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香港內科學會

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Dr Marco Ho revisited the role of methotrexate in the management of paediatric atopic dermatitis in the context of emerging biologic therapies, focusing on efficacy, safety and cost-effectiveness. Long-term

safety data over 25 months is available. Nearly 86% of patients achieved treatment goals. Regular monitoring of liver function, renal function and blood count is required. Methotrexate offers advantages in cases with overlapping or less clear-cut disease patterns. Administered orally, it may be used as first-line therapy, in combination with biologics, or in a step-down approach.

Respiratory syncytial virus (RSV) can cause severe lower respiratory tract infection in high-risk groups. Dr Mike Kwan highlighted that up to 20% of hospitalised older adults with RSV require intensive care or mortality. Compared with influenza patients, hospitalised RSV patients experience more complications, greater reliance on supplemental oxygen, higher rates of acute kidney

injury, and increased mortality. In the absence of specific antiviral treatment, vaccination is of paramount importance.

Dr PT Cheung discussed several therapeutic agents, including novel options, for the management of severe short stature in selected paediatric patients.

Dr CM Chow shared that children are less likely to develop complications from *Helicobacter pylori* infection, and eradication does not consistently improve gastrointestinal symptoms. The estimated prevalence of *H. pylori* infection in Hong Kong is approximately 13%. However, *H. pylori* infection is associated with gastric cancer and various extraintestinal diseases in adults, underscoring the importance of long-term surveillance.



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LRTI = lower respiratory tract infection; RSV = respiratory syncytial virus.

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Revisiting Methotrexate in the Era of Biologic Therapy for Paediatric Atopic Dermatitis: A Review Article



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Key words:

Atopic dermatitis (異位性皮膚炎);
Dupilumab (度普利尤單抗); Methotrexate
(甲胺蝶呤); Paediatrics (兒科)

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease in children, characterised by intense pruritus, eczematous lesions, and a significant impairment in quality of life for patients and their families. For decades, the management of moderate-to-severe AD refractory to topical corticosteroids and calcineurin inhibitors relied on systemic immunosuppressants, with methotrexate being a cornerstone therapy.¹ The landscape of paediatric AD treatment has been revolutionised by the advent of targeted biologic agents, most notably dupilumab, a monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signalling, approved for children as young as 6 months.² This paradigm shift raises critical questions about the role of conventional systemic agents like methotrexate. In Hong Kong, where healthcare decisions must balance

efficacy, safety and cost within a mixed public-private system, this debate is particularly relevant. This review aims to revisit the position of methotrexate in the contemporary management of paediatric AD, evaluating its efficacy, safety, cost-effectiveness and practical utility alongside and in comparison with biologic therapies, with specific attention to the local context.

Mechanism, historical efficacy, safety profile

Methotrexate, a folate analogue, exerts anti-inflammatory effects in AD through multiple pathways, including inhibition of dihydrofolate reductase, interference with T-cell proliferation, and promotion of adenosine release, which has anti-inflammatory properties.

Efficacy in paediatric AD

Prior to the biologic era, methotrexate was a first-line systemic therapy. Evidence, though largely from retrospective cohorts and open-label studies, consistently supported its effectiveness. A seminal prospective, open-label study by El-Khalawany et al. in children with severe AD demonstrated a significant improvement in SCORAD (Scoring Atopic Dermatitis) scores, with 85.7% of patients achieving a 50% reduction (SCORAD 50) after 12 weeks.³ Long-term data, such as from a retrospective review by van Geel et al., showed that methotrexate was effective and well tolerated over a mean treatment period of 25 months, with a drug survival rate of 68% at 36 months.⁴ Dosing in children typically follows a weekly regimen, often starting at 0.2–0.4 mg/kg and titrated based on response and tolerability.

Safety and monitoring

The safety profile of methotrexate is well established but requires vigilant monitoring. Common side effects include gastrointestinal symptoms, fatigue and stomatitis, often manageable with folic acid supplementation. The paramount concerns are hepatotoxicity (requiring periodic liver function tests) and myelosuppression (requiring complete blood count monitoring). Long-term use necessitates monitoring for hepatic fibrosis, though the risk is considered low in children treated for inflammatory skin disease at low cumulative doses. Renal function must also be assessed. Unlike some biologics, methotrexate is contraindicated in pregnancy.⁵

The biologic revolution: Dupilumab and beyond

The approval of dupilumab for adults in 2017, and subsequently for children down to 6 months of age, has transformed treatment paradigms. Dupilumab targets the IL-4 receptor alpha subunit, blocking the signalling of IL-4 and IL-13, which are key cytokines in the type 2 inflammatory pathway central to AD.⁶

Efficacy in paediatric trials

The LIBERTY AD clinical trial program has provided robust level 1 evidence. In the pivotal phase 3 trial for adolescents (LIBERTY AD ADOL), dupilumab significantly improved disease severity, pruritus and quality of life compared with placebo.⁷ Similar profound efficacy was shown in school-age children⁸ and infants/toddlers.² Rapid and sustained improvements in Eczema Area and Severity Index (EASI) scores and itch numerical rating scale are hallmarks of its effect.

Safety profile

Dupilumab's safety profile is favourable, with conjunctivitis and injection-site reactions being the most common adverse events. The lack of need for routine laboratory monitoring for organ toxicity represents a significant advantage over methotrexate. Other biologics (eg, tralokinumab, lebrikizumab) and novel oral Janus kinase (JAK) inhibitors (eg, upadacitinib, abrocitinib) are also emerging, offering more options but with distinct safety considerations (eg, JAK inhibitors carry black box warnings for serious infections, malignancy and cardiovascular events).⁹

Contemporary positioning of methotrexate

In the era of biologics, methotrexate retains several distinct advantages and niches, many of which are acutely pertinent in Hong Kong's healthcare environment.

Cost and accessibility

This is arguably methotrexate's most significant advantage, especially in the Hong Kong context. Methotrexate is exponentially less expensive than biologic therapies. A 2021 cost-effectiveness analysis by *Silverberg* et al. concluded that for adults with moderate-to-severe AD, methotrexate was cost-saving compared with dupilumab.¹⁰ In Hong Kong, while dupilumab is available in the public hospital system and through the Samaritan Fund, access is often restricted to the most severe cases due to high drug cost. Methotrexate, being inexpensive and widely available, is frequently the first-line systemic agent in public clinics, ensuring equitable access. A Hong Kong-based review of systemic therapy use confirmed methotrexate's primary role as a conventional systemic agent prior to the biologic era and highlighted cost as a major barrier to universal biologic access.¹¹

Broad anti-inflammatory action

While dupilumab excellently targets the type 2 axis, AD can have heterogeneous endotypes. Methotrexate's broader, less-specific mechanism may be advantageous in children with overlapping psoriasiform or autoantibody-driven features, or in those with a less clear-cut type 2 signature. It may also be beneficial for concomitant conditions like vitiligo¹² or alopecia areata.¹³

Role in combination and sequencing therapy

Methotrexate has a role as a combination agent. There is emerging interest in using low-dose methotrexate to suppress immunogenicity and improve the efficacy of biologic drugs. Furthermore, in a treatment sequence, methotrexate can serve as an effective first-line systemic agent, with biologics reserved for inadequate responders or intolerable side effects – a 'step-up' approach that aligns with the common practice in Hong Kong's public sector to optimise resource allocation. Conversely, methotrexate may also be used as a 'step-down' or consolidation therapy after disease control is achieved with a biologic, though this strategy lacks robust data in AD.¹⁴

Practical administration and dosing flexibility

Methotrexate can be administered orally, which is often preferred by children and families over injections. While dupilumab injections are infrequent (every 2 or 4 weeks), the fear of needles can be a barrier. Methotrexate dosing can be finely titrated, and the therapy can be more readily discontinued and restarted if needed.¹⁵

Comparison of efficacy

Direct head-to-head trials of methotrexate versus dupilumab in children are lacking. Indirect comparisons suggest that dupilumab may offer a faster onset of action and potentially higher rates of

clear or almost-clear skin (eg, Investigator Global Assessment for Atopic Dermatitis 0/1 or EASI-75). However, methotrexate demonstrates strong long-term efficacy. A 2020 retrospective comparative study by *Gerbens* et al. in adults suggested similar effectiveness for methotrexate and azathioprine compared to dupilumab at 16–20 weeks when used in real-world practice, though study limitations were notable.¹⁶

Safety considerations in the paediatric context

The safety comparison is nuanced:

- **Methotrexate** carries risks of organ toxicity (liver, bone marrow), requiring regular blood monitoring, which can be burdensome. Long-term data in paediatric AD over many years is reassuring regarding hepatic fibrosis risk at dermatologic doses.⁴
- **Dupilumab** has an excellent organ safety profile but is associated with conjunctivitis, which can be problematic in children, and potential eosinophilic/arthritis phenomena.¹⁷ Its long-term effects over decades of use, starting in infancy, are still unknown.
- **JAK inhibitors**, although highly effective, their systemic immunosuppressive profile and black box warnings position them generally after biologics in many guidelines.⁹

Thus, for a child with pre-existing liver steatosis (eg, related to obesity) or poor adherence to monitoring, dupilumab may be safer. For a child with significant recurrent conjunctivitis or ocular surface disease, methotrexate might be preferable.

Guidelines, expert consensus, Hong Kong perspective

Current international guidelines, such as those from the American Academy of Dermatology and the European Task

Force on Atopic Dermatitis (ETFAD), still list methotrexate as a first-line conventional systemic agent alongside cyclosporine.¹⁸ The ETFAD acknowledges dupilumab as a first-line systemic treatment but emphasises that conventional agents like methotrexate remain important, especially due to cost and access issues.¹⁸

Hong Kong's position

There is no single, formal Hong Kong-specific guideline for paediatric AD. However, prevailing practice among paediatric dermatologists and allergists, particularly in the public sector, often reflects a pragmatic, stepwise approach due to funding constraints. Methotrexate is widely regarded as the first-line systemic immunosuppressant of choice for moderate-to-severe paediatric AD refractory to topical therapy. Local expert opinion, as reflected in departmental protocols and discussions, supports initiating methotrexate in suitable patients, reserving dupilumab for patients with:

- Contraindications or intolerance to methotrexate
- Inadequate response to an adequate trial of methotrexate
- Exceptionally severe disease where the fastest, most potent response is urgently needed

This approach is consistent with the Hong Kong Hospital Authority's drug formulary management principles, which emphasise cost-effectiveness. The high annual cost of dupilumab necessitates strict eligibility criteria, often requiring documented failure or intolerance to conventional systemic agents like methotrexate before approval for public funding.¹¹

Future perspectives and unanswered questions

Key research questions remain, with specific relevance to Hong Kong:

- **Head-to-head trials:** There is a critical need for randomised controlled trials directly comparing methotrexate

and dupilumab in children. Local multicentre studies could provide valuable real-world efficacy and pharmacoeconomic data relevant to the Asian population and Hong Kong's healthcare system.

- **Biomarkers for therapy selection:** Research into predictive biomarkers could guide whether a child is more likely to respond to a targeted biologic versus a broad agent like methotrexate.
- **Combination therapy:** Prospective studies on the efficacy and safety of methotrexate–dupilumab combination therapy in paediatric AD are warranted.
- **Long-term data:** Continued registries tracking the long-term outcomes of children treated with methotrexate versus those starting biologics in early childhood are essential. A Hong Kong-based patient registry would be invaluable for understanding local treatment patterns and outcomes.

Conclusion

The introduction of dupilumab and other targeted therapies represents a monumental advance in paediatric AD care, offering highly effective treatment with a favourable safety profile for many children. However, methotrexate is far from obsolete, and its role is particularly well defined in cost-conscious healthcare systems like Hong Kong's. It remains a highly effective, cost-effective, and accessible systemic therapy with a well-characterised long-term safety profile. Its role has evolved but remains vital. In the contemporary era, methotrexate should be considered as:

- A first-line systemic option in public healthcare settings and for families where cost is a primary concern
- A therapeutic alternative for children who do not respond adequately to, or cannot tolerate, biologics
- A potential combination agent or sequential therapy within a long-term management strategy

The decision between methotrexate and a biologic like dupilumab for a child with moderate-to-severe AD must be individualised. In Hong Kong, this decision is significantly influenced by the healthcare funding pathway (public vs private), severity of disease, response to conventional therapy, and family preference. Methotrexate, therefore, retains a secure, important, and often primary place in the modern therapeutic arsenal for paediatric atopic dermatitis, ensuring that effective treatment is accessible to all children in need.

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† DUPIXENT® is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy. DUPIXENT® is indicated for the treatment of severe atopic dermatitis in children 6 months to 11 years old who are candidates for systemic therapy.^{4,5}

‡ Real World Data (EASI, POEM, DLQI) of up to 84 weeks.⁷

§ Peak pruritus NRS score improvement ≥4 points from baseline at week 2.

¶ The most common adverse reactions in atopic dermatitis are injection site reactions (includes erythema, oedema, pruritus, pain and swelling), conjunctivitis, conjunctivitis allergic, arthralgia, oral herpes, and eosinophilia.^{4,5}

¶ In adult patients with AD.

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, numerical rating scale; POEM, Patient Oriented Eczema Measure; QoL, quality of life.

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DUPIXENT Abbreviated Prescribing Information

Presentation: Dupilumab solution for injection in a pre-filled syringe with needle shield. **Indications:** *Atopic Dermatitis (AD):* Moderate-to-severe AD in adults and adolescents ≥12 years who are candidates for systemic therapy; severe atopic dermatitis in children 6 months to 11 years old who are candidates for systemic therapy. *Asthma:* In adults and adolescents ≥12 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment. In children 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with medium to high dose ICS plus another medicinal product for maintenance treatment. For 300 mg only – *Chronic rhinosinusitis with nasal polyps (CRSWNP):* As an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSWNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. *Prurigo Nodularis (PN):* Moderate-to-severe PN in adults who are candidates for systemic therapy. *Eosinophilic esophagitis (EoE):* In adults and adolescents ≥12 years, weighing ≥40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy. **Dosage & Administration:** Subcutaneous injection. *AD adults:* Initial dose of 600 mg (two 300 mg injections), followed by 300 mg Q2W. *AD adolescents (12-17y/o):* Body weight <60 kg- initial dose of 400 mg (two 200 mg injections), followed by 200 mg Q2W. Body weight ≥60 kg- same dosage as adults. *AD children (6-11y/o):* Body weight 15kg-<60 kg- initial dose of 300 mg on Day 1 followed by 300 mg on Day 15, then 300mg Q4W. Body weight ≥60 kg- same dosage as adults. * The dose may be increased to 200 mg Q2W in patients with body weight of 15 kg-<60 kg based on physician's assessment. *AD children (6 months-5y/o):* Body weight 5kg-<15 kg- initial dose of 200 mg, then 200 mg Q4W. Body weight 15kg-<30 kg- initial dose of 300 mg, then 300 mg Q4W. Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, e.g. face, neck, intertriginous and genital areas. Consider discontinuing treatment in patients who have shown no response after 16 weeks. *Asthma adults and adolescents:* Initial dose of 400 mg, followed by 200 mg Q2W. For patients with severe asthma and on oral corticosteroids or with severe asthma and co-morbid moderate-to-severe AD or adults with co-morbid severe CRSWNP- initial dose of 600 mg, followed by 300 mg Q2W. *Asthma children (6-11y/o):* Body weight 15kg-<30 kg- 300 mg Q4W. Body weight 30kg-<60 kg- 200 mg Q2W, or 300 mg Q4W. Body weight ≥60 kg- 200 mg Q2W. For paediatric patients (6-11y/o) with asthma and co-morbid severe atopic dermatitis, as per approved indication, the recommended dose should follow AD children (6-11y/o). Patients receiving concomitant oral corticosteroids may reduce steroid dose gradually once clinical improvement with dupilumab has occurred. The need for continued dupilumab therapy should be considered at least annually as determined by a physician. *CRSWNP:* Initial dose of 300 mg, followed by 300 mg Q2W. Consider discontinuing treatment in patients who have shown no response after 24 weeks. *PN:* Initial dose of 600 mg (two 300 mg injections), followed by 300 mg Q2W. Dupilumab can be used with or without topical corticosteroids. Consider discontinuing treatment in patients who have shown no response after 24 weeks. *EoE:* 300 mg QW. Dupilumab 300 mg QW has not been studied in patients with EoE weighing <40 kg. Dosing beyond 52 weeks has not been studied. **For Missed dose instructions, please refer to the full prescribing information. Contraindications:** Hypersensitivity to dupilumab or any of the excipients. **Precautions:** Not to be used to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Do not discontinue corticosteroids abruptly upon start of dupilumab. Reduction should be gradual and performed under supervision of a physician; it may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. Biomarkers of type 2 inflammation may be suppressed by systemic corticosteroid use. If systemic hypersensitivity reaction occurs, discontinue dupilumab and initiate appropriate therapy. Be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients with eosinophilia. Treat pre-existing helminth infections before initiating dupilumab. If patients become infected while receiving dupilumab and do not respond to anti-helminth treatment, discontinue dupilumab until infection resolves. Cases of enterobiosis were reported in children 6 to 11 years old in the paediatric asthma development program. Advise patients to promptly report new onset or worsening eye symptoms. Patients who develop conjunctivitis, dry eye and keratitis that does not resolve following standard treatment should undergo ophthalmological examination. Sudden changes in vision or significant eye pain that does not settle warrant urgent review. Patients with comorbid asthma should not adjust or stop asthma treatments without consultation with physicians. Carefully monitor patients after discontinuation of dupilumab. Avoid using live and live attenuated vaccines concurrently with dupilumab. Patients should be brought up to date with immunisations before starting dupilumab. **Drug Interactions:** Immune responses to Tdap vaccine and meningococcal polysaccharide vaccine were assessed. Patients receiving dupilumab may receive concurrent inactivated or non-live vaccinations. **Pregnancy and lactation:** Should be used during pregnancy only if potential benefit justifies potential risk to foetus. Unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. Decision must be made whether to discontinue breast-feeding or dupilumab taking into account benefit of breast feeding for the child and benefit of therapy for the woman. **Undesirable effects:** Most common adverse reactions reported- injection site reactions, conjunctivitis, conjunctivitis allergic, arthralgia, oral herpes, eosinophilia and injection site bruising. Safety profile observed in adolescents and children 6 months to 11 years old consistent with that seen in adults. **For other undesirable effects, please refer to the full prescribing information. Preparation:** 2 x 300mg/2ml in pre-filled syringe with needle shield, 2 x 200mg/1.14ml in pre-filled syringe with needle shield. **Legal Classification:** Part 1, First & Third Schedules Poison **Full prescribing information is available upon request.** APH-K-DUP-23.10

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
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The Severe Sequelae of Respiratory Syncytial Virus Infection – Could We Prevent It?



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Key words:

Adult immunisation (成人免疫接種); Long-acting monoclonal antibody (長效單株抗體); Maternal immunisation (孕婦免疫接種); Respiratory syncytial virus infection (呼吸道合胞病毒感染); Short-acting monoclonal antibody (短效單株抗體)

Respiratory syncytial virus (RSV) infection is usually considered a mild illness in a healthy population – all humans have been infected with RSV at least once by the age of 2 years, and reinfection throughout life is common.¹ RSV is a leading cause of acute respiratory illness and bronchiolitis in infants, the elderly and the immunosuppressed, and 2–3 out of every 100 infants under the age of 6 months are hospitalised with RSV every year.² Over 70% of RSV hospitalisations occur in healthy full-term infants.^{3–9} However, RSV can lead to serious illnesses and even mortality in

high-risk individuals, particularly in children born preterm; children aged below 1 year old; some young children and adults with coexisting medical illness such as heart or lung conditions, diabetes, or weakened immune systems; and older adults.^{10–13} RSV infection occurs throughout the year in Hong Kong.¹² It can also cause outbreaks in vulnerable settings, such as nursing homes, paediatric wards and neonatal intensive care units.¹⁴

The virus can survive on surfaces or objects for about 4–7 hours. The average incubation period is usually 5–7 days.^{11,12,15} RSV infection induces a wide range of clinical manifestations, like that of other viral respiratory pathogens, which include cough, nasal congestion, rhinorrhoea, sore throat, dyspnoea, decreased appetite, body ache or weakness, headache and occasionally otitis media. Lower respiratory tract infection (LRTI) is common and may result in severe bronchiolitis, pneumonia, respiratory failure or death.¹⁶ Occasionally, children present with trouble breathing and difficulty in feeding. Symptoms of bronchiolitis can last for 1–2 weeks but occasionally can last longer.¹⁷

RSV infection is possibly associated with recurrent wheezing or reduced pulmonary function, and it poses a substantial health burden in children.^{18–20} Severe RSV infection with lower respiratory tract involvement is more strongly associated with the development of recurrent wheezing of early childhood or asthma than non-severe RSV infection. However, the evidence on cause of association is mixed and inconclusive.¹⁹

For older adults in the community, RSV infection is estimated to develop annually in 3–7% of healthy elderly patients and in 4–10% of high-risk

adults.²¹ Among hospitalised older patients, about 10–20% of cases end up in intensive care unit admission or mortality.²² The illness is mild in most adults; however, adults with history of chronic obstructive pulmonary disease, heart disease, stroke, diabetes mellitus, kidney disease, obesity or immunosuppression stand a higher risk of severe illness from RSV, which requires hospitalisation.²³ Similar to younger subjects, adults with RSV may have persistent cough, wheezing, worsening of chronic lung conditions, pneumonia, respiratory failure, and exacerbation of underlying chronic diseases, with or without fever. Compared with influenza viral infection, RSV infection in hospitalised adults is associated with more severe clinical manifestations, including elevated incidence of pneumonia, more severe respiratory complications, greater reliance on supplemental oxygen therapy, acute kidney injury and increased mortality rates.^{22,23}

RSV infections are often associated with bacterial coinfection.^{24,25} One reason for this is the impairment of innate immunity, which extends beyond the period of viral shedding. Bacterial coinfection in RSV infection has been associated with significantly longer hospital stays, more need for ventilator support, and higher needs for intensive care. Higher serum C-reactive protein levels and hyponatraemia were the most significant independent predictors of bacterial coinfection in children younger than 1 year old who have RSV infection.²⁴ In adults, a study found that laboratory-confirmed viral–bacterial coinfection as a non-specific group had a higher mortality, and among patients with viral infection alone, RSV and parainfluenza infection resulted in lower survival rates than influenza. The

mortality difference persisted even in the subgroup of patients without chronic lung disease and congestive heart failure.²⁵

Viral–viral coinfection can also occur with RSV, including coinfection with other respiratory viruses such as influenza and SARS-CoV-2. Coinfection has been associated with poorer clinical outcomes, including higher mortality and an increased risk of complications, compared with RSV infection alone. A Canadian study of adults hospitalised with RSV reported that older adults, particularly those aged 65 years and above, were more likely to experience severe outcomes such as admission to the intensive care unit.^{26,27}

There is no specific antiviral medication for fighting RSV.^{28,29} Most RSV infections go away on their own in a week or two. Patients, parents and caregivers should focus on relieving symptoms and providing supportive care across all age groups, making the patients comfortable and monitoring for complications.¹²

Virology

RSV is an enveloped, negative-sense, single-stranded RNA virus of the family *Paramyxoviridae*. It encodes 11 proteins, including the fusion (F) and attachment (G) surface glycoproteins that are the targets for virus-neutralising antibodies. The mature F protein is a trimer of heterodimers consisting of disulfide-linked F1 and F2 subunits. This highly conserved protein exists on the surface of virions in a prefusion conformation that drives an irreversible conformational change that brings the viral and host-cell membranes together as it adopts a stable postfusion conformation. Most of the neutralising activity detected in a human immunoglobulin preparation can protect at-risk infants from RSV disease and has been found to be directed against the prefusion conformational change of RSV F,³⁰ thus blocking viral entry into the host cells.

Multiple elements of the innate and adaptive immune response³¹ contribute

to the control of RSV infection. Despite successful viral clearance, protective immunity against RSV is short-lived, and reinfection throughout life is common.³²⁻³⁴ This poor induction of long-lasting immunity has made the development of an effective vaccine a difficult task.

Prevention is better than cure

To protect infants and young children, older adults, and individuals with chronic or immunocompromising conditions, precautions for RSV prevention include maintaining good personal hygiene, avoiding places where crowds gather at the time of epidemic seasons, wearing a properly fitted surgical mask when going outdoors, and observing respiratory hygiene etiquette by covering mouth and nose when coughing or sneezing.¹²

If necessary, parents may consider giving their babies RSV antibody injections for protection (passive immunisation). Pregnant women may also receive RSV vaccination (maternal immunisation) so that maternal antibodies can be transferred to the baby through the placenta. The general population may consult their doctors based on their clinical needs. Adults, particularly those with chronic conditions, should consider similar preventive measures, including hand hygiene, avoiding crowds, maintaining good respiratory etiquette, and receiving appropriate and timely vaccination (adult immunisation).¹²

Immunisation in infants

Possible options for immunisation against RSV include (1) infant immunisation with RSV long-acting monoclonal antibodies (mAbs), (2) maternal RSV vaccine for pregnant women and (3) infant immunisation with short-acting mAbs for preterm and high-risk babies.

During the development of preventive strategies against RSV infection, it is important to avoid the binding of non-neutralising antibodies or antibodies binding to viral antigens at subneutralising

concentrations without adequately blocking or clearing the infection, because this can lead to antibody-dependent enhancement (ADE) of infection or ADE of disease severity.^{35,36}

Long-acting mAbs

Infant immunisation involves the use of long-acting mAbs that mimic the antibodies our bodies naturally produce to fight infections. mAbs provide passive immunity, which means they offer direct and immediate protection without requiring the immune system to respond. These antibodies are made to target specific structures on the surface of pathogens and remain in the body for an extended period to provide prolonged protection.^{37,38}

A recently published meta-analysis reviewed the real-world effectiveness of RSV long-acting mAbs binding to site Ø of the RSV prefusion (F) protein. It showed that these long-acting mAbs are able to reduce RSV-related LRTI, hospitalisation and intensive care unit admissions by 75%, 83% and 81%.³⁹ Proven sustained efficacy against RSV disease in infants has been demonstrated in pivotal clinical trials with durations of protection at least 6 months and with sustained levels of RSV-neutralising antibodies through 1 year.⁴⁰⁻⁴⁴ In another meta-analysis, long-acting mAbs were associated with reduced LRTI-related hospitalisations and emergency department visits in infants and young children.⁴⁵ These findings support the potential of long-acting mAbs to reduce respiratory-related morbidity and health care utilisation in young children. A study in Spain found that universal long-acting mAb prophylaxis in infants markedly reduced RSV-related hospitalisations and outpatient morbidity, with reductions in RSV-related LRTI hospitalisations sustained into the second season and with no signal of adverse shift in RSV morbidity.⁴⁶

Maternal immunisation

The bivalent RSV prefusion F–targeting (RSVpreF) vaccine used in maternal

immunisation contains stabilised prefusion F glycoproteins⁴⁷ from the two main cocirculating antigenic subgroups (RSV-A and RSV-B). Maternal immunisation involves vaccinating pregnant women with the RSVpreF vaccine at specific periods (recommended gestational ages from different societies and countries vary, including a recommended gestational age to be above 26 weeks, 28 weeks, and 32 weeks) to protect both mother and infants from infectious diseases. When a pregnant woman is vaccinated, her immune system produces antibodies against the targeted pathogens, and the antibodies are then transferred to the foetus through the placenta. The transferred antibodies provide passive immunity to newborns, protecting them during the first few months of life, when their immune system is still developing and they are most vulnerable to infections.^{38,48-50} This strategy is employed to protect infants from tetanus, pertussis, COVID-19 and influenza.

A phase 3 clinical study (MATISSE), in which the vaccine was administered at 24–36 weeks gestation, demonstrated vaccine efficacy in preventing severe LRTI in infants within 90 days (81.8%) and 180 days (69.4%) after birth.^{51,52} Safety profiles are generally similar to placebo. In the real-world setting of the first season of vaccine implementation in England and Scotland, maternal RSVpreF vaccination was effective and equivalent to trial settings in reducing the risk of hospitalisation in infants with RSV-associated acute LRTI. The adjusted effectiveness of maternal RSVpreF vaccination for preventing infant hospitalisation was 58% for infants whose mothers were vaccinated at any time before delivery and 72% for infants whose mothers were vaccinated more than 14 days before delivery.⁵³

The Scientific Committee on Vaccine Preventable Disease (SCVPD), Centre for Health Protection, Department of Health, reached interim consensus on the use of RSV vaccination in January

2025. Although vaccination is effective in preventing severe RSV-associated lower respiratory tract disease among infants born to vaccinated mothers for up to 6 months after birth, clinical trial data showed a higher percentage of preterm births in the vaccinated group. Conversely, in a US postmarketing study, maternal RSV vaccination did not show an increased risk for preterm birth; however, an increased risk of hypertensive disorders of pregnancy was observed. Hence, pending additional safety data for maternal RSV vaccination, SCVPD does not recommend universal vaccination for pregnant women. SCVPD is of the view that pregnant women may receive RSV vaccination to protect their newborn infants against RSV disease, as an individual decision, and under informed consent, in consultation with their family doctor or the doctor providing them with antenatal care.⁵⁴

On the other hand, in a cohort study of pregnant individuals who delivered at 32 weeks' gestation or later, the RSVpreF vaccine was not associated with an increased risk of preterm birth and perinatal outcomes.⁵⁵ Similarly, a recently published large observational study in France found no major safety concerns associated with RSVpreF vaccination during pregnancy.⁵⁶

In France, a first season comparison evaluated passive infant immunisation with a long-acting mAb versus maternal vaccination with the RSVpreF vaccine. While passive infant immunisation with long-acting mAbs was associated with lower risks of RSV-related hospitalisation and severe outcomes, both approaches remain valuable and potentially complementary strategies for protecting infants, particularly as programs evolve to optimise coverage and address varying risk profiles.⁵⁷

Short-acting mAbs

RSV prophylaxis with monthly injection of short-acting mAbs, which bind to site II of the RSV prefusion protein, should be

considered for 5–6 months after hospital discharge among preterm infants born at <29 weeks gestational age; it should also be considered for children aged <1 year with haemodynamically significant congenital heart disease or bronchopulmonary dysplasia.^{58,59}

All the above three preventive strategies (long-acting mAbs, short-acting mAbs and maternal immunisation) have been proven to be effective in preventing RSV LRTI, especially for high-risk infants (preterm, with immunocompromised condition, or with chronic lung or heart disease).

Immunisation in adults

The possible options for immunisation against RSV in adults aged ≥60 years include (1) adjuvanted RSV vaccine and (2) non-adjuvanted bivalent RSVpreF vaccine. Adjuvanted RSV vaccine is approved for use in adults aged 50–59 years with increased risk due to underlying health conditions in Hong Kong, while non-adjuvanted bivalent RSVpreF vaccine is also approved for use in adults aged 18–59 years with increased risk due to underlying health conditions.^{60,61} Additionally, adjuvanted RSV vaccine in the European Union is approved for all adults ≥18 years; extension of this broader indication remains under regulatory review in Hong Kong.⁶²

The US Advisory Committee on Immunization Practices (ACIP) recommends a single RSV vaccine dose for adults aged ≥60 years, particularly those with chronic respiratory, cardiovascular, renal, hepatic, neurologic, metabolic or immunocompromised conditions, based on shared clinical decision-making. In June 2024, ACIP extended this recommendation to adults aged 50–59 years with similar high-risk conditions.⁶³

Adjuvanted RSV vaccine contains an adjuvant that enhances immune response, particularly in older or immunocompromised adults, with first-season clinical trials showing 82.6% efficacy against RSV-related lower respiratory

tract disease (LRTD) and 94.1% against severe LRTD with ≥ 2 signs, with protection sustained for approximately three RSV seasons.^{60,64,65} Bivalent RSVpreF vaccine targeting RSV-A and RSV-B pre-fusion proteins demonstrated protection across two RSV seasons. In season 1, VE was 65.1% for LRTI with ≥ 2 symptoms and 88.9% for LRTI with ≥ 3 symptoms. In season 2, VE remained high at 55.7% for LRTI with ≥ 2 symptoms and 77.8% for LRTI with ≥ 3 symptoms, with efficacy across both seasons reaching 81.5% for LRTI with ≥ 3 symptoms.^{61,66}

A community-based study showed that adjusted RSV VE was 50.8% against any RSV infection and 59.8% against symptomatic RSV. The study also suggests that a higher antibody level may be associated with a reduced risk of RSV infection.⁶⁷

The SCVPD reached interim consensus in January 2025 that adults aged ≥ 75 years living in residential care homes may receive a single dose of RSV vaccine after consultation with their healthcare provider.⁵⁴

Although the RSV vaccine has been proven effective in preventing RSV infection, a minor risk of adverse reactions remains after vaccination, including the potential for Guillain–Barré Syndrome (GBS). The risks of GBS following vaccination with non-adjuvanted bivalent RSV vaccine and adjuvanted RSV vaccine were assessed in self-controlled case series analyses using risk windows of 1–42 days after vaccination and control windows of 43–90 days after vaccination. The analyses of all GBS cases based on claims data suggest an increased risk of GBS during the 42 days following vaccination, with an estimated nine excess cases of GBS per million doses of non-adjuvanted bivalent RSVpreF vaccine, as well as an estimated seven excess cases of GBS per million doses of adjuvanted vaccine administered to individuals ≥ 65 years of age.

A more recent study used a data platform containing electronic health

records for more than 270 million patients across the United States. For vaccine safety analysis, all participants aged 60 years or older who received the RSV vaccine from 1 July 2023 to 30 June 2024 were included. Data were analysed from August 2024 to March 2025. The analyses showed a significantly higher risk of GBS associated with bivalent RSVpreF vaccine, with 18.2 excess cases per million doses of the non-adjuvanted bivalent vaccine, and a non-significant increase of 5.2 excess cases per million doses of adjuvanted vaccines administered to participants aged 60 years or older.⁶⁸

Background risks of GBS in study populations influence excess GBS case estimates and may differ between studies and analyses within a study, precluding direct comparisons of excess GBS case estimates from other vaccine studies or populations.^{69,70} For further details, please refer to the information published by the Hong Kong Drug Office on 8 January 2025.⁷¹

Newer product

On 9 June 2025, the US Food and Drug Administration approved another long-acting mAb, which acts against site IV of the RSV fusion protein for the prevention of RSV LRTI in neonates and infants born during or entering their first RSV season. It is a fully humanised, RSV-F protein-specific neutralising mAb isolated from primary human memory B cells. In preclinical studies, this mAb has been shown to bind with high affinity to a region on antigenic site IV of the RSV-F protein and preferentially to the pre-fusion F conformation interfering with viral fusion with host cells. Its epitope on site IV is highly conserved among RSV-A and RSV-B to protect against both strains, with a high barrier to resistance.⁷²

This site IV RSV fusion protein-binding mAb is detected in the upper respiratory tract with the potential to neutralise RSV and prevent development of LRTI.⁷³ The Fc region of this mAb

incorporates half-life-extendingYTE (three amino acid substitutions in FC region 2) substitutions, with the goal of providing protection for an RSV season with a single dose.

This mAb demonstrated efficacy against mild, moderate, and severe RSV disease when administered as a single dose for infants of all weights, including term and preterm healthy infants and those with increased risk for RSV disease.⁷²⁻⁷⁴ It met the primary efficacy endpoint of reducing the incidence of medically attended LRTI requiring ≥ 1 indicator of LRTI or severity, compared with placebo, through 5 months by 60.4% ($p < 0.001$).³ It also met the key secondary efficacy endpoint of reducing RSV-associated hospitalisation, compared with placebo, through 5 months by 84.2% ($p < 0.001$).⁷⁴ For the tertiary endpoint of RSV LRTI hospitalisation, through 6 months, efficacy of 91.2% was observed.⁷⁴ Its safety profile was generally comparable to placebo, in healthy preterm and full-term infants born during or entering their first RSV season.⁷⁴ This product is not yet licensed in Hong Kong.

Evaluation of RSV infection prevention strategies

Prevention of RSV illness in the population is a major public health priority. An overseas modelling study and cost-effectiveness analysis has shown that both long-acting mAb and maternal immunisation could substantially reduce the burden of RSV disease in the infant population.^{75,76} Hong Kong needs to perform similar health economic studies on the health burden of RSV infection in babies, young children, adolescents and the elderly, to assess the cost–benefit ratio regarding the use of various preventive methods, including maternal immunisation, long- and short-acting mAbs for children, and RSV vaccines for individuals in the community.

International and global recommendations

The World Health Organization identified RSV as the most important cause of acute LRTI in infants and a significant burden in older adults and those with underlying conditions, calling for global surveillance and vaccine development.⁷⁷ In a joint appeal published in *The Lancet*, the World Society for Pediatric Infectious Diseases, the Asian Society for Pediatric Infectious Diseases, the Asia Pacific Pediatric Association, and 41 leading scientific and social organisations from across the globe are calling on Gavi, the Vaccine Alliance, to take urgent action to save millions of young lives by protecting them against RSV.⁷⁸

On 20 November 2025, World Children's Day, the Hong Kong Chinese Medical Association, together with 33 medical and nursing societies, issued the joint statement "Caring for Infants and Vulnerable Individuals with Respiratory

Syncytial Virus (RSV) at Home and Their Prevention"⁷⁹ to increase public awareness on this issue.

Regarding the detailed recommendations in different regions and countries,

please refer to the relevant local and regional experts and societies.

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

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COPD=Chronic obstructive pulmonary disease; LRTD=Lower respiratory tract disease; RSV=Respiratory syncytial virus
References: 1. Hong Kong Arexvy Prescribing Information. 2. Drugs Database, Drug Office, Hong Kong. Accessed 25 Jan 25. Available at https://www.drugoffice.gov.hk/eps/do/tc/consumer/search_drug_database2.html. 3. Ison MG, et al. CHEST. Oct 4-9 2004;339:14. 4. Walsh EE, et al. N Engl J Med. 2024;391:1459-1461.
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GSK

Novel Therapeutic Approaches to Short Stature Guided by Advanced Delineation of Cartilage Growth Plate Physiology and Pathophysiologies



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Physeal growth plate (GP) is the primary site for postnatal skeletal linear growth, the dysregulation of which contributes to various causes of clinical short stature (Table 1).¹

Since late 19th century, common causes of growth failure secondary to macronutrient and micronutrient deficits have been defined and effectively corrected through remedies including structured public health and nutritional recommendations.

Discovery of important endocrine systems led to replacement therapy being offered to growing persons affected by hypothyroidism with improved (catch-up) linear growth, among other metabolic benefits.

Severe short stature secondary to GH deficiency

In the 1950s, pituitary growth hormone (GH) was found to be effective in

promoting linear growth in subjects deficient in GH. In fact, Choh Hao Li (a Chinese-American biochemist in UC Berkeley) was one of the key persons identifying and purifying GH from mammalian pituitary gland (including human).² The high species specificity of GH (in contrast to other peptide hormones like insulin) restricted its source for extraction to human cadavers, which unfortunately dictated its withdrawal in 1985 because of neurodegeneration from contaminating prions.³

It happened that recombinant DNA-based human GH (rhGH) was successfully produced and proven effective and got approved by the US Food and Drug Administration (FDA) in the same year, rendering GH supply basically unlimited. Clinical studies exploring the use of rhGH for promoting height gain in various non-GH deficiency (non-GHD) short patient groups yielded positive results in many of the studies, though not in all. Accordingly, indications for GH therapy expanded to include children suffering from chronic renal failure, Turner syndrome, Prader-Willi syndrome, small-for-gestation age, SHOX deficiency and Noonan syndrome.³

Of note is that in 2003, the FDA approved the use of GH for idiopathic short stature (ISS), a heterogenous category of children with short stature with still-undefined pathological causes. Notably, the drug's application for this similar clinical indication was disapproved by the European Medicines Agency in 2006.³

In parallel, a small peptide endocrine/paracrine factor, insulin-like growth factor-1 (IGF-1), had been discovered to be working closely with GH physiologically to promote growth. Eventually, this offered another effective peptide factor

for correcting short stature due to primary IGF-1 deficiency (PIGFD), characterised by short stature (standard deviation score [SDS] ≤ 3.0), low circulating IGF-1 concentrations (SDS ≤ 3.0), and normal or elevated GH concentrations.⁴

Around the turn of millennium, basic research works suggested that while both GH and IGF-1 actively promote growth plate chondrocyte proliferation and differentiation into prehypertrophic and hypertrophic chondrocytes, GH serves additional functions like stimulating skeletal stem cell (residing in the resting zone) expansion, thereby recruiting these cells into the proliferative and prehypertrophic phases of endochondral ossification.⁵ Recent studies employing more advanced cellular labelling further consolidate such conclusion.⁶

This could explain why IGF-1 therapy per se may not be as potent as GH in promoting linear growth in non-PIGFD patients. Hence, more in-depth understanding of differential regulation of skeletal stem cells through various developmental stages, which is key to healthy osteogenesis, may lead to additional innovative strategies like combinational/sequential use of these and other new therapeutic agents. Studies on targeted delivery of GH and IGF-1 to the GP have recently been reported.^{7,8}

Delaying GP senescence may improve final height

One crucial physiological linear growth checkpoint is closure of the physeal GP observed after human puberty (not necessarily observed in every mammalian species). That this is primarily driven by oestrogen in both sexes (instead of androgen for males and oestrogen for females) was definitively concluded in the

Table 1. Growth plate disorders causing short stature.

I. Primary growth plate disorders

Intrinsic genetic defects causing a wide range of clinical disorders have been traditionally classified under skeletal **dysplasia, often characterised by disproportionate short stature and specific radiographic abnormalities.**

With extensive genetic workup being clinically affordable, increasingly more related mutations are found to have milder presentations to the extent that some could have been categorised as **idiopathic short stature.**

Selected list for illustration

Mechanisms	Gene	Disease	
A. Paracrine signalling Coordinating the functional growth plate organisation into resting (stem cells), proliferating and hypertrophic chondrocyte zones in preparation for endochondral ossification	<i>FGFR3</i> (fibroblast growth factor receptor 3)	Achondroplasia; hypochondroplasia	
	<i>CNP</i> (C-type natriuretic peptide) and its receptor, NPR2	Acromesomelic dysplasia, Maroteaux type	
	<i>PTHrP</i> (parathyroid hormone-related protein) and its receptor, PTH1R	Jansen's metaphyseal chondrodysplasia; Blomstrand chondrodysplasia	
B. Cartilage extracellular matrix Offering structural scaffold properties of healthy extracellular matrix milieu and mediating dynamic regulatory growth factor signalling	<i>COL2A1</i> (type II collagen)	Spondyloepiphyseal dysplasia congenita; spondyloepimetaphyseal dysplasia	
	<i>ACAN</i> (aggrecan)	Spondyloepimetaphyseal dysplasia, aggrecan type; Spondyloepiphyseal dysplasia, Kimberley	
	<i>COMP</i> (cartilage oligomeric matrix protein)	Pseudoachondroplasia; multiple epiphyseal dysplasia	
C. Intracellular signalling Mediating cellular differentiation (may be de-differentiation as well), growth and corresponding metabolic functions, and even hypertrophic chondrocyte apoptosis to make way for osteogenesis			
	• Ras–MAPK signalling	<i>PTPN11</i> , <i>KRAS</i>	Noonan syndrome
	• G-protein signalling	<i>GNAS</i>	Albright hereditary osteodystrophy
	• Chondrocyte transcription factors	<i>SOX9</i>	Campomelic dwarfism
		<i>SHOX</i>	Leri–Weill dyschondrosteosis; Langer mesomelic dysplasia; Madelung deformity
	• Epigenetic dysregulation	<i>KMT2A</i>	Wiedemann–Steiner syndrome
D. Extracellular matrix metabolism	<i>GALNS</i> (N-acetylgalactosamine-6-sulfatase)	Mucopolysaccharidoses IVA	
	<i>SLC26A2</i> (sulfate transporter)	Diastrophic dysplasia	

II. Secondary growth plate disorders

These are caused by **extrinsic factors** that impair the function of an otherwise intrinsically normal growth plate, more commonly resulting in **proportionate short stature.**

A. Endocrine disorders (hormonal deficiency/excess)

- Growth hormone deficiency and insensitivity, hypothyroidism, glucocorticoid excess (Cushing's syndrome), later phase of precocious puberty

B. Inflammatory and systemic diseases

- Chronic juvenile inflammatory arthritis, chronic kidney disease, inflammatory bowel disease

C. Metabolic and nutritional deficiencies

- Chronic malnutrition/caloric deficiency
- Rickets: nutritional and genetic (eg, vitamin D–dependent rickets)

D. Iatrogenic/toxin-induced

- Glucocorticoid therapy, iron chelation therapy, retinoic acid therapy
- Haematopoietic stem cell transplantation
- Radiation to the spine, cranial radiation

early 1990s, following the delineation of oestrogen resistance caused by loss of function mutation of oestrogen receptor (alpha) in an ever-growing 28-year-old man.⁹ Further work showed that oestrogen causes accelerated GP programmed senescence, leading to proliferative exhaustion, which eventually effects an abrupt fusion.¹⁰

Studies were then conducted to investigate the use of aromatase inhibitors (mainly letrozole and anastrozole) to delay GP senescence, to bargain for improving final adult height in adolescents. Such need often becomes more acute in the context of short individuals with rapidly advancing/very advanced bone age (eg, those with 'early and fast puberty') and hence, poor predicted adult height. Such approach may be adopted in concerned individuals, after an informed decision-making process.¹¹

Novel therapeutic agents for achondroplasia

Better understanding of the molecular mechanisms involved in growth plate development has paved the way for developing plausible corrective therapeutic strategies.

In 1994, the gain-of-function mutation of FGF receptors (FGFR3) was proven to be responsible for the most common human monogenic skeletal dysplasia (SD), achondroplasia,¹² and a spectrum of related SDs, like hypochondroplasia and thanatophoric dysplasia. Mutant FGFR3 constitutively activates the mitogen-activated protein kinase (MAPK) signalling pathway in GP chondrocytes, inhibiting endochondral ossification. Targeting the overactive receptor and postreceptor activities became an obvious focus for development of novel therapeutic agents for achondroplasia.

Just within a few years of this discovery, overexpressing B-type natriuretic peptide (BNP, the second member identified after atrial natriuretic peptide) in mouse models surreptitiously yielded skeletal overgrowth as phenotype. More

experimental proof that C-type natriuretic peptide (CNP) regulates endochondral ossification through the guanylyl cyclase pathway followed. Finally came the groundbreaking evidence that natriuretic peptide receptor 2-mediated guanylyl cyclase-cyclic guanosine monophosphate signalling could inhibit FGFR3 overactivated MAPK pathway, by crossing mice strains overexpressing CNP with those with FGFR3 overactivation.¹³

Ultimately, clinical studies based on such knowledge led to the first CNP analog vosoritide (daily subcutaneous injection) being approved by the FDA in 2021 for children over 5 years old and later expanded to all ages in 2023.^{14,15} In addition, a once-weekly long-acting analog¹⁶ is currently under FDA review for approval.

Directly tackling the pathophysiology at the receptor level also yielded fruitful results. So infigratinib, an oral selective FGFR-receptor inhibitor has been offered expedited review by the FDA based on related work (Table 2).¹⁷

On the other hand, a number of clinical trials are ongoing to study the possible

efficacy of vosoritide in improving height in other short stature groups (Table 3).

Mild phenotypes from growth plate disorders

With expanding ability and increasing efficiency in delineating genetic variants and mutations, exponentially more definitive molecular diagnoses have been confirmed, revealing a wider phenotypic spectrum for many monogenic disorders. These include many SDs.

The ACAN gene – which encodes aggrecan, the primary chondroitin sulfate proteoglycan found in articular and growth plate cartilage – illustrates such a modern trend well. Aggrecan is essential for structural integrity and functional resilience of cartilage. Mutations in ACAN are known to cause classic SDs, including spondyloepimetaphyseal dysplasia and spondyloepiphyseal dysplasia, Kimberley type. However, in 2014, heterozygote ACAN mutations were found to cause human short stature with advanced bone age, premature growth cessation and early-onset osteoarthritis.¹⁸

Table 2. New therapeutic agents for improving height in achondroplasia.

Drug	Status (FDA)	Administration route
Vosoritide (Voxzogo)	<ul style="list-style-type: none"> Initial approval in November 2021 for patients 5 years old or above Expanded approval in October 2023 for children under 5 years old 	SC (daily)
Navepegritide (TransCon CNP)	Approved on 27 February 2026 for patients 2 years old and above	SC (weekly)
Infigratinib	Designated breakthrough therapy since September 2024	Oral (daily)

CNP, C-type natriuretic peptide; FDA, US Food and Drug Administration; SC, subcutaneous

Table 3. Additional ongoing clinical trials investigating efficacy of vosoritide therapy for improving stature beyond achondroplasia.

Clinical trial registered	Disease(s) studied
NCT05849389	Turner syndrome
NCT05845749	Mucopolysaccharidosis type IVA and VI
NCT04219007	Selected genetic causes of short stature (ACAN deficiency, CNP deficiency, NPR2, RASopathies, SHOX)
NCT06382155	Idiopathic short stature

CNP, C-type natriuretic peptide

Over the past decade, mutations in this gene have been identified in many asymptomatic subjects easily labelled ISS,¹⁹ and many have shown reasonable response to GH therapy.²⁰ If selected ACAN mutation positivity could be predictive of GH response, and more genes share such profile, then an overarching diagnostic label of ISS would be less sound in the future.

Mutations of another important GP cartilage extracellular matrix protein, type 2 collagen, have also demonstrated a protean range of clinical phenotypes, with clinical guidelines proposed for these type 2 collagenopathies.²¹ It is therefore prudent for clinicians taking care of families/subjects with short stature be aware of these less known clinical presentation and features,²² and when appropriate, consider additional investigations and referral to related specialists.

Exactly how vigilant (or exhaustive) diagnostic workup should be before reaching a diagnostic label of ISS and being accepted as the basis for choosing a therapeutic agent like GH has long been debated by experts in the field.^{23,24} Pertaining to relevant genetic workup for children with short stature, a set of guidelines have recently been proposed by the International Growth Genetics Guideline Consortium.²⁵

Old problems, new understanding, novel solutions

Not surprisingly, the well-known improvement of linear growth simply by adequate nutrition has earned modern scientific understandings down to some exact molecular and cellular mechanisms.²⁶ Catch-up growth following correction of secondary causes, like glucocorticoid excess, has also been donned with advanced stem cell perspectives.²⁷

It is thus reasonable for us to hope for more practical solutions for some yet-unresolved problems. New solutions could stem from better mechanistic, cellular or molecular understandings. While

the successful development of a new class of drug like vosoritide is exemplary, we should not be surprised that refined understanding of more biology may lead to the use of older drugs like GH in a more creative and targeted way.²⁸

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Helicobacter pylori Infection in Children: To Treat or Not to Treat?



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Key words:

Helicobacter pylori infection (幽門螺旋桿菌感染); Peptic ulcer (消化性潰瘍); Urea breath test (幽門螺旋桿菌吹氣測試)

H*elicobacter pylori* is a gram-negative spiral bacterium that infects the epithelial lining of the stomach, which was first cultured in 1982 by Dr Barry James Marshall and Dr John Robin Warren. *H. pylori* is one of the most common human infections worldwide. Marshall and Warren also demonstrated that *H. pylori* eradication cures gastroduodenal ulcers.¹ Chronic infection with *H. pylori* is an important cause of gastrointestinal pathology. However, children are much less likely to develop complications of infection than adults. Furthermore, there is no evidence that *H. pylori* eradication improves functional gastrointestinal pain-related symptoms. As a result, different strategies for screening, diagnosis and treatment of *H. pylori* are used for children than for adults. However, once

a child turns 18 years old, the guidelines from adult gastroenterology and infectious disease associations strongly recommend eradication therapy for all active *H. pylori* infections with functional dyspepsia and prevention of gastric cancer. There is challenge for paediatric providers in deciding who and when to treat.

Epidemiology of *H. pylori* infection

H. pylori infection is mostly acquired during childhood, usually before 10 years of age, by intrafamilial transmission. In resource-limited countries, infection is often acquired even earlier, usually before 3 years of age. The infection usually persists lifelong, thus increasing prevalence with age. Overall, a lower prevalence of *H. pylori* infection has been reported in younger people, high-income countries, or countries with high levels of universal health coverage. Recently, the estimated global prevalence of *H. pylori* infection decreased from 58.2% (95% CI, 50.7–65.8) in the 1980–1990 period to 43.1% (95% CI, 40.3–45.9) in the 2011–2022 period, with the largest decline in the World Health Organization (WHO) African region.² Meta-regression analysis showed a 0.39–0.83% decline in worldwide prevalence per year. The prevalence of *H. pylori* infection is highest in Africa (79.1%), Latin America and the Caribbean (63.4%), and Asia (54.7%), whereas prevalence is lowest in North America (37.1%) and Oceania (24.4%).³ In Hong Kong, the prevalence was 54.9% among the healthy blood donors.⁴ In children, the prevalence is 40–80% in Africa, 30–50% in Latin America, 12–22% in Asia, and conversely, 15% in Australia and 7% in Northern America.⁵

The estimated rate of *H. pylori* infection in healthy school children (n=2,480) was 13.1% by urea breath test in Hong Kong.⁶ Among 602 children who underwent oesophagogastroduodenoscopy at a tertiary centre for peptic ulcer symptoms, the *H. pylori* infection rate decreased from 25.6% in 2005 to 12.8% in 2017.⁷

Complications of *H. pylori* infection

Most of the infected patients remain asymptomatic. However, 15–20% of *H. pylori* infected patients have peptic ulcer diseases. In 2010, globally, 3.5 deaths per 100,000 population were caused by peptic ulcer disease. There are 5–10% infected patients with dyspepsia. A subset of *H. pylori*-infected persons experiences changes in the gastric epithelium that, in 1–2% of them, progress to non-cardia gastric adenocarcinoma or mucosa-associated lymphoid tissue lymphoma.⁸ In 1994, the WHO classified *H. pylori* as a Class 1 carcinogen for its causal role in 87% of gastric cancers. In 2014, the WHO's International Agency for Research on Cancer recommended *H. pylori* eradication as a measure for gastric cancer prevention. The American College of Gastroenterology has recommended universal treatment of all infected persons since 2017. However, still nearly 800,000 new cases of gastric cancer worldwide were attributed to *H. pylori* infection. Studies have shown that *H. pylori* may interfere with many biological processes and determine or influence the occurrence of many extraintestinal diseases such as idiopathic thrombocytopenic purpura (ITP) and iron deficiency anaemia (IDA).⁹ It also contributes to vitamin B12 deficiency, insulin resistance, metabolic syndrome,

diabetes mellitus and non-alcoholic liver disease. It may increase the risk of acute coronary syndrome, cerebrovascular disease, neurodegenerative disease and other miscellaneous disorders. Different pathogenic mechanisms have been hypothesised, including the occurrence of molecular mimicry and the induction of a low-grade inflammation. These associations inform the broader indications for *H. pylori* testing in adults as well as what has been termed a "screen-and-treat" management strategy. However, in comparison with adults, these complications are rare in children. Furthermore, the causal relationship between *H. pylori* infection and functional gastrointestinal symptoms in children is not established.

Diagnostic evaluation in children

The primary goal of clinical investigation of gastrointestinal symptoms should be to look for the underlying cause of the symptoms and not solely the diagnosis of *H. pylori*. Methods of assessment include biopsy collection from an oesophagogastroduodenoscopy, which involves both histological evaluation and rapid urease testing, as well as primary culture of the organism. Both histological evaluation and rapid urease testing have high sensitivity and specificity. Primary culture of *H. pylori* carries low sensitivity but high specificity. Culture also enables antibiotic sensitivity testing, which becomes more important due to the rise of resistant strains. During oesophagogastroduodenoscopy, mucosa of the gastrointestinal tract can be inspected carefully to evaluate for other possible aetiologies or complications of *H. pylori* infection, such as peptic ulcer diseases. However, oesophagogastroduodenoscopy is an invasive procedure that carries procedural and sedation/anaesthesia risks to patients. Non-invasive tests for active infection, including a two-step monoclonal faecal antigen test and the 13C urea breath test (UBT), are more attractive to patients and parents. The

two-step monoclonal faecal antigen test is valid for all age groups and is preferred for younger children.¹⁰ UBT is a reliable and accurate non-invasive test in children. However, a meta-analysis shows that the UBT test is less accurate for the diagnosis of *H. pylori* infection in children <6 years old,¹¹ due to the lower distribution volume and different CO₂ production rates, technical difficulties in swallowing the substrate, and contamination from oral urease-producing organisms. Serologic tests do not distinguish between active and past infection; however, they have very good negative predictive value of *H. pylori* infection.

Molecular tests for *H. pylori* in saliva, dried blood, urine, stool and dental biofilm are attractive for paediatric populations because of these tests' non-invasive natures. However, these assays have not yet been validated for paediatric applications and require additional evaluation across various populations and geographic regions.

To treat or not to treat?

A challenge for paediatric providers is in deciding who and when to treat.

Worsening antibiotic resistance, poor adherence with the eradication regimens, and a potential lack of symptomatic benefit (symptomatic improvement following eradication therapy is best predicted by the presence of peptic ulcer disease) further complicate the management of this chronic infection in children. Eradication regimens are associated with adverse events such as cramps, diarrhoea, microbiome disruption and superinfection with organism (eg, *Clostridium difficile*). In general, the reinfection rate is higher in children than in adults and may end up with the need for retreatment afterwards, even with successful eradication initially. Children <5 years old have an annual recurrence rate of 30%, and this rate decreases to 8% in children >11 years old.¹² Reinfection rate also varies among different geographical areas. Increased societal development, marked by higher life expectancy, educational attainment, and gross national income per capita, was inversely related to recurrence rates. For example, rate of reinfection was 22.8% in children <10 years old and 7.1% in children >10 years old in Hubei, China.¹³ On the other hand,

Table 1. Indications of eradication therapy for *Helicobacter pylori* infection between ESPGHAN/NASPGHAN and JSPGHAN guidelines.

ESPGHAN/NASPGHAN 2023	JSPGHAN 2020
Gastric or duodenal ulcers and/or erosions	Gastric and/or duodenal ulcers
Refractory IDA (other causes ruled out)	IDA when iron deficiency is recurrent or refractory to iron supplementation
	Chronic ITP
First-degree relative with gastric cancer	First-/Second-degree relative with gastric cancer
Incidental finding during endoscopy for other gastrointestinal diseases, after discussion of risks and benefits	Patients who underwent diagnostic upper gastrointestinal endoscopy for abdominal symptoms
	Histological evidence of chronic gastritis/ gastric atrophy
	Gastric MALT lymphoma
	Protein-losing gastroenteropathy if other aetiologies are not found

ESPGHAN, European Society for Paediatric Gastroenterology Hepatology and Nutrition; IDA, iron-deficiency anaemia; ITP, idiopathic thrombocytopenic purpura; JSPGHAN, Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition; MALT, mucosa-associated lymphoid tissue; NASPGHAN, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

in Japan and Ireland, rate of reinfection for children >5 years old was 2–2.4% only.^{14,15} Consideration of these different factors has resulted in guidelines from different regions having different recommendations. Table 1 shows the indications of treatment by ESPGHAN/NASPGHAN 2023 and JSPGHAN 2020.^{16,17}

How to treat?

If testing is feasible, the choice of therapy should be guided by antimicrobial susceptibility testing and administered with the optimal treatment interval. Globally, the resistance to common antibiotics used in eradication therapy (eg, clarithromycin, metronidazole and quinolones) is increasing. According to a meta-analysis published in 2018, the prevalence of resistance to clarithromycin was 10% (95% CI, 5–17) in Hong Kong; the prevalence of resistance to metronidazole was 53% (95% CI, 39–66).¹⁸ A single centre study in Hong Kong comparing the eradication rate in 1997–2004 with that of 2005–2017 found that in all children with *H. pylori* infection treated with 1-week triple therapy of clarithromycin 7.5 mg/kg/dose thrice daily (max. 400 mg/dose), amoxicillin 20 mg/kg/dose thrice daily (max. 500 mg/dose) and omeprazole 20 mg twice daily (10 mg twice daily for patients <20 kg), the failure rate increased from 10% to 29.3%.⁷ For triple therapy, a 14-day course is associated with significantly higher eradication rates compared with shorter courses of therapy. In addition to tolerability and compliance of treatment, the degree of gastric acid suppression is one of the most important factors in determining the success of *H. pylori* eradication. Esomeprazole is less susceptible to degradation by rapid metabolisers with relevant cytochrome polymorphisms and therefore is preferred. The treatment regimen should be simple to use and well tolerated, with good compliance and high efficacy (>85%).¹⁹ In Hong Kong, triple therapy with a proton pump

Table 2. Treatment regimens for eliminating *Helicobacter pylori* in children.

Triple therapy	<ul style="list-style-type: none"> • PPI • Amoxicillin • Clarithromycin/metronidazole • +/- Probiotics For 14 days
Triple therapy with high-dose amoxicillin and metronidazole	<ul style="list-style-type: none"> • PPI • Amoxicillin • Metronidazole • +/- Probiotics For 14 days
Bismuth quadruple	<ul style="list-style-type: none"> • PPI • Amoxicillin • Bismuth subsalicylate • Clarithromycin/metronidazole • +/- Probiotics For 10–14 days
Penicillin allergy	<ul style="list-style-type: none"> • Triple therapy: PPI + CLA + MET • Bismuth quadruple therapy: bismuth + PPI + tetracycline + MET (for children >8 years old)

CLA, clarithromycin; MET, metronidazole; PPI, proton pump inhibitor

inhibitor, clarithromycin/metronidazole, and amoxicillin for 14 days remains the first-line option in children because of the relatively low resistance to clarithromycin in Hong Kong (Table 2). Patients allergic to amoxicillin should receive metronidazole instead of amoxicillin. Bismuth quadruple therapy can be regarded as second-line treatment when antimicrobial susceptibility testing is unavailable. However, the tolerability and availability of bismuth compounds could limit the widespread use of bismuth-based therapy.²⁰ Probiotics can be considered for prevention of side effects of treatment, including diarrhoea, which may enhance the eradication rate.²¹ Eradication should also be confirmed after completion of treatment for 4–8 weeks.

Conclusion

In view of the heterogeneity of the prevalence, reinfection rate, gastric cancer risk, and social economic status, a joint decision-making is needed between the health provider and family, with a thorough discussion regarding the potential benefits and risks of treatment. Recommendations should just serve as general guidelines and principles; they

should not serve as an exclusive protocol for all children. Variations, based on clinical judgment considering individual, family and national circumstances, and age are appropriate and important. The patients' values, preferences, goals and circumstance should be taken into account for the patient-centred practice, which aims to improve the health outcomes of individual patients.

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

Aptamil PHP 親熠

關鍵致敏蛋白* 近乎 0 發現¹



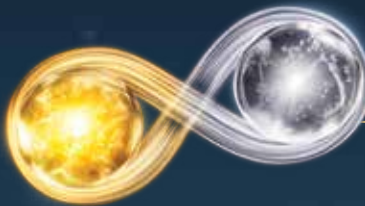
納米級水解 小分子蛋白²

研究顯示100%切斷關鍵致敏蛋白³



全新升級 5HMO⁴

低聚糖含量與母乳水平相約⁵



益生菌+益生元 SYNEOTM

幫助降低52%小敏感風險⁷

適度水解蛋白配方



*β-乳球蛋白

1. a. 關鍵致敏蛋白：指完整的β-乳球蛋白。β-乳球蛋白是牛乳中的主要過敏原，約有82%的牛乳過敏患者對β-乳球蛋白過敏。He, S.F. et al. Journal of Food Safety and Quality Apr., 2019. b. 近乎0發現：指近似於零。特定的檢測結果顯示，Aptamil ESSENSIS PHP親熠4配方的β-乳球蛋白未檢出。(實驗室資料) 2. 乳清蛋白的分子大小為納米水準。de Wit. Nutritional and Functional Characteristics of Whey Proteins in Food Products. J Dairy Sci.1998; 81: 597-608. 3. 在Aptamil部分水解配方乳清蛋白水解產物中觀察到關鍵致敏蛋白β-乳球蛋白的完全水解。van Esch, Betty C A M et al. "In vivo and in vitro evaluation of the residual allergenicity of partially hydrolysed infant formulas." Toxicology Letters vol. 201.3 (2011): 264-9. 4. 5HMO (0.7g克/100g克)：2'-FL, LNT, 3-FL, 6'-SL, 3'-SL. 5. 結合scGOS/lcFOS (5.3g/100g)；低聚糖含量達9.1g/L，與母乳水平相約。6. SYNEO，是指M-16V與GOS/FOS的組合。7. 根據一項多國、隨機、雙盲、對照臨床研究，使用含scGOS/lcFOS和短雙歧桿菌M-16V的配方奶餵養50名寶寶約22周，發生皮膚疾病的寶寶比例和對照組相比下降了約52%。Chua M C et al. Journal of Pediatric Gastroenterology and Nutrition, 2017, 65(1):102. 約52%為試驗資料，供消費者參考，具體效果因人而異。

只供醫護人員使用

The Severe Sequelae of Respiratory Syncytial Virus Infection – Could We Prevent It?

Dr Kwan Yat Wah, Mike

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***Helicobacter pylori* Infection in Children: To Treat or Not to Treat?**

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