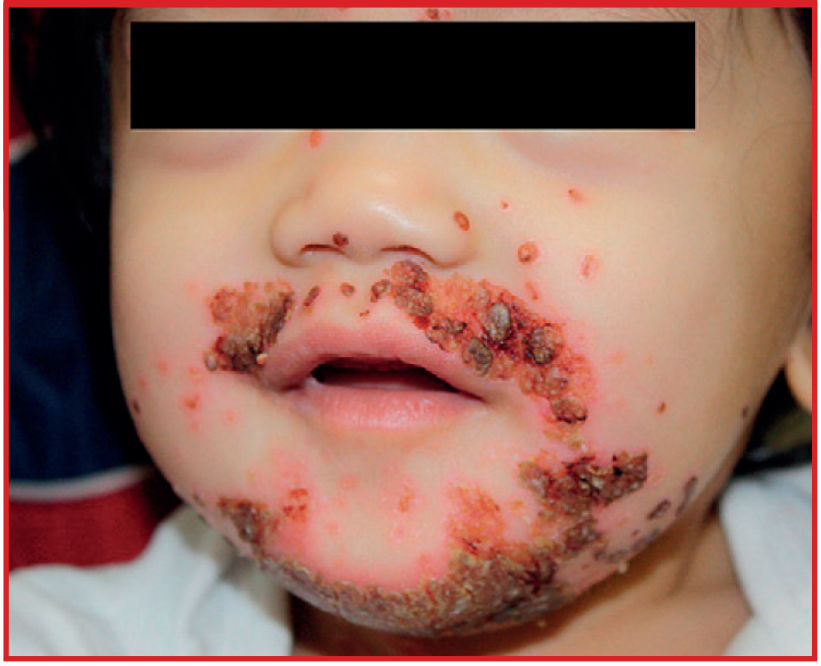


Figure 7. Atopic dermatitis with secondary infection.



ute to emergence of resistance to topical corticosteroid (TCS) treatment.

The cytokines generated during inflammation in AD downregulate the natural production of antimicrobial peptides in the epidermis – cathelicidin and defensin. This results in increased susceptibility to colonization with *Staphylococcus* and the yeast *Malassezia furfur*, the latter plays an important role in head and neck eczema. Patients with AD are predisposed to eczema herpeticum and eczema vaccinatum because of a reduced production of cathelicidin, which has potent antiviral activity.

The underlying mechanisms for pruritus, the most important symptom of AD, are not known. Antihistamines are not always effective in relieving the pruritus. This argues against a prominent role for histamine in causing AD-related pruritus. Neuropeptides, proteases, kinins and cytokines may play an important role in inducing pruritus.

AD is more prevalent in urban, nuclear families compared with rural areas. The 'hygiene hypothesis' postulates that declining family size, improvement in personal amenities and higher standards of the personal cleanliness have reduced the opportunity for infections in young children and increased susceptibility to AD.

Clinical Features

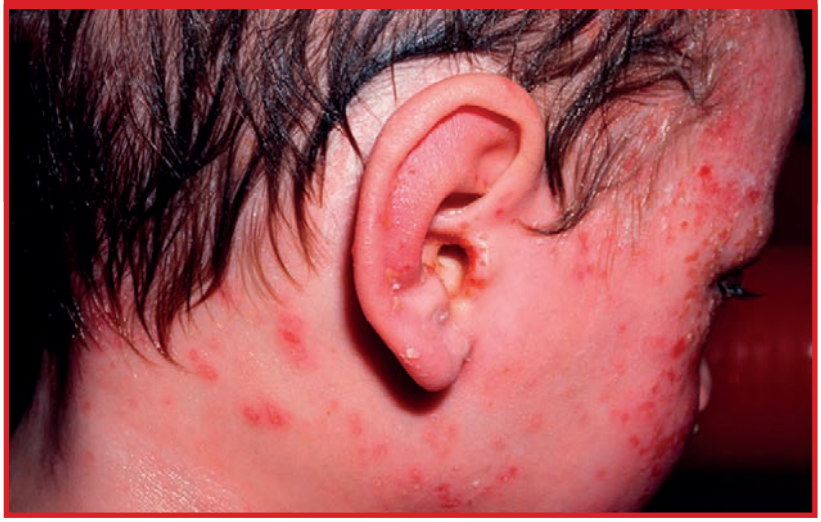
During the first few months of life, AD typically affects face and scalp. Intensely pruritic erythematous papules affect cheeks and forehead (Figure 1). Periorbital and perioral areas are relatively spared. The lesions show significant oedema, leading to oozing and crusting unrelated to secondary infection. Flare-up of lesions around mouth is common with teething and initiation of solid foods. This is probably due to irritation caused by saliva and foods. It is important to keep in mind contact urticaria to food when the lesions are predominantly around mouth. Pruritus and dry scaling of scalp are common (Figure 2). The scalp lesions may represent overlap with seborrhoeic dermatitis.

The lesions may remain localized to the face or extend to the trunk and extensor aspects of the

Table 1. Clinical features seen with increased frequency in children with atopic dermatitis

Keratosis pilaris	Follicular-based keratotic papules; lateral aspects of face, extensor aspects of arms, and anterior thighs
Lichen spinulosus	Round collections of numerous, tiny, skin-coloured to hypopigmented dry spiny papules
Pityriasis alba	≥ 1 cm hypopigmented patches, sometimes with fine scale; especially on face, upper arms
Hyperlinear palms	Accentuated markings on the palms and soles
Atopic pleat (Dennie–Morgan fold)	Groove of the lower eyelid; often present from infancy
Allergic shiners	Slate-grey to violaceous infraorbital discolouration with or without swelling
White dermographism	Paradoxical blanching of skin on stroking firmly with a blunt pointed object

Figure 8. Eczema herpeticum.



extremities. By 8–10 months of age, the extensor surface of the arms and legs are involved, perhaps because of the friction associated with crawling (Figure 3). The lesions on the trunk and extremities are often symmetric, scattered, ill-defined erythematous patches. AD typically spares diaper area. This is because of the combination of increased hydration in the diaper area, protection from triggers by the diaper, and inaccessibility to scratching and rubbing.

Involvement of the antecubital and popliteal fossae, hands, feet, ankles, wrist periorbital area, perioral area, and neck is more common in older children and adolescents (Figure 4). However, these sites might also be affected in infants and young children. Older children are less likely to have the exudative lesions of infancy and, instead, exhibit more lichenified papules and plaques representing more chronic disease (Figure 5). Alhough flexural areas are commonly involved, some children show an 'inverse' pattern with primarily involvement of extensor areas.

In children 1 year of age or older, coin-shaped, sharply defined erythematous scaly plaques (nummular lesion – Figure 6) might accompany the more typical dry scaling erythematous patches of AD. It is important not to confuse them with tinea corporis. Nummular lesions tend to be more recalcitrant to topical therapy and are frequently secondarily infected. In Africaribbean children, the lesions of AD are often more papular (follicular AD).

Generalized dry skin (xerosis) is common. Pruritus is frequently severe, leading to sleep disturbances. Lymphadenopathy in the severely affected area may be prominent owing to inflammation and secondary bacterial infection.

Post-inflammatory hypopigmentation or hyperpigmentation is common, especially in darker skinned children. Hyperpigmentation is particularly common in lichenified areas. The pigmentary changes are transient and are reversible when the underlying inflammation is controlled. Scarring is not a prominent feature but might result from secondary infection and deeply excoriated areas.

Table 2. UK Working Party's diagnostic criteria for atopic dermatitis

Must have
An itchy skin condition (or parental report of scratching or rubbing in a child)

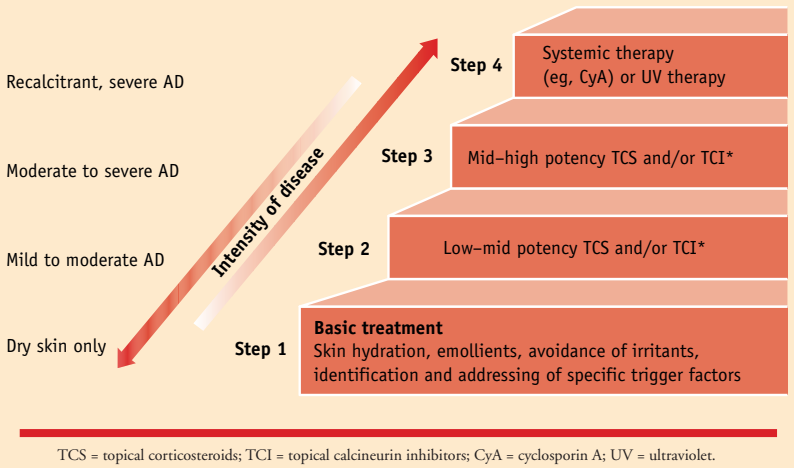
Plus three or more of the following
1. History of involvement of the skin creases such as folds of elbows, behind the knees, fronts of ankles, or around the neck (including cheeks in children under 10).
2. A personal history of asthma or hay fever (or history of atopic disease in a first-degree relative in children under 4).
3. A history of a general dry skin in the last year.
4. Visible flexural eczema (or eczema involving the cheeks/forehead and outer limbs in children under 4).
5. Onset under the age of 2 (not used if child is under 4).

Several clinical signs (Table 1) are seen with increased frequency in children with AD, although they do occur in non-atopic children.

Repeated *S aureus* infections are common (Figure 7). *S aureus* infections are characterized by intense erythema, exudation, crusting, and pustules. Beta-haemolytic streptococcal infections can present with similar clinical features and require prompt treatment with systemic antibiotics. During infective episodes, patients might experience flare-up of AD or fail to respond to appropriate therapy. Children with AD are also prone to disseminated viral infections. Molluscum contagiosum, a common cutaneous viral infection in children, tends to be more disseminated and difficult to treat. Molluscum contagiosum lesions are often associated with pruritus and eczema around them, and also cause flare-up of AD.

Eczema herpeticum (Kaposi's varicelliform eruption) is an explosive development of vesiculopustular eruption in the patches of AD, secondary to herpes simplex virus infection (Figure 8). Clustering and umbilication of vesicles are characteristic. Eczema vaccinatum is disseminated vaccinia viral lesions, due to accidental infection with vaccinia virus when children come in contact with adults receiving small pox vaccination.

Figure 9. Management strategy for atopic dermatitis (AD) (adopted from Akdis *et al*).



TCS = topical corticosteroids; TCI = topical calcineurin inhibitors; CyA = cyclosporin A; UV = ultraviolet.

Diagnosis

Diagnosis is often clinical, based on morphology and distribution of lesions, pruritus and chronicity of the disease. It is important to keep scabies in mind in a child presenting with generalized pruritic rash. Absence of xerosis in the background skin is a clue to scabies. Various diagnostic criteria have been proposed. Table 2 lists the UK Working Party's diagnostic criteria.

Positive bacterial cultures in the right clinical context are helpful in diagnosing *S aureus* infec-

Table 3. Potential triggers for atopic dermatitis

- Harsh detergents/soaps, toiletries containing alcohol, astringents, or fragrances
- Abrasive clothing (wool or synthetics)
- Inhalant allergens – dust mite, animal dander, pollen
- Infections
- Overheating/sweating
- Psychological stress
- Food allergens

tion. Direct fluorescent assay helps in rapid diagnosis of eczema herpeticum while viral cultures are confirmatory. When these tests are not available, smears taken by scraping the floor of the vesicle show multinucleate viral giant cells. Biopsy is rarely performed for diagnosis of AD. When diagnosis is in doubt, histology of skin biopsy shows spongiotic dermatitis.

MANAGEMENT

Developing good rapport with the child and the family is the cornerstone of successful management of AD. Any management decisions have to be made in agreement with the family. This will help ensure compliance with the treatment. Step-wise treatment strategy is depicted in Figure 9. Chronicity of AD, punctuated with flare-ups and secondary infections are frustrating for the child and the parents. Educating the family about the nature of the disease and setting the realistic expectations about the treatment outcomes are crucial. Age-appropriate educational sessions for parents are shown to improve objective severity of eczema and quality of life scores. A team approach with doctor and nurse experienced in the management of AD works well.

Psychological support from the health-care professionals, family, school and support groups is important. Recognition of psychological factors and involvement of child psychologist will go a long way in reducing the stress involved in coping with a chronic condition like AD.

Avoidance of Triggers

Potential triggers for AD vary among patients. Common triggers are listed in Table 3. Substitution of soaps and detergents with bath emollients and emollient-based soap substitutes prevent further dryness and damage to the epidermal barrier. Early recognition and treatment of infections help prevent flare-ups. Oral antihistamines are beneficial when aeroallergens are suspected to be triggering AD, particularly when associated with allergic rhinitis. It is important to emphasize that avoidance of triggers may result in improvement in AD but not complete cure.

Food allergy may be associated with AD in up to 30% of patients. Food allergy should be considered in children who have reacted previously to a food with immediate symptoms or in infants and young children with moderate to severe atopic eczema that has not been controlled by optimum management, particularly if associated with gut dysmotility or failure to thrive. Careful history and food diaries are essential. Specific serum IgE for food and skin prick tests in the context of a thorough allergy history might be helpful, although some cases are not IgE-mediated. A positive IgE or skin prick test does not necessarily indicate an underlying ongoing allergy and might be representing past sensitization. Atopy patch testing might be useful in some cases with suspected allergy to cow's milk, egg or soya. Dietary restrictions should only be recommended in cases of an established diagnosis of food hypersensitivity. A therapeutic/diagnostic trial of food exclusion might be justified and is easier to try in infants owing to the limited dietary variety required at that age and, generally speaking, accept-

ance of alternative milk products. Parents should be cautioned against uncontrolled restriction diets. Children with eczema who are suspected of having food allergy as a trigger might benefit from being reviewed in a paediatric clinic with a special interest in allergy. An involvement of a paediatric dietician is crucial.

The role of breastfeeding in the prevention of AD is debatable. Exclusive breastfeeding for the first 4 months decreases the cumulative incidence of AD in the first 2 years of age in high-risk infants. Exclusive breastfeeding beyond 4 months does not confer specific additional benefit. There is lack of evidence for the role of maternal diet during pregnancy or lactation.

There is no evidence to support delayed introduction of solid foods beyond the sixth month of life having an impact on AD and atopic sensitization at 2 years of age. This applies for foods thought to be highly allergenic such as cow's milk, fish, eggs and peanuts. Data on the role of probiotics in the prevention of AD in high-risk infants are conflicting. Further studies are needed to clarify this issue.

Emollients

Regular application of emollients remains the mainstay of general management of AD. Emollients reduce dryness of skin, reduce trans-epidermal water loss and also help in reducing pruritus and inflammation. It is important to stress that emollients need to be applied continuously even when the skin is not inflamed. The choice of the emollient depends on the individual skin status, time of the day, and seasonal and climatic conditions. Ointments tend to be greasy, while creams and lotions are cosmetically more appealing for application during daytime. A combination of cream/lotion during the day and ointment during night is useful, particularly in adolescents. In our clinic, patients are asked to try samples of emollients and prescription is issued for the emollient of patient's choice. Recently, several emollients with ingredients claimed to have anti-inflammatory properties have been introduced as steroid-sparing agents. Further studies are needed to establish the role of these products in the management of AD.

Bathing

Bathing in lukewarm water with a bath emollient is helpful in skin hydration and removal of exudates and crusts. However, prolonged bathing in very hot water with strong detergent or bubble baths cause further dryness of the skin. Application of emollient immediately after the bath ('soak and seal') prevents drying up of skin. After bath, gently pat the skin dry with a towel, rather than rubbing.

In patients with repeated *S aureus* infections, chlorine in swimming pool water is beneficial in reducing *S aureus* colonization. Swimming for 20 minutes three times a week is helpful. If this is not practical, a 'swimming pool' can be created at home by adding a small amount of household bleach to bath water. Bleach baths reduce the number of infections and the need for antibiotics. Long-term bleach baths, in addition to intermittent intranasal mupirocin ointment, are also shown to reduce the severity of eczema by reducing *S aureus* infection and colonization. However, an emollient needs to be applied immediately after coming out of the pool to prevent dryness of skin.

Topical Corticosteroids

Topical corticosteroids remain the first-line treatment for control of flare-ups. TCSs have anti-inflammatory, anti-proliferative, immunosuppressive, and vasoconstrictive actions. The current British system of classification stratifies TCSs into four groups based on the vasoconstrictor assay: mild, moderate, potent and very potent. The difference in potency between groups is often dramatic. Clobetasol propionate 0.05% ointment (very potent) is

~1,800 times more potent than hydrocortisone 1% ointment (mild).

A potent TCS can be used intermittently for short periods of time to control the flare-ups. Alternatively, an initial therapy with a potent TCS, followed by changeover to low-potency preparation for longer period is also effective. The choice of an adequate vehicle is important to achieve optimal therapeutic effect. Ointments are preferred for treatment of dry lichenified patches as they are associated with better penetration and efficacy. TCS preparations should be applied no more than twice daily. Only mild to moderately potent preparations should be used on genital, facial and intertriginous areas. Intermittent twice weekly application of fluticasone propionate 0.05% cream up to 24 weeks is shown to reduce the number of flare-ups.

TCSs are also used sequentially with topical calcineurin inhibitors (TCIs). Initial control of flare-up with TCS is followed by 2–3 times a week application of TCI for a period of up to 1 year to maintain remission.

Children with atopic eczema and their caregivers should be informed that TCSs and TCIs should be applied only to areas of active atopic eczema, which may include areas of broken skin.

Prolonged use of TCSs might result in loss of efficacy by 'tachyphylaxis'. *S aureus* enterotoxin contributes to the emergence of resistance to TCSs. Prolonged use of potent TCSs is associated with local and systemic side effects. Local side effects include atrophy, telangiectasia, striae, hypopigmentation, rosacea, perioral dermatitis, acne, cataracts, and glaucoma. Systemic absorption might result in suppression of hypothalamic-pituitary-adrenal axis, Cushing's syndrome, growth retardation, and reduced bone mineral density. However, these complications are rare when TCSs are used judiciously. Concerns about adverse effects have resulted in 'steroid phobia' in parents. Addressing these concerns is important to ensure compliance and avoid suboptimal treatment. Relatively new TCS preparations like mometasone furoate and fluticasone propionate have lower atrophogenic potential.

Topical Calcineurin Inhibitors

Tacrolimus 0.03% ointment and pimecrolimus 1% cream are approved for second-line treatment of moderate to severe AD in children above 2 years of age for short-term continuous use (up to 6 weeks) and long-term non-continuous use (up to 12 months). They provide an effective, steroid-free therapeutic alternative in the management of AD. TCIs block the production and release of proinflammatory cytokines after antigen-specific or non-specific activation of T cells and mast cells. Sequential use of TCIs with TCSs reduces the number of flare-ups. Clearance of patches of eczema by application of appropriate-strength TCSs for few days is followed by application of tacrolimus 0.03% ointment twice daily for 2–6 weeks. After this period, if skin lesions remain well controlled, the frequency of topical tacrolimus is reduced to two or three times a week for a period of up to 12 months.

A frequently observed side effect is transient burning sensation at the application site. However, with continued use, this sensation will subside. TCIs are not associated with atrophy as they do not inhibit collagen synthesis. Therefore, they are useful treatment options for sensitive skin areas such as face and intertriginous area. TCIs are not associated with increased incidence of bacterial infections, but they should not be used in the presence of infection. One study showed slightly increased risk of herpes simplex virus infection. TCIs have high molecular weight (more than 800 kDa). Molecules above 500 kDa have limited potential for systemic absorption. Repeated studies involving much higher concentrations of TCIs failed to show systemic absorption. Concerns about lymphomas and systemic

malignancy have not been substantiated by large population-based studies. However, effects of long-term use of TCIs on immune surveillance in the skin are not known. Long-term follow-up studies and careful photo-protection measures are advisable.

Application of topical agents is time-consuming, and some of the topical preparations can sting particularly during acute flare-ups. Both the child and parents need constant encouragement and advice on quantity of medication to be used. The fingertip unit (FTU), defined as the amount of topical medication extending from the tip to the distal interphalangeal crease on the palmar aspect of the index finger, is a useful guide to estimate the amount of topical medication needed to cover a given area. One FTU is 0.5 g of ointment or cream. One FTU is sufficient to cover an area of two adult hand areas.

Adjunctive Therapy

Sedating antihistamines such as hydroxyzine and chlorpheniramine maleate are useful in improving sleep during flare-ups, although they probably do not have direct effects on the pruritus associated with AD. Non-sedating antihistamines are less useful for relieving pruritus. However, they may benefit patients with allergic triggers. Anecdotally, melatonin has been beneficial in some cases.

Antimicrobial Agents

The skin of children with AD is heavily colonized with *S aureus*, and infections are frequent. Prompt recognition and treatment with topical and oral antibiotics will help clear the infection and control the flare-up of AD. Topical antibiotics should be used with caution to prevent emergence of resistant strains and contact sensitization. Fusidic acid resistance remains high in spite of local community guidelines to restrict the use of this topical antibiotic. Topical emollients with antiseptics may help reduce colonization of *S aureus*.

Bleach baths in addition to topical nasal mupirocin will help reduce the number of infections and need for antibiotics. Viral and fungal infections need to be recognized early and treated promptly to prevent dissemination.

Wet Wraps

Wet wraps are useful in treating the refractory areas, particularly on the limbs. Wet wraps increase skin hydration, promote penetration of topical medications, and serve as an effective barrier to scratching. A wide variety of wet-wrap techniques have been used. Wet wraps with once-daily application of TCSs is an effective short-term intervention. Incorrect use of wet wraps may cause maceration of the skin and secondary infections, or promote skin dryness. Patient education and close supervision by experienced medical staff are essential. Wet wraps should not be used in the presence of infection.

Systemic Therapies

Second-line therapies in the form of phototherapy or systemic immunomodulatory medications such as prednisolone, cyclosporine, azathioprine, and mycophenolate are reserved for severe AD not responding to optimum topical therapy. As these modalities involve frequent visits to the hospital and blood tests for monitoring side effects, risks and benefits have to be discussed in detail and parents be given sufficient time to make decisions. Printed information leaflets available on the British Association of Dermatology website (www.bad.org.uk) are useful. Such treatments are initiated after involving a dermatologist.

CONCLUSIONS

AD is a common, chronic skin disease that starts

Learning points

- Moisturizing the skin with regular daily topical emollients would help to reduce itching and minimize the frequency of relapses.
- Intermittent topical corticosteroids (TCSs) are the main anti-inflammatory agents in the management of atopic dermatitis (AD).
- The use of topical calcineurin inhibitors (TCIs) would decrease the need for TCSs. Concern about skin cancer from TCIs seems unfounded, but a careful approach with dose and duration is always prudent.
- Under-treatment, usually through fear of side effects, is harmful and leaves the child in distress continuously.
- Management should include a holistic approach.
- Children with difficult AD and certainly those that might require systemic therapy should be reviewed by a dermatologist with expertise in children's eczema.
- Food allergy should be sought for especially in the first 2 years of life and mainly in those with a severe degree of AD and/or those with concomitant history of immediate reactions.

early in life and can adversely affect a child's overall health and development. Regular use of emollients and intermittent use of TCSs remain the cornerstone of therapy. TCIs have been shown to provide an effective, steroid-sparing alternative for appropriate patients, particularly those who are prone to frequent flares and need AD treatment in sensitive skin areas. In conjunction with these pharmacological treatments, the overall management depends on (1) educating caregivers about AD's chronic, unpredictable course characterized by flares that can occur despite best efforts; (2) appreciating the compromised epidermal barrier and the importance of proper skin care; (3) approaching trigger avoidance carefully and with the understanding that, in general, AD is a multifactorial disease; and (4) using a team-oriented approach that includes primary care physicians, specialists, nurses, psychologists, behavioural therapists, and other health-care professionals to better achieve long-term success for patients with AD.

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Clinical Case
Rotting Teeth in a Young Girl

Simon Wooley, BDS, MPHC; Kaye Roberts-Thomson, BDSc, MPH

Answer:

COMMENTARY

This case is a stark reminder that few preschool children access dental care, this being especially difficult in rural and remote areas. All GPs and other health providers who are visited for health and immunization checks can play a key role in the prevention and management of dental caries (tooth decay) in this age group.

To this end, the 'lift the lip' strategy was introduced by the South Australian Dental Service and has been adopted in other states and territories as a response to the decline in oral health of children, and to improve the early identification and referral (to public or private practitioners) of children experiencing tooth decay (see www.sadental.sa.gov.au for details, including a photographic guide/tool to assist caries identification). In 2008/2009, 28,000 Australian children, 8,000 of whom were younger than 5 years of age, were hospitalized for dental extractions and restorations, most of which were preventable.

Figure 1

In the case scenario presented here, the first priority is to highlight to Tracey's mother the need for prompt dental referral and assessment. Treatment recommended by a dental practitioner would be subject to a detailed history and examination, including assessment of the expected exfoliation of the deciduous teeth in question, the severity and extent of the decay in general, and the ability of the child to cope with treatment in the dental chair. The need for a general anaesthetic is a real possibility.

It is also a timely opportunity to introduce information about the causes and prevention of tooth decay in general and early childhood caries (or baby bottle caries/decay) with the parent and child in a non-blaming manner. This information would be reinforced by the dental clinician. Early childhood caries generally affects the upper front deciduous teeth but can affect all teeth. It is typically associated with prolonged exposure (such as comfort sucking while sleeping) to

a sweet drink (eg, soft drink, cordial, juice).

Almost 44% of 5-year-olds in Australia have tooth decay. Of the total incidence of tooth decay, 80% is experienced by 20% of young children (those under the age of 6 years). Decay is a dynamic process of demineralization/remineralization, which is potentially reversible when confined to enamel, the outer layer of the tooth. The model of decay as a 'balance' between demineralization (risk factors) and remineralization (protective factors) of teeth is useful. The aim is to minimize the risk factor exposure and maximize the protective factors – that is, to tip the 'balance' in favour of remineralization.

Risk or demineralization factors include:

- a high frequency or prolonged consumption of fermentable carbohydrates and sugary foods or drinks
- comfort sucking with a sweet drink (even plain milk), particularly sleeping with a bottle
- delaying commencement of tooth brushing with a junior fluoride toothpaste; this should begin at 18 months of age
- inadequate oral hygiene and plaque removal; parents should assist children with brushing up to about the age of 8 years.

Protective or remineralization factors include the following:

- tap water is the best drink (fluoridated ideally) to satisfy thirst
- after 6 months of age, infant-feeding cups rather than infant-feeding bottles are preferred for drinks other than formula or breast milk
- twice daily plaque removal with a soft brush and junior fluoride toothpaste (from 18 months to 6 years); adult toothpaste should be used from 6 years of age
- children should be told to spit but not rinse after brushing to maximize the fluoride benefit from toothpaste
- professionally applied fluoride agents such as fluoride varnish should be used in children at high risk of tooth decay
- fissure sealing of selected teeth is recommended.

Although uncommon, an abscessed deciduous tooth has the potential to affect the development of the permanent successor, subject to the severity and timing of the infection to coincide with the development of the successor crown. Upper permanent incisors usually have completed their crown development by a year or two before the expected eruption at about 6 years of age. Should a deciduous tooth require premature extraction, there is an increased risk of space loss and crowding in the secondary dentition. This risk is greater for early loss of posterior deciduous teeth as compared with anteriors. This may necessitate space maintenance for the permanent successor and/or future orthodontic assessment and intervention, which might otherwise have been avoidable.

The notion of 'soft teeth' is often a misconception of a parent seeking a cause for the decay outside of their control and therefore their responsibility. Deciduous and permanent teeth can have development defects of enamel and dentine (hypoplasia); however, these are relatively uncommon and are often not carious.

CONCLUSION

Good oral health in young children is declining. This is especially so in rural and remote areas where exposure to fluoride and access to clinical dental care may be problematic. Good oral health is important to general health. All health practitioners can play an active role in the prevention of tooth decay and early intervention if they 'lift the lip'.

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TAKE THE WORRY OUT OF ATOPIC DERMATITIS.

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3. Glycyrrhetinic acid, Hyaluronic acid, Shea butter, Vitis vinifera, Telmesteine, Vitamin C & E

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1 Point

Ovarian Cancer Screening—An Update

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INTRODUCTION

Ovarian cancer is a major cause of mortality from malignancies in developed countries. It is the fourth and fifth most common cause of cancer death in women in the UK and US, respectively.[1,2] In Asia, ovarian cancer ranks fifth and sixth in cancer mortality in Singapore and Hong Kong, respectively. Ovarian cancers have vague symptoms such as abdominal discomfort or bloating, and therefore the majority of the cases present at an advanced stage. A late diagnosis may be a major contributing factor in the overall poor prognosis. Stage I disease gives a relatively good 5-year survival of 85%, but this falls to about 15–30% for stage III and IV disease. Hence, ovarian screening has been proposed in order to improve early diagnosis of the disease and overall outcome. In this article, we will discuss:

1. Difficulties with ovarian cancer screening
2. Screening methods being investigated
3. Update on data from large randomized trials
4. Possible future directions.

Most screening methods involve the measurement of serum CA 125 and/or the use of transvaginal ultrasound to assess the ovarian morphology.

DIFFICULTIES WITH OVARIAN CANCER SCREENING

Although ovarian cancer satisfies many World Health Organization criteria for screening,[3] there are several intrinsic problems that render ovarian cancer screening difficult. Unlike cervical cancer, ovarian cancer appears to be a heterogeneous group in which there is no well-defined precursor lesion and the rate of disease progression can be highly variable. This contributes to the difficulty of finding an effective screening test that can detect early disease and hence improve survival. Furthermore, unlike in cervical cancer screening in which a positive smear can be further investigated by colposcopy and biopsy, and precursor lesions, such as cervical intraepithelial neoplasia, can be treated by a minor procedure such as a large loop excision of the transformation zone, a positive test for ovarian screening would lead to a relatively

Table. Diagnosis and survival by stage.

Diagnosis	Women diagnosed in the Thames cancer registry area, UK (1992–1996)[a], %	Women diagnosed in Hong Kong (2007)[b], %	Women diagnosed in the US (1999–2006)[c], %	5-year survival in the UK (1992–1996)[a], %	5-year survival in the US (1988–2001)[c], %
Local (stage I)	20	41.8	15	73	89
Direct extension (stage II)	8	5.3	–	34	66
Lymph nodes or distant metastases (stages III & IV)	41	26.1	79	16–27	18–34
Unstaged	31	26.9	7	39	–

[a]Data from http://info.cancerresearchuk.org/cancerstats/types/ovary/survival/#stage.
[b]Data from Hospital Authority: Hong Kong Cancer Registry Web site. www3.ha.org.hk/cancereg/e_stat.asp. Accessed January 2011.
[c]National Cancer Institute Surveillance Epidemiology and End Results Web site. http://seer.cancer.gov/statfacts/html/ovary.html#survival. Accessed January 2011.

invasive surgical intervention, eg, diagnostic laparoscopy and bilateral salpingo-oophorectomy, with its potential surgical complications. This further adds to the importance of finding a highly specific test. A screening test with 100% sensitivity and 99.6% specificity would still subject 10 women to surgery for each case of malignancy established.[4]

POSSIBLE SCREENING TESTS

CA 125

Despite the above problems, active search for a good screening test has been underway for the last 10–15 years. Most screening methods involve the measurement of serum CA 125 and/or the use of transvaginal ultrasound (TVS) to assess the ovarian morphology. CA 125 is an antigenic determinant on a high-molecular-weight glycoprotein that is recognized by the monoclonal antibody, OC 125, produced by immunizing a human serous cystadenocarcinoma cell line.[5] It is expressed by tissues derived from the coelomic epithelium. Apart from in ovarian cancers, it is also expressed in cells of mesothelial origin such as the peritoneum, pericardium, and pleura. It is raised in about 80% of women with advanced epithelial ovarian cancer, but it is raised in only 50% of women with early disease.[6] Since it is expressed by other tissues of coelomic origin, it is also raised in a number of benign gynaecological and non-gynaecological conditions such as endometriosis, uterine fibroids, peritonitis, and appendicitis. Therefore, using CA 125 alone would not be sensitive or specific enough.

It has been shown that TVS has a better sensitivity but a lower specificity than CA 125 alone.

Since CA 125 levels in women without ovarian cancer would remain normal while those in women with cancer would rise, assessment of serial CA 125 in an individual using a 'risk of ovarian algorithm', which takes into account the rate of change and age instead of a single cut-off value, may improve the performance of the test.[7]

Transvaginal Ultrasound

The use of TVS alone is limited by its low positive predictive value. TVS can detect abnormalities in ovarian size and morphology but fails to differentiate between a benign and malignant lesion. It has been shown that TVS has a better sensitivity but a lower specificity than CA 125 alone. The positive predictive value was only 9.3% in 14,469 asymptomatic women over the age of 50.[8] This may be improved by using Doppler ultrasound and a morphology index, but the performance varied amongst different operators.[9,10]

TVS + CA 125

Combining TVS and CA 125 could potentially

Combining transvaginal ultrasound and CA 125 could potentially improve the performance of either test alone.

improve performance over either test alone. A pilot randomized, controlled trial combining CA 125 at a cut-off of 30 U/mL and TVS was published in 1999.[11] A total of 21,935 post-menopausal women were randomized to either three annual screens with CA 125 and TVS if CA 125 was elevated or to a control group with no intervention. The patients were followed up for 7 years. There were 16 cases and 20 cases of ovarian cancers in the screened and control groups, respectively. The median survival was significantly longer in the screened groups (73 months vs 42 months; $P = 0.011$), but the trial was not sufficiently powered to demonstrate any significant difference in mortality rate.[11] This trial gives the basis for large randomized trials using these modalities.

UPDATE ON DATA FROM LARGE RANDOMIZED TRIALS

The Prostate Lung Colorectal and Ovarian (PLCO) cancer screening trial randomized 34,261 women between 1993 and 2001 from 10 screening centres in the US to screening arm versus control. The screening arm consisted of annual CA 125 and TVS for 4 years plus two additional years with CA 125 alone. Results from four rounds of screening were published in 2009.[12] A total of 89 invasive ovarian or peritoneal cancers were diagnosed, of which 60 were screen-detected. Overall, 19.5 surgeries were done for each screen-detected cancer; and despite screening, 72% of screen-detected cases were late stage (stage III/IV). Mortality data were still being awaited. TVS led to most of the unnecessary surgeries but detected most of the early-stage disease.

A high surgery rate was also reported in a Japanese trial in which asymptomatic post-menopausal women were randomized to an intervention group (n = 41,688) or a control group (n = 40,799) with a follow-up of 9.2 years.[13] The intervention consisted of annual screens with sequential pelvic ultrasound and serum CA 125. Overall, 33 surger-

Women with a family history of or genetic predisposition to ovarian cancers may benefit more from intensive screening.

ies were done to detect one case of cancer. The proportion of early-stage ovarian cancer was higher in the screened group compared with the control group (63% vs 38%), but this did not reach statistical significance. Again, mortality data were not yet available.

The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) is the largest randomized trial published to date. Between 2001 and 2005, 202,638 post-menopausal women were randomly assigned to one of three arms: a control arm with no screening (n = 101,359); a TVS arm (n = 50,639); or a multimodal screen (MMS) arm in which women were screened annually with CA 125 (interpreted using a risk of ovarian cancer algorithm) and TVS as a second-line test (n = 50,640). Results of the interim analysis comparing the MMS group and the TVS group were published in 2009.[14] There were no significant differences in sensitivity between the two groups (89.5% vs 75.0%) but specificity was significantly different (99.8% vs 98.2%). There were 2.9 operations done per case of cancer detected in the MMS group compared with 35.3 operations in the TVS group. There appeared to be a stage shift towards early disease with 50% of the cases detected in the early stages. However, for the ultimate question of whether there is any impact on mortality, we would still need to wait until sufficient events have accrued for a comparison with mortality in the control group when the trial is completed in December 2014.

TVS led to most of the unnecessary surgeries but detected most of the early-stage disease.

FUTURE DIRECTIONS

Targeting High-risk Populations

Women with a family history of or genetic predisposition to ovarian cancers are at higher risk for the disease and may benefit

more from intensive screening. The presence of one first- or second-degree relative with ovarian cancer increases the relative risk to 3.1 (95% confidence interval, 2.2–4.4); with two or three relatives with ovarian cancer, the relative risk increases to 4.6 (95% confidence interval, 1.1–18.4).[15] Women with hereditary breast and ovarian cancer syndromes are at marked increased risk of developing ovarian cancer. *BRCA1* mutation carriers have a lifetime risk of 60% while *BRCA2* carriers have a slightly lower risk of 15–25%.[16] In this group of patients in which the incidence of ovarian cancer is much higher, a screening test does not need to be as specific to achieve the same positive predictive value. Therefore, screening modalities that appeared to be not effective enough in the low-risk population may perform much better in this group. Published series suggested that the current techniques (CA 125 and TVS) have acceptable positive predictive values but annual screening does not detect all cancers at an early stage and interval cancers could occur.[17] These issues are currently under investigation in the on-going UK Familial Ovarian Cancer Screening Study (UKFOCSS) trial in which annual TVS would be combined with more frequent CA 125 measurements with the use of a CA 125 algorithm.

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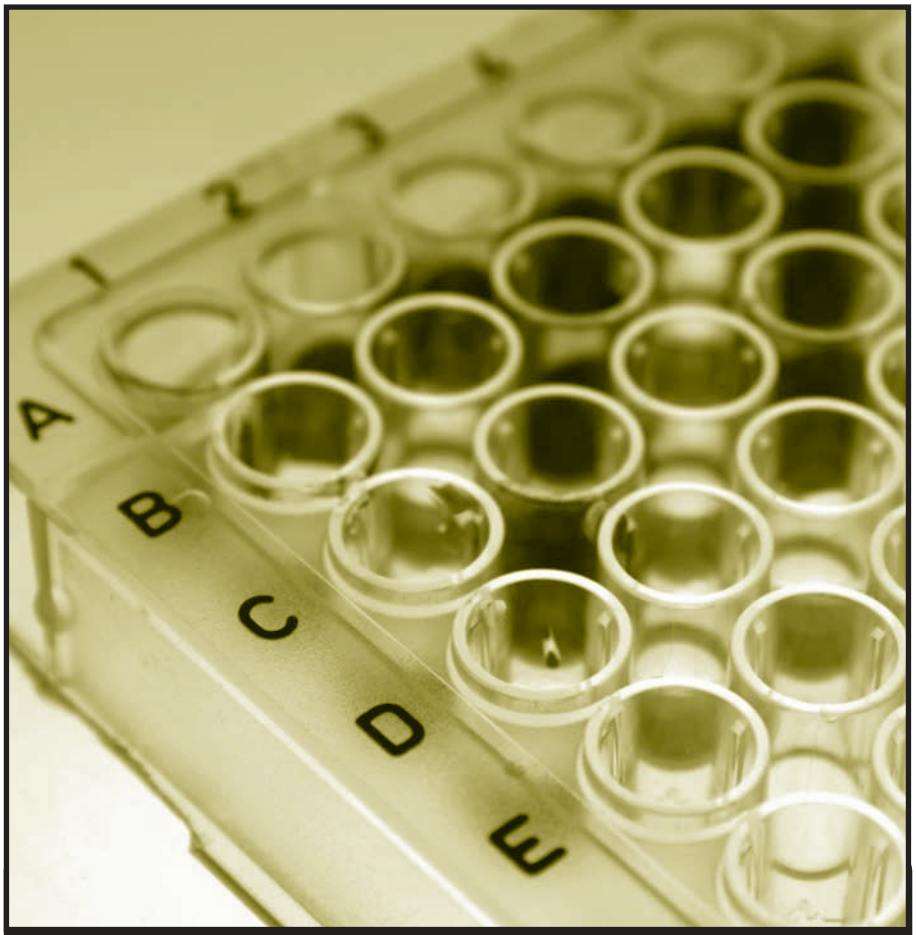

Apart from CA 125, a number of other biomarkers have been identified to be associated with the development of ovarian cancers.

New Biomarkers

Apart from CA 125, a number of other biomarkers have been identified to be associated with the development of ovarian cancers. The human epididymis protein 4 (HE4) is one of the most promising new serum biomarkers. It was reported to be expressed in 32% of ovarian cancers without elevated CA 125 expression.[18] HE4 in combination with CA 125 could better differentiate malignant ovarian masses from benign ones,[19] and HE4 has been reported to outperform CA 125 as a first-line screen owing to its high sensitivity.[20] Further studies are needed to investigate whether multimodal screening with TVS and a biomarker algorithm incorporating CA 125 and HE4 would improve on the current

Finding the appropriate screening strategy for ovarian cancer remains a challenge.

screening methods. There are many other new biomarkers identified (eg, M-CSF, OVX1, LPA, CA 72–4, prostasin, osteopontin), but none of these markers alone appeared to be better than CA 125 alone. The use of a panel of markers would potentially improve the sensitivity and specificity. A quantitative analysis of six biomarkers on a multiplex platform gave a sensitivity of 95.3% and a specificity of 99.4%.[21] Similarly, proteomics techniques, by analyzing protein cluster patterns, may be able to identify ovarian cancer with 100% sensitivity and 95% specificity.[22] The clinical usefulness of these new biomarkers and techniques still needs to be validated in large randomized trials.

...there is a high proportion of aggressive ovarian tumours that present as high-stage, high-grade disease, and this is the group that the current screening strategies may fail to detect.

CONCLUSION

Finding the appropriate screening strategy for ovarian cancer remains a challenge. Refinement of the current available methods, together with the new biomarkers and proteomic techniques, may help to provide more effective screening tests. It is also important to define the most appropriate target population to be screened. A different strategy may be needed for populations with different risks. Lastly, ovarian cancer is a heterogeneous group of disease. Current screening methods are based on the assumption that the disease originates from the ovary and would progress gradually from an early to

Learning points

- ❒ No ideal screening strategy has been established for ovarian cancer, and therefore routine screening cannot yet be recommended.
- ❒ CA 125 is raised in only 50% of early disease and is also raised in a number of benign conditions; therefore, using CA 125 alone as a screening test would not be sensitive or specific enough.
- ❒ Transvaginal ultrasound can effectively detect ovarian masses but cannot accurately assess the nature of the mass. TVS alone leads to a high number of unnecessary operations.
- ❒ A combination of serial CA 125 measurements and transvaginal ultrasound is the commonest screening strategy being investigated in large randomized trials.
- ❒ Combining CA 125 with transvaginal ultrasound may reduce the number of unnecessary surgeries.
- ❒ Current data from large randomized trials show a possible trend towards earlier diagnosis, but more data on the exact effect on overall mortality are still being awaited.

a late stage and that screening can detect the early-stage disease and thus reduce mortality. However, there is a high proportion of aggressive ovarian tumours that present as high-stage, high-grade disease, and this is the group that the current screening strategies may fail to detect. Targeting the differences in carcinogenesis between the tumours with different biological behaviour may allow new approaches, such as those based on molecular genetic markers, to be developed to detect these aggressive tumours, and this will have more impact on reducing mortality from this disease.

In summary, results from large randomized trials so far could not yet clearly demonstrate that the current screening methods could allow earlier detection of the disease, and information on mortality from the large trials are not yet available. Based on the current evidence, routine population-based screening in asymptomatic women cannot yet be recommended.

About the Author

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Ovarian Cancer Screening—An Update

Please indicate on your answer sheet whether the following statements are **True** or **False**.

1. Ovarian screening is recommended for post-menopausal women.
2. CA 125 is a specific test for ovarian cancer.
3. CA 125 is raised in 80% of early ovarian cancers.
4. CA 125 can be raised in endometriosis.
5. The use of an algorithm that takes into account the rate of change of CA 125 may perform better than a single cut-off value in ovarian cancer screening.
6. Transvaginal ultrasound is more sensitive than CA 125 in detecting early ovarian cancers.
7. Based on the results of UKCTOCS, screening with transvaginal ultrasound alone leads to more operations than screening with transvaginal ultrasound and CA 125.
8. Results from large randomized trials published showed that ovarian cancer screening can reduce mortality from this disease.
9. In women with a genetic predisposition to ovarian cancers, there is good evidence that annual screening can detect the cancers early.
10. The lack of a test that is sensitive and specific enough is one of the major obstacles in ovarian cancer screening.