Issue 2: April - June 2024

Pederm Insights

An official publication of Pediatric Dermatology Foundation

In this Issue

Dear Colleagues,

We thank you for welcoming our first issue of the Pediatric Dermatology Foundation newsletter with support and suggestions to enhance this endeavor.

I am delighted to welcome our readers to the second issue of the PDF newsletter. Recently, increasing use of the new molecular kid 'JAK inhibitors' has revolutionized the therapeutic outcomes of various dermatological conditions. But surprisingly, there is no robust evidence in the literature regarding the safety and efficacy of JAK inhibitors in children. Their current clinical use is based on anecdotal evidence for most of the dermatoses. In India, the easy availability of tofacitinib has compelled dermatologists to use this as an off-label drug for various dermatological conditions. The major question is: are we justified in using this drug? This issue highlights the current evidence regarding JAK inhibitors in children, along with an intriguing case vignette, a photo quiz, information on the usage of oral antibiotics in children, and solutions to the Brain-teasing Crossword. There is also a fascinating section for residents who enjoy challenges.

I thank all the editorial members for their support and contributions.

Happy reading!

Sahana M Srinivas

Editor-in chief

Forthcoming Events

Gene Genome Genetics

For Pediatric Dermatologists on
21st April 2024 at Mumbai

Pediatric Dermatology Updates 2024

September 28-29, NIMHANS, Bengaluru

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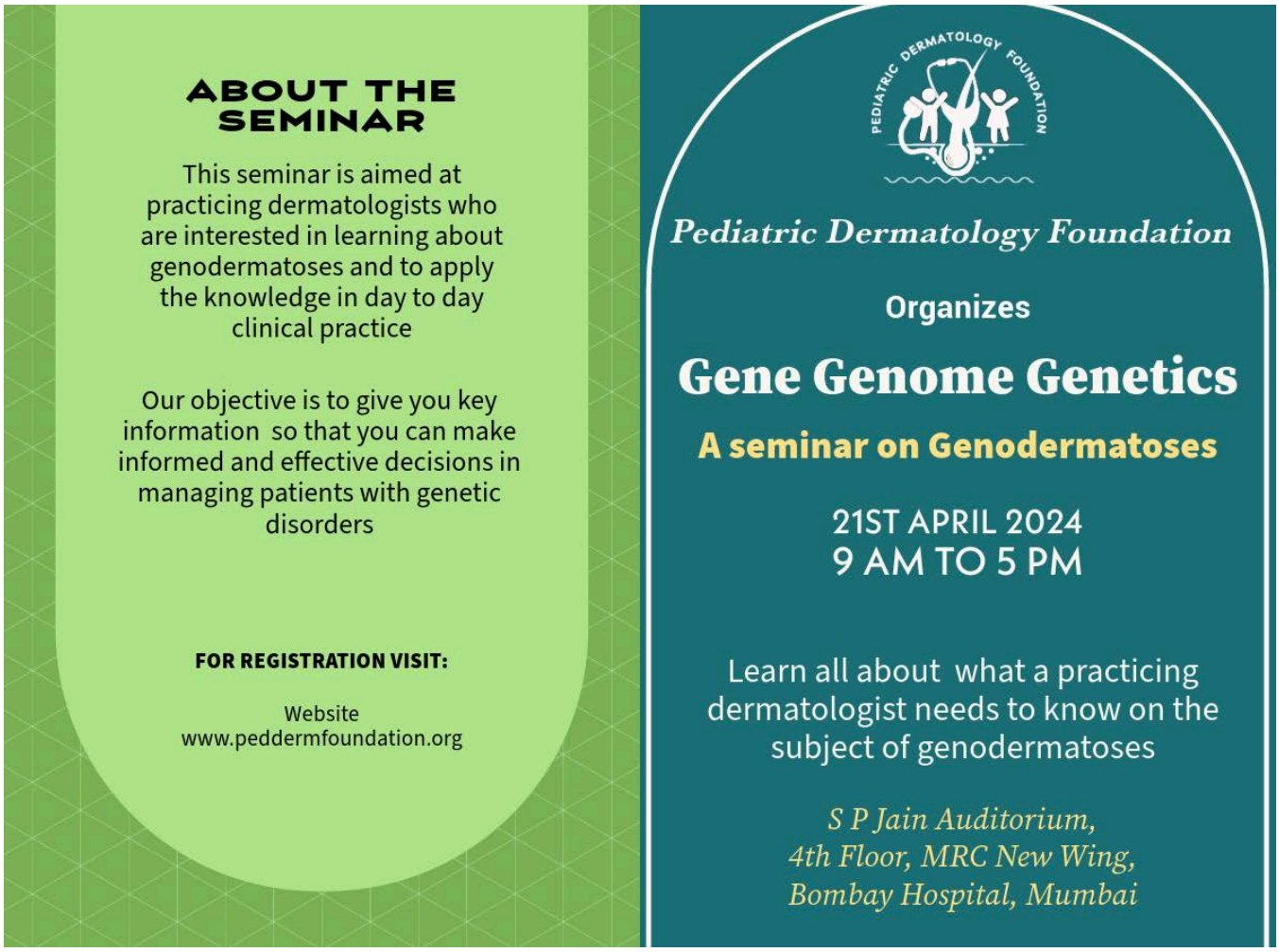

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Journal Review

Contributors: Sahana M Srinivas, Preeti K Sheth, Jeta Buch, Divya Gupta

Torrelo A, Rewerska B, Galimberti M, Paller A, Yang CY, Prakash A, et al. Efficacy and safety of baricitinib in combination with topical corticosteroids in paediatric patients with moderate-to-severe atopic dermatitis with an inadequate response to topical corticosteroids: results from a phase III, randomized, double-blind, placebo-controlled study (BREEZE-AD PEDS). Br J Dermatol. 2023 Jul 7;189(1):23-32.

Baricitinib, an oral reversible and selective JAK1/JAK 2 inhibitor has been approved for the treatment of moderate to severe atopic dermatitis (AD) in adult patients. In this phase III, multicentric, double-blind, randomized placebo-controlled trial, the authors have aimed to evaluate the efficacy and safety of three doses of baricitinib in combination with low-to-moderate potency topical corticosteroids in pediatric patients ages 2 to < 18 years with moderate-to-severe atopic dermatitis based on a validated Investigator Global Assessment (vIGA score of >3), Eczema Area and Severity Index (EASI) score ≥ 16 and body surface area involvement ≥ 10 percent. A total of 483 children were randomised 1:1:1:1 to placebo or once-daily baricitinib 1mg (low dose), 2mg (medium dose) or 4 mg (high dose) equivalent dosing for 16 weeks. The primary endpoint was the proportion of patients achieving vIGA-AD of 0/1with a ≥ 2-point improvement at week 16 by 16.4% of those given placebo vs. 18.2%, 25.8% and 41.7% of those given baricitinib 1mg, 2mg and 4 mg equivalent, respectively, the latter being statistically significant. The baricitinib 4 mg equivalent group achieved significant improvement compared with placebo for all secondary 16-week endpoints (EASI -75, EASI-90, mean change in EASI score, SCORAD 75 and itch NRS 4-point improvement for participants > 10 years). Few participants discontinued due to adverse events: 1.6% for placebo and 0.6% for those given baricitinib. There were no deaths, venous or arterial thrombotic events, cardiovascular events, malignancies, gastrointestinal perforations or opportunistic infections. The most common treatment-emergent adverse events in this study with a baricitinib 4 mg equivalent dose were abdominal pain, acne, headache, diarrhoea, nasopharyngitis and upper respiratory tract infection.

(Submitted by Sahana Srinivas)

Paller AS, Ladizinski B, Mendes-Bastos P, Siegfried E, Soong W, Prajapati VH, et al. Efficacy and Safety of Upadacitinib Treatment in Adolescents with Moderate-to-Severe Atopic Dermatitis: Analysis of the Measure Up 1, Measure Up 2, and AD Up Randomized Clinical Trials. JAMA Dermatol. 2023;159(5):526-535

This study aimed to assess the efficacy and safety of upadacitinib to treat moderate to severe atopic dermatitis in adolescents aged 12 to 17 years, enrolled in three randomized, double-blind, placebo-controlled phase 3 trials in more than 20 countries from July 2018 through December 2020. Around 552 adolescents (290 girls; 262 boys) were randomized (1:1:1) to once-daily oral upadacitinib 15 mg, 30 mg or placebo alone (Measure Up 1 and Measure Up 2) or with topical corticosteroids (AD Up). In Measure Up 1, Measure Up 2, and AD Up, respectively, a greater proportion of adolescents achieved at least 75% improvement in the EASI score at week 16 with upadacitinib 15 mg (73% , 69% , 63%), and upadacitinib 30 mg (78% , 73%, 84%), than with placebo (12% , 13% , 30%). Similarly, a greater proportion of adolescents treated with upadacitinib achieved a vIGA for Atopic Dermatitis score of 0 or 1 at week 16 and improvements in quality of life than with placebo. Mild to moderate acne was the most common adverse effect seen. Other side effects included, headache, upper respiratory tract infection, elevated creatine phosphokinase and nasopharyngitis. The overall efficacy and safety profile of upadacitinib was similar to that observed in adults, supporting a favorable benefit-risk profile for upadacitinib in adolescents aged 12 to 17 years.

(Submitted by Sahana Srinivas)

Comments (by Sahana Srinivas)

JAK INHIBITORS

Though many of the available JAK inhibitors are not approved, they are being used off-label to treat various pediatric dermatoses, which has sparked significant safety concerns. The JAK family is composed of JAK 1, JAK 2, JAK 3 and TYK2 (tyrosine kinase 2). JAK inhibitors selectively target the various kinases, causing a suppression in the activity by immunomodulatory or antiproliferative effect. JAK 1 plays an important role in the expression of IL-4, IL-5, IL-13, and IL-31, which are associated with pro-inflammatory signalling pathways in atopic dermatitis. Among the available JAK inhibitors topical ruxolitinib 1.5% cream, upadacitinib and abrocitinib is approved for atopic dermatitis in adults. Recently only oral upadacitinib has been approve by US FDA in 2022 in children aged 12 years and older. .**[Dermatol Ther (Heidelb). 2023 Mar;13(3):729-749].**

In the above studies by Torrelo *et al.* and Paller *et al.* both baricitinib and upadacitinib have shown favourable improvement in children aged less than 18 years (the youngest age being 2 years in BREEZE-AD-PEDS study) with moderate to severe atopic dermatitis. The overall efficacy and safety profile of baricitinib and upadacitinib were consistent with that observed in adults with moderate-to-severe atopic dermatitis. However, both of these studies have the limitation of assessing the participants for a 16-week trial only, impeding full characterization of the safety and efficacy in the long-term outcomes. Also, in the baricitinib trial, the use of topical corticosteroid and calcineurin inhibitors were potential confounders. Since the timeframe and extent of exposure limits the assessment of long-tern outcomes, the BREEZE-AD PEDS study continues to monitor the study participants up to four additional years. Further results of this study will clarify the risk-benefit profile of JAK inhibitors in pediatric age group.

There is no doubt that in children with moderate to severe atopic dermatitis, selectively targeted therapies such as JAK inhibitors are welcome drugs. However, at present the safety and efficacy of these JAK inhibitors in long-term is questionable. In India, the JAK inhibitors available are tofacitinib and baricitinib. Tofacitinib, due to its widespread availability, has compelled dermatologists to use this drug for various dermatoses, including atopic dermatitis. But surprisingly, **literature review has shown no clinical studies of tofacitinib in children for atopic dermatitis.** There are few case reports and case series in adults with severe atopic dermatitis not responding to conventional immunosuppressants and biologics, being treated with tofacitinib 5mg two times a day with good improvement. The period of treatment ranged from 7 months to 16 months **[J Dermatolog Treat. 2022 ;33(6):2873-2875].** Infections were the most common side effect seen in the adult cohort. Another paramount issue in prescribing JAK inhibitors is the laboratory monitoring. It is recommended to get a baseline blood count, biochemistry profile, Mantoux test, IGRA test for tuberculosis, hepatitis B, C and if necessary HIV testing, lipid profile and CPK levels. If the baseline investigations are normal the tests can be repeated at 1 month and subsequently at every 3 monthly follow up. **Currently, there is no evidence regarding the use of JAK inhibitors in children for atopic dermatitis**. Future studies with robust data would give us a clear picture.

Olamiju B, Craiglow BG. Tofacitinib cream plus narrowband ultraviolet B phototherapy for segmental vitiligo in a child. Pediatr Dermatol. 2020 Jul;37(4):754-755.

A four-year-old boy was referred for evaluation of segmental vitiligo that had developed abruptly about 6 months previously. He had been using alclometasone 0.05% cream twice daily for 6 weeks without improvement. On physical examination, he had a well-demarcated depigmented patch involving his right chin and anterior neck. Given the prominent facial involvement and that he was going to start elementary school later in the year, the patient's family was interested in optimizing the chances of successful treatment. He discontinued alclometasone and started tofacitinib 2% cream twice daily along with narrowband ultraviolet B phototherapy using a handheld unit (administered at home) to the affected area three times weekly. Freckling was observed within 4 weeks, and after 3 months, only three depigmented linear macules remained on the chin. At 6 months, there was complete repigmentation. Although a taper was recommended, the patient discontinued treatment after another month, and the area remained fully repigmented for approximately 6 months before a few depigmented macules began to reappear, at which time he restarted the prior regimen. The patient tolerated treatment well without any adverse effects.

(Submitted by Divya Gupta)

Berbert Ferreira S, Berbert Ferreira R, Neves Neto AC, Assef SMC, Scheinberg M. Topical Tofacitinib: A Janus Kinase Inhibitor for the Treatment of Vitiligo in an Adolescent Patient. Case Rep Dermatol. 2021 Apr 1;13(1):190-194.

We report on the case of a 17-year-old boy with stable nonsegmental vitiligo with acrofacial involvement with a 15-year evolution. He had no other clinical or autoimmune condition and denied any family history of vitiligo. Previous treatments included oral corticosteroids for 4 years, alternating 6 months each because of unstable vitiligo, antioxidants, and oral vitamin D, topical tacrolimus for 6 months, and topical corticosteroids for another 6 months. He had received 1 year of phototherapy (NB-UVB) with no improvement at all, as well as NBUVB associated with topical corticosteroids and topical tacrolimus during 3 years, with little improvement. The patient was started on a combined therapy: topical tofacitinib 2% + vehicle (ointment) (Chemistry Rx Compounding and Specialty Pharmacy, Folcroft, PA, USA) twice daily only on the facial lesions, combined with NB-UVB phototherapy, 3 times a week. After 9 months of therapy, significant repigmentation of the forehead, nose, eyes, and lips was observed. He had minor adverse events such as erythema and transient acne.

Comments (by Divya Gupta)

Small molecules, especially JAK inhibitors (JAK-I's), are emerging as an additional option in the therapeutic armamentarium for various skin conditions like alopecia areata, psoriasis, atopic dermatitis and vitiligo. While some are US FDA approved for specific conditions, many are being used as off-label. In India, there has been an upswing in the use of these molecules, possibly because of easy availability, affordability and also the novelty factor of trying something new. The Janus kinase signal transducer and activator of transcription (JAK-STAT) pathway is an intracellular signalling cascade that modulates gene expression in response to cytokines. Dysregulation of the JAK-STAT pathway is implicated in many autoimmune and inflammatory skin disorders. By inhibiting various JAKs, JAK Inhibitors can decrease downstream signal transduction of the STATs, suppressing further immune-specific responses. In vitiligo, self-reactive CD8+ T cells produce IFN-γ, which activates JAK1 and JAK2, leading to the phosphorylation of STAT1 and STAT2 and further recruitment of CD8+ T cells and eventual melanocyte destruction. Hence JAK-I's have a therapeutic role.

While searching the literature, **it was surprising to note that there are no original articles with regards to oral JAK-inhibitors in adult or pediatric vitiligo**. There are a few case reports and small case series with oral tofacitinib and oral baricitinib in adult vitiligo, where they have given good results in combination with NBUVB. However, there are no controlled trials or large cohort studies/ case series' to prove it's superiority over other established therapies. There are many isolated case reports of topical 2% tofacitinib in pediatric vitiligo where it has given good results. The other JAK-I's that have been tried for vitiligo include topical ifidancitinib, topical delgocitinib and topical 1.5% ruxolitinib, with the latter being the only one that is US FDA-approved. In the above report, while topical tofacitinib led to re-pigmentation, it was followed by eventual relapse, not unlike what is seen with other medications too. This begs the question whether tofacitinib is indeed superior to currently FDA-approved therapies and whether its rampant use is justified.

In my practice I have compounded 2% tofacitinib (Xeljanz) for long term maintenance therapy in cases where lesions were refractory to topical calcineurin inhibitor (TCI), and phototherapy was not available or possible. I have also used compounded 2% tofacitinib in combination with TCIs. The topical formulation seems safe on long term usage with no side effects noted. The compounded tofacitinib with the original innovator molecule was felt to be superior in result to the commercially ready-to-use topical formulations available in India, although cost was a major barrier with the former.

To conclude, based on the current literature review, topical 2% tofacitinib can be used off-label for maintenance in pediatric vitiligo as a steroid sparing agent, either alone or in combination with NB-UVB and/or TCI. However, sufficient evidence is not yet available to prescribe oral JAK-I's, especially in pediatric vitiligo. Dermatologists must refrain from prescribing the same for this indication till more data on safety and efficacy becomes available.

Phan K, Sebaratnam DF. JAK inhibitors for alopecia areata: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2019 May;33(5):850-856.

There have been a number of case reports and small clinical trials reporting promising outcomes of Janus Kinase (JAK) inhibitors tofacitinib, ruxolitinib and baricitinib for alopecia areata (AA). The majority of the literature to date is based on small volume data, with a lack of definitive evidence or guidelines. To determine the expected response of AA to JAK inhibitor therapy and factors which influence response and recurrence rates, a systematic review and meta-analysis was performed according to PRISMA guidelines. From 30 studies and 289 cases, there were (72.4%) responders, good responders (45.7%) and partial responders (21.4%). Mean time to initial hair growth was 2.2 ± 6.7 months, and time to complete hair regrowth was 6.7 ± 2.2 months. All 37 recurrences occurred when treatment was ceased after 2.7 months. Oral route was significantly associated with response to treatment compared to topical therapy. There was no difference between responders and non-responders in terms of age, sex, duration of AA, AA subtype, JAK inhibitor nor the duration of treatment. No difference was found between paediatric and adult cases in proportion of responses. An overall low complication rate was found which included upper respiratory tract infections and urinary tract infections. Laboratory abnormalities were minimal and prevalence was low.
(Submitted by Jeta Buch)

Comments (by Jeta Buch)

JAK inhibitors are efficacious and safe for the treatment of AA. Demographic factors including age, sex, previous failure of systemic therapy and duration of AA did not appear to influence response to therapy. JAK inhibitor treatment needs to be maintained in order for hair regrowth to be sustained. Future large-sized randomized studies are required to confirm findings.

Hamilton CE, Craiglow BG. JAK Inhibitors for the Treatment of Pediatric Alopecia Areata. J Investig Dermatol Symp Proc. 2020 Nov;20(1):S31-S36.

Various first-generation JAK inhibitors, which include Ruxolitinib (JAK1/2 inhbitor), Tofacitinib (JAK1/3>2 inhibitor) and Baricitinib (JAK1/2 inhibitor) have been found to be highly efficacious and well tolerated in patients with psoriasis, atopic dermatitis, vitiligo and AA among others. However, only a handful of case series and reports have investigated the safety and efficacy of JAK inhibitors for AA in children and adolescents. Eight case series which included 38 children in the age range of 4-17 years were analysed. In children aged 4-5 years with AT or AU, dose was initiated at 2.5 mg daily whereas in those aged 8-17 years, dose administered was 5 mg twice a day in all studies. These studies demonstrated that success rate of JAK inhibitors in children is comparable to those with adults with an average 30-100% change in SALT score. Side effects were minimal and included mild infections, diarrhoea and transient laboratory abnormalities.

A series of six patients aged 3-17 years treated with application of 2% topical tofacitinib or 1% ruxolitinib found variable responses. Another series of 11 patients ranging from 4-11 years treated with 2% tofacitinib experienced an average of 32.3% change in Severity of Alopecia Tool Score. A final case report of patient in her late teens exhibited near full growth of eyebrows after 12 weeks of treatment with 0.6% ruxolitinib cream but only 10% regrowth of scalp hair. In all three studies, minimal adverse effects were noted, consisting of mild laboratory abnormalities and application site irritation. Large trials provide an important insight into the pharmacokinetics of JAK inhibitors in pediatric patients: Phase 1 trial of ruxolitinib in children with refractory solid tumors and hematological malignancies, Phase 1 trial of tofacitinib in children with juvenile idiopathic arthritis and a compassionate use protocol of baricitinib in interferenopathies. Pharmacokinetics of JAK inhibitors is largely different than in adults. Baricitinib has a significantly shorter half-life than in adults necessitating 3-4 times daily dosing for optimal effect. Drug levels vary by weight and renal function, so dose needs to be caliberated according to weight and glomerular filtration rate. Tofacitinib also has a shorter half-life as well as faster clearance rate requiring higher dosage than adults.
(Submitted by Jeta Buch)

Comments (by Jeta Buch)

Oral JAK inhibitors are largely safe, well tolerable and highly effective therapy for moderate to severe alopecia areata in paediatric population. Topical JAK inhibitors are a more appealing treatment option in paediatric population in the treatment of limited disease or distinct areas of desired growth (e.g., eyebrows and eyelashes) with lower theoretical risk of complications compared to oral agents.

JAK inhibitors in Psoriasis

Commentary (by Preeti K Sheth)

Psoriasis is a chronic, autoimmune, inflammatory disease characterised by sharply demarcated erythematous lesions, topped by silvery scales. The IL-23/Th17 axis plays a crucial role in the psoriasis inflammatory process.

How JAK-STAT pathway is involved in the pathogenesis?

Cytokines are a group of proteins (such as IL-2, IL-4, IL-6, IL-9, IL-15, IL-22, IL-23, interferons) which when bind to their receptors, induct the intracellular Janus Kinase enzymes (JAKs). The JAKs (JAK1, JAK2, JAK3, TYK2) join in pairs to the intracellular portion of cytokine receptor and are thus activated. They in turn attract STAT (signal transducer and activator of transcription) proteins. The STAT proteins (STAT 1,2,3,4,5A,5B,6) are translocated to the central nucleus after dimerization. Herein, they regulate the gene transcription of the inflammatory cytokines responsible for the development of psoriasis. The signal transduction of Type 1 interferons occurs following the TYK2/JAK1 pairing via STAT1 and STAT2. The signal transduction of IL-23 and IL-12 are secondary to the TYK2/JAK2 pairing via STAT3 and STAT4. This leads to the activation of Th17 and Th1 cells which is central to the pathogenesis of psoriasis.

So, do JAK inhibitors help in psoriasis?

JAK inhibitors offer a good therapeutic advantage in controlling inflammation as they target more than one JAK enzyme. However, this action is also associated with more adverse effects, particularly with the older generation of JAK inhibitors as compared to the newer, more selective, molecules. TYK2/JAK2 pairing is crucial to the development of psoriasis as stated above. Speaking of tofacitinib, it primarily inhibits JAK1/3. Also, it was found to be more useful in higher doses of 10 mg bid as compared to 5 mg bid. A black box warning was issued for the higher dose which was associated with an increased risk of pulmonary embolism and dose dependent toxicities. Hence, tofacitinib, owing to its non-selective nature and a low therapeutic index, is not approved by FDA for the treatment of psoriasis.

Other JAK inhibitors under evaluation for treatment in psoriasis are ruxolitinib (JAK1/2), baricitinib (JAK1/2) and solcitinib (JAK1).

Which JAK inhibitor is approved in psoriasis?

The only FDA approved JAK inhibitor for psoriasis is deucravacitinib. It is a selective allosteric TYK2 inhibitor. It binds selectively to the regulatory domain of TYK2 and specifically inhibits only TYK2, with reduced cross reactivity to Jak1/2/3 enzymes. Thus, deucravacitinib inhibits TYK2 mediated signalling of IL-23 and type 1 interferons and subsequently their downstream functional responses. Given in a dose of 6 mg od in adults, it is an oral and well tolerated medication for moderate to severe plaque psoriasis. Deucravacitinib demonstrated superiority over placebo and apremilast in terms of efficacy at weeks 16 and 24 in clinical trials based on primary points of PASI 75 and sPGA 0/1. Responses were maintained through 52 weeks with continued treatment. Additionally, despite having a short half-life of approximately 10 hours, deucravacitinib demonstrated a sustained response for nearly 28 weeks after withdrawal of therapy. Side effects encountered were nasopharyngitis, upper respiratory tract infections, herpes zoster, acne and folliculitis; but none were severe enough to warrant discontinuation. Laboratory abnormalities were mild and transient. The rates of malignancies and cardiovascular events were low and comparable to that of general population. The safety profile of deucravacitinib comes as a sharp contrast to the other JAK 1/2/3 inhibitors. This is due to the unique allosteric mechanism of selective inhibition of TYK2 over JAK 1/2/3. Hence, it is an efficacious, safe, well tolerated, once a day oral drug for moderate to severe plaque psoriasis. Newer TYK2 inhibitors under evaluation with promising results in adults are ropsacitinib and brepocitinib.

So far, none of the JAK inhibitors are approved for psoriasis in children.

There has been only one open-label trial to study the safety and efficacy of tofacitinib in childhood psoriasis. 47 children with a median age of 12.3 years were enrolled were given tofacitinib 5mg twice a day for 36 weeks. More than 50% of them achieved PASI 75 and almost clear response of PGA at week 12; and nearly 70% of them achieved desirable results at week 36. Few minor side effects were reported. Overall, it was well tolerated and led to a significant improvement in disease and subsequently their quality of life.

Topical JAK inhibitors in psoriasis have not yielded convincing results.

Childhood psoriasis responds well to the already existing drugs in its therapeutic armamentarium. Tofacitinib's prime action is against JAK1/3 pairing, which is not the central focus in the pathogenesis of psoriasis. Hence, to achieve a good therapeutic response, one may have to pump in the drug at higher doses and thus subject the child to more severe adverse effects. **It is prudent to continue with the existing medications in childhood psoriasis till newer, more selective and efficacious molecules are approved.**

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Solitary hyperkeratotic plaque on the knee: what did we miss?

Author: Rashmi Agarwal

A 14-year-old boy presented to the pediatric dermatology outpatient department with an asymptomatic scaly thick lesion on the left knee, which the parents had noticed first when the child was about 4 years old. There was no prior history of trauma at the site of the lesion. The lesion was initially small and has gradually increased in size and thickness since then. He had been treated several times in the past in the lines of chronic eczema with moisturizers and topical steroids but without any significant improvement. Cutaneous examination revealed a single irregular 3x2.5 cm scaly plaque on the left knee (**Figures 1,2**). On closer examination, the plaque was studded with multiple hyperkeratotic papules with few showing hemorrhagic crusts.

Figure1 Scaly hyperkeratotic plaque on left knee

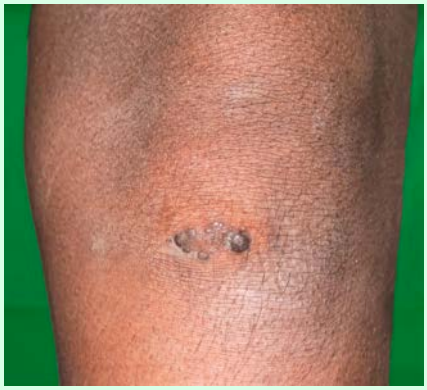


Figure 2 Hyperpigmented and hyperkeratotic papules and nodules on the plaque (became more distinct post application of interface liquid prior to dermoscopy)

Dermoscopic examination (Videodermoscopy: fotofinder, 20X magnification, polarized) of the lesion was done to look for other clues. It revealed the presence of blue and pink-purple lacunae which is characteristic of vascular lesions (**Figure 3**). Other features were prominent hyperkeratosis, alveolar appearance (more at the periphery of the plaque), bluish white veil in some areas with hemorrhage on the surface of a nodule (**Figure 4**).

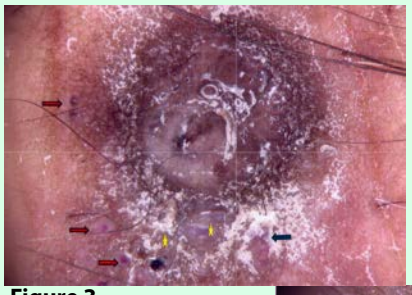


Figure 3

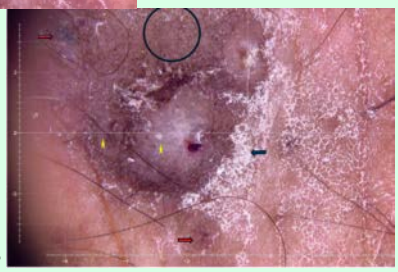


Figure 4

Fig 3 & 4: Videodermoscopy image (20x magnification) of the plaque showing blue and pink-purple lacunae (red arrow), prominent hyperkeratosis (blue arrow), bluish-white veil (yellow star) and alveolar appearance (black circle).

A 4mm punch biopsy was done to confirm the diagnosis with differentials of angiokeratoma and verrucous hemangioma (VH). Histopathological examination revealed presence of epidermal hyperkeratosis, acanthosis and papillomatosis with numerous dilated thin-walled capillaries of various sizes in the papillary dermis extending down into the deeper dermis and subcutaneous tissues, confirming the diagnosis of verrucous hemangioma. Few of the capillaries were congested with blood.

Verrucous hemangiomas are rare, usually solitary, unilateral and localized vascular malformations commonly located on the lower extremities. This condition typically manifests at birth or in early childhood, although cases presenting in adulthood have been reported.

Atypical presentations of verrucous hemangioma can encompass a wide spectrum of clinical variations (like giant VH, linear VH, painful/pruritic VH) which may pose challenges in diagnosis and management. Similarly, small localized hyperkeratotic plaque in children, especially those located on bony prominences can frequently be overlooked and misdiagnosed. Various entities presenting as a solitary warty plaque in children include verruca vulgaris, verrucous epidermal nevus, hypertrophic lichen planus, angiokeratomas, verrucous hemangioma and lichen simplex chronicus (**Table 1**). Hence, a thorough clinical evaluation, including history, physical examination, dermoscopy and biopsy, may be necessary to establish the correct diagnosis, which can guide appropriate management.

Clinicians should maintain a high index of suspicion for vascular lesions if there is presence of pink-purple/red/blue lacunae on dermoscopy. Dark red lacunae represent dilated vascular spaces with thrombosis. Deeper vessels give bluish colour to the lacunae and overlying hyperkeratosis and acanthosis is represented by a bluish white veil.

Table 1: Differential Diagnosis of solitary warty plaque on extremities.				
Features	**Hypertrophic Lichen Planus**	**Lichen simplex chronicus**	**Angiokeratoma circumscriptum neviforme**	**Verrucous hemangioma**
Onset	Acquired	Acquired	At birth or in early childhood	At birth or in early childhood
Location	Distal extremities (shins, ankles)	Commonly occurs in areas accessible to scratching, such as the neck, wrists, ankles.	Distal extremities (most common)	Distal extremities (most common)
Clinical features	Hyperkeratotic plaques and nodules	Thickened, hyperpigmented plaque due to chronic scratching or rubbing. The skin may appear rough, and may have exaggerated skin markings.	Red-colored macules which progressively transform into dark red to blue violaceous, warty and/or hyperkeratotic nodules or plaques.	Soft blue-red lesions that progressively enlarge to form hyperkeratotic and verrucous bluish-black plaques (size varying from 4 mm to more than 8 cm), especially after repeated infections and trauma. Small satellite lesions may be present
Symptoms	Intensely pruritic	Itching	Occasional bleeding and pain with minimal trauma.	Itch, oozing, bleeding
Dermoscopy	Pearly white areas (Wickham striae), peripheral striations, comedo-like openings, red dots and globules, grey-blue globules, brownish black globules, yellow areas	Accentuated skin markings, focal areas of scale, and sometimes dotted or linear vessels.	Well-demarcated, round lacunae, a whitish veil	Bluish-white hue (hyperkeratosis), reddish-blue or bluish lacunae
Histopathology	Epidermal hyperplasia, acanthosis, hypergranulosis Compact and lamellated hyperkeratosis centered on follicular infundibula and acrosyringia. Basal cell damage confined to the tips of rete ridges. Band-like may not be visible Vertically oriented collagen bundles in the papillary dermis with an increased number of eosinophils	Hyperkeratosis with foci of parakeratosis, prominent granular cell layer, elongated and irregularly thickened epidermal rete, acanthosis, pseudoepitheliomatous hyperplasia, papillary dermal fibrosis, and perivascular as well as interstitial inflammation in the superficial dermis.	Hyperkeratosis, acanthosis and papillomatosis in epidermis, dilated capillaries in the papillary dermis	Hyperkeratosis, acanthosis and papillomatosis in epidermis, vascular component in dermis and subcutaneous tissue
GLUT-1 expression	-	-	Positivity not reported	Mostly positive

PDF - Photoquiz 1

Author: Sirisha Varala

Clinical Data

A seven-year old boy presented with swelling of left leg of three months duration. Started initially as a small red raised lesion and progressed to involve the lower half of the left leg circumferentially. Associated with redness, pain and fever for 20 days following which the child was treated elsewhere with oral antibiotics and surgical debridement with no improvement. There was no history of prior trauma. Cutaneous examination revealed a single well defined hyperpigmented plaque, firm in consistency, present on the left leg involving the entire lower half circumferentially until the ankle joint (**figure 1**).

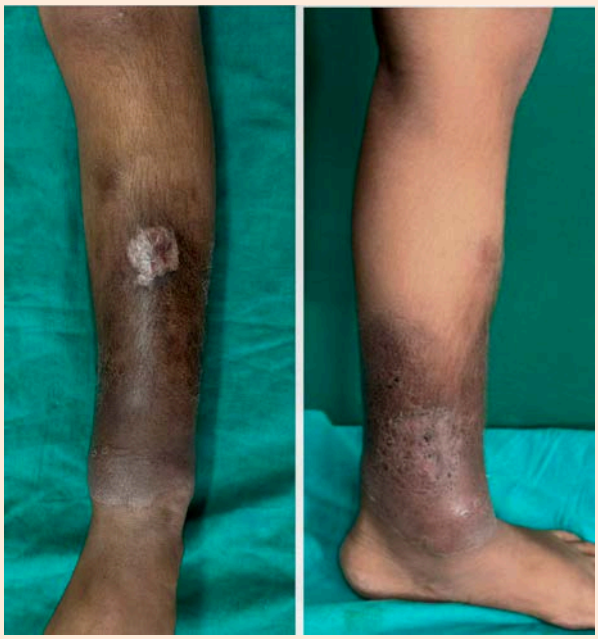


Figure1

Healed scar was present over the debridement site. There was no regional lymphadenopathy. Complete blood picture, liver and renal function tests, Mantoux and chest X ray were normal. ESR was raised (20mm/hr). An incisional biopsy was done and sent for histopathological examination with special stains (**figures 2, 3, 4**) and cultures (fungal and bacterial).

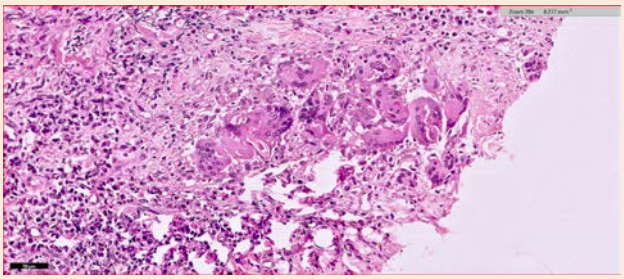


Figure 2

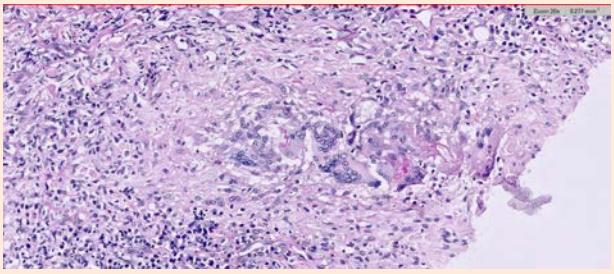


Figure 3

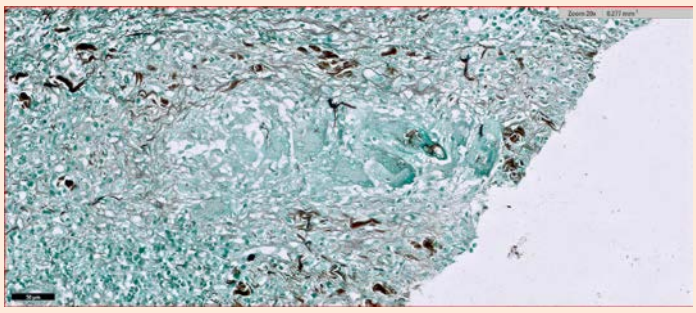
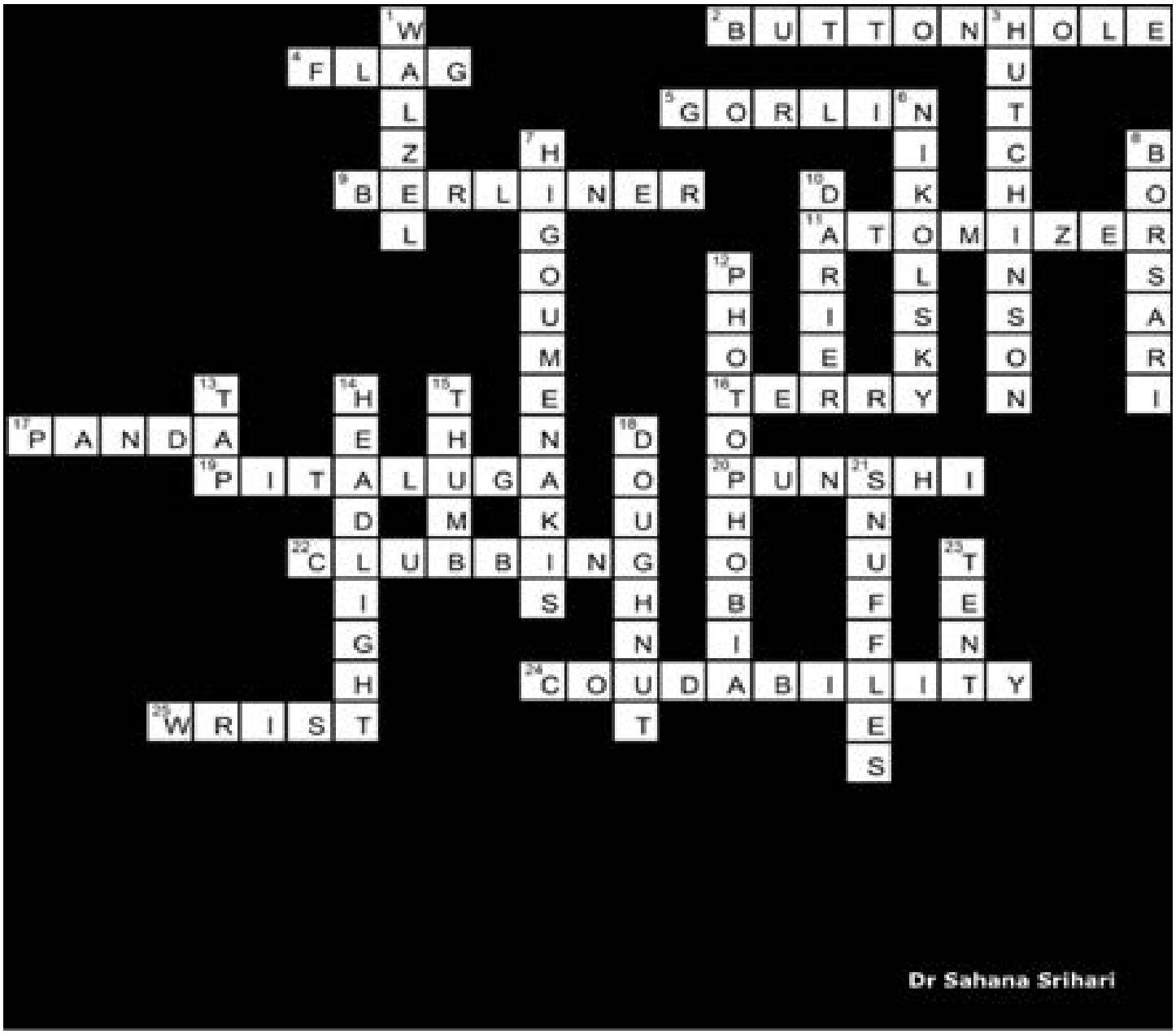


Figure 4

What is your diagnosis?

[Kindly mail your answers along with your affiliation to peddermfoundation@gmail.com before 10th June 2024. The winners of the PDF Photoquiz 1 will be announced in the next issue]

Answers to CROSSWORD PUZZLE – 1



The correct answer was given by

Dr Arulselvan M

Final year post graduate

Pondicherry Institute of Medical Sciences

The Editorial board congratulates Dr Arulselvan M for winning the first crossword. Free complimentary registration will be provided for the upcoming 'Pediatric Dermatology Updates' conference 2024

Challenges in Paediatric dermatology - diagnostic and therapeutic challenges

Author: Dr. Anubhab Bhattacharyya, MD, PDCC (Pediatric Dermatology),

JIPMER, Puducherry

As part of the advantage of being in an institute that runs a postdoctoral fellowship programme in paediatric dermatology, I had the opportunity of being in a position of observing paediatric cases being brought to our department with a wide gamut of dermatological issues. In my brief (thanks to COVID 19 pandemic) but meaningful stint as a post graduate trainee posted with a paediatric dermatology senior resident, I could realize how significantly different this subspeciality of clinical dermatology is, from our general repertoire of cases. The full weight of this realization, however, has hit me in the past 6-7 months as I find myself nearing the end of my year-long fellowship in paediatric dermatology from the same institute I did my post-graduation from.

1. Explaining the diagnosis - the good and bad:
Explaining the parents what is happening with their child can present a challenge in both aspects. Sometimes when the skin condition is a benign one (but looks ominous, like an HFMD/ exaggerated insect bite reaction/ paederus dermatitis/ pityriasis rosea) and we advise nothing but reassurance, few parents seem unconvinced with our diagnosis -the big question mark looming over their faces bear proof to that. And then there are times when we literally go overboard with counselling the parents about the need of regular follow-up visits / or regular treatment for their child's skin condition, which, apparently do not bother them enough, despite us explaining to them how the particular condition or the treatment being given may have systemic implications in the child. Examples of such a scenario are abound, ranging from parents not getting metabolic workup done for child having acanthosis nigricans, or systemic workup for ichthyosis patients to taking oral retinoids for months without getting lipid profile checked.

2. <u>Diagnostic dilemma between close mimickers</u>:
The clear distinction between childhood psoriasis and atopic eczema is often difficult, thus necessitating the use of clues like lesion morphology, boundary definition, erythema, distribution, presence of xerotic lesions elsewhere, atopic stigmata and presence of any similar history in family to differentiate between the two mimickers. Though prevalence of atopic eczema or contact dermatitis is generally more than psoriasis, and the basic management in both the conditions is largely similar, the conditions do differ in terms of extracutaneous features, and an early distinction may have a role in the long-term treatment plans.

3. Diagnostic procedures in children:
Carrying out biopsies and patch tests in children can be an exceptionally difficult task – posing a different challenge in each age group. While babies can have stranger anxiety and cry when laid on a table or separated from the parents, older children (toddler and school-going) most often do not understand why the procedure is being performed and building up trust with them is essential using simple language that they understand, toys, candies, treats etc. in contrast to them, adolescent children may come out with worries and problems of their own and the physician should lend a patient ear to them prior to explaining the need for a biopsy procedure. Sedation can be reserved for extremely uncooperative cases where biopsy is imperative and it is advisable to involve a paediatrician in the loop – as we do in our centre. Getting parental consent and verbal assent from children between 7 to 18 years is also important. Diagnostic tests like patch test are difficult to perform for two reasons – difficulty of getting a lesion-free area of skin large enough and problems of compliance to pre- and post-patch test recommendations (limiting sun exposure, avoiding bathing). In small children, the patch test can be done in sessions to circumvent the first problem. Even simpler investigations like taking sample for a potassium hydroxide or a tzanck smear can be difficult in non-cooperative children. Non-invasive imaging modalities like MRI or CT can also be fraught with difficulties like keeping them stationary and arranging for sedation and contrast agents in specific scenarios.

4. The illicit use of steroids and antibiotics:
As it is, this is a huge problem in the general Indian medical scene, but I got to experience a different, much more sinister perspective when it came to children and general physicians giving them all sorts

of steroid-antifungal-antibiotic-cocktail, high-potent halogenated steroid formulation empowered by salicylic acid) and unwanted use of antibiotics for simple inflammatory skin conditions have all paved way for children developing side effects from steroid abuse (including HPA axis suppression), chronic steroid dependence , change in morphology of the primary skin lesion, persistence of cutaneous infection, sensitization to essential antibiotics, etc. The real challenge is then to explain to the parents the danger of using these products as they seen convinced of their "magical" abilities to heal the rash. Personally, I also try to be careful how I phrase it to them, as throwing shade on another doctor's clinical judgement (which I am pretty sure was done with good intentions) just to drive home my point does not seem a sustainable way of getting things done.

1. Chronic diseases and treatment compliance:
Chronic illnesses like psoriasis, atopic dermatitis, lichen planus, vitiligo which demand long term participation from the caregivers take a toll on some families and it is sometimes difficult to give them a definite timeframe in which the condition may improve. As definitive cure is not possible in many cases, appropriate counselling (maybe multiple, spaced-out sessions) is needed for parents to reach-in terms with the disease prognosis.

2. The genodermatoses conundrum:
In the part of India where our setup is, consanguineous marriages are in vogue and as a result, there is no shortage of genodermatoses that we encounter on a regular basis in our OPD. As most of those conditions lack a definite cure and relies mostly on supportive management, making the parents have clear understanding of prognosis and disease course becomes vital – and the counselling sessions can exceed beyond the first visit. My experience with talking to parents of an Epidermolysis Bullosa-afflicted newborn has taught me a lot on how difficult the process is – as all our theoretical know-how mean nothing in face of real human conversation with parents who are worried about their child's future. Another important aspect is to speak to parents about genetic testing for diagnosis -which can prove beneficial for the child in the long run and to plan for prenatal diagnosis in future pregnancies. The implication for prenatal diagnosis is also widely variable based on the inheritance pattern of the disease in question and parents' desires. Though acceptance rates for genetic testing have been generally low, we have seen current generation of parents being more open to undergoing such tests. Giving them a realistic picture, while not sounding totally hopeless is a challenging task even for someone well-seasoned. I feel improving our own personal understanding of the diseases and observing how our seniors handle themselves in such scenarios can help us learn better.
Below listed are some (national and global) support groups that parents and patients can contact for assistance in management of their conditions:

-Support groups for rare genodermatoses in India:
a. DEBRA India and Centre of Human Genetics (Bangalore) – Epidermolysis Bullosa
b. MERD India Foundation – for Metabolic Errors and Rare Diseases Organization of India
c. IORD (Indian Organization of Rare Diseases) support group for Congenital Ichthyosis

- International support groups
a. DEBRA International
b. XPFSG – Xeroderma Pigmentosum Family Support Group
c. CLOVES Syndrome – clovessyndrome.org
d. FIRST – Foundation for Ichthyosis and Related Skin Types
e. ISG – Ichthyosis Support Group (United Kingdom)

These were some of the challenges that I have faced in my limited time in pediatric dermatology. From what I have experienced thus far, I have realized that dealing with pediatric patients calls for a lot of patience and commitment from the dermatologist. Many a times we have to work closely with the paediatrician or paediatric surgeon – thus highlighting the importance of a good teamwork. Understanding individual patient problems, tailoring the dose and formulation of the medicine to each individual child and factoring in parents' concerns, participation and compliance issues, caregiver burnout are all important aspects in the daily practice of a paediatric dermatologist. Surely problems exist, but I guess as we learn to navigate through them, we emerge as better clinicians.

Antibiotic dosing for the pediatric age group

Author: Malathi Muniswamy

Antibiotics in pediatric dermatologic therapy are indicated for:

- Antimicrobial role - Skin and soft tissue infections; toxin mediated disorders like Staphylococcal scalded skin syndrome, scarlet fever, toxic shock syndrome; erythrasma; cutaneous anthrax; ecthyma gangrenosum; rickettsial infections; meningococcal infections, etc – beta lactam group of antibiotics (penicillins and first generation cephalosporins) and clindamycin (for toxin mediated disorders) are preferred.
- Anti-inflammatory/immunomodulatory role- psoriasis; chronic bullous dermatosis of childhood; pityriasis lichenoides chronica, acne vulgaris, etc - tetracyclines and macrolides are preferred antibiotics for this indication.

Fundamental precautions to be followed in pediatric antibiotic dosing:

- Dosage calculation based on age bands is context specific and result in a significant proportion of children receiving doses outside the recommended range while weight banded dose selection is applicable across populations and considered the most practical choice when exact weight is available. Hence it is essential to assess the child's recent weight and calculate the appropriate pediatric doses. However, exact weight-based dosing might not fit well with fixed dose combinations.
- Always verify dosages from pediatric references – Indian Academy of Pediatrics pediatric formulary; ICMR guidelines; national centre for disease control; MicroGuide(R) SCAN Antibiotic Prescribing Guidelines App.
- Antibiotic choice should be guided by the culture sensitivity report and local resistance patterns.
- Dose adjustment needs to be done in conditions associated with dehydration, renal and hepatic dysfunction.
- In immunocompromised children, higher doses for a longer duration are required
- For conditions like undrained abscess, higher doses will be required to achieve tissue concentration.
- Need to pay attention to the patterns of antibiotic action if "Time dependent" (beta lactams, macrolides) or "concentration dependent" (fluroquinolones, aminoglycosides) and accordingly focus on increasing "frequency" or "dose" respectively.
- First generation cephalosporins (cephalexin) and penicillin group of antibiotics are considered as first line treatment options for Skin and soft tissue infections. Amoxicillin, amoxiclav are preferred for Streptococccal infections; Cloxacillin, Cephalexin are preferred for Staphylococcal infections (MSSA); Co-trimoxazole, doxycycline, clindamycin and linezolid for Methicillin resistant Staphylococcal infections (MRSA).
- Flucloxacillin and dicloxacillin have better absorption and better availability than cloxacillin; Dicloxacillin has lesser hepatic adverse effects while flucloxacillin has lesser renal adverse effects.
- Tetracyclines are contraindicated for routine use in children less than 8 years due to their association with permanent tooth discoloration. Doxycycline with its decreased affinity for calcium binding has the lowest incidence of tooth discoloration and can be safely given for children for difficult-to-treat infections with limited alternative therapies for a shorter treatment duration of 7 to 10 days.
- Fluoroquinolones are contraindicated in children due to reports of fluoroquinolone-induced arthropathies and black box warning of tendon rupture and its potential for developing antibiotic resistance. However, with limited reports and controversies on safety in children, use of fluoroquinolones can be limited to treatment of infections for which no safe and effective alternative exists.
- Linezolid can result in thrombocytopenia even with shorter duration of therapy (less than two weeks) and hence need monitoring.
- Tetracyclines and macrolides are given at half of the antibiotic dose for anti-inflammatory effect.

Drug dosage of commonly used antibiotics in pediatric dermatologic therapy:		
Antibiotics	**Dose**	**Oral Formulations**
Penicillins		
Penicillin V	40–50 mg/kg/day in 3 divided doses	Tablet 250mg/500mg Oral Suspension, powder for suspension
Amoxicillin	50 mg/kg/day po in 3 divided doses	Dispersible tablet, Capsule 250mg/500mg Oral Suspension, powder for suspension 5ml = 125mg/200mg/250mg/400mg 1ml=100mg
Amoxiclav	25 mg/kg/day of the amoxicillin component in 2 divided doses	Tablet 375mg; Dispersible tablet 228.5mg Oral Suspension, powder for suspension, drops 5ml =156.25mg/228.5mg/312.5mg/457mg 1ml=62.5mg; 91.4mg 0.6ml=90mg
Cloxacillin	50-100mg/kg/day in 3 to 4 divided doses	Capsule 250 mg/500mg Oral solution, oral suspension, powder for suspension 5ml = 125mg/250mg
Flucloxacillin		Capsule 250 mg/500mg Oral solution, oral suspension, powder for suspension 5ml = 125mg/250mg
Dicloxacillin	25–50 mg/kg/day in 4 divided doses	Capsule 250 mg/500mg oral suspension, powder for suspension (not easily available) 5ml = 62.5mg/250mg
Ampiclox	50 -100 mg/kg/day in 3 divided doses	Tablet 250 mg Powder for suspension 5ml=250 mg
Cephalosporins		
Cephalexin	25-50 mg/kg/day in 2-3 divided doses	Dispersible Tablet, Capsule 250mg; 500mg Oral suspension, powder for suspension, drops 5ml = 125mg/250mg 1ml = 100mg
Cefadroxil	25-50 mg/kg/day in 2-3 divided doses	Oral suspension, powder for suspension, drops 5ml = 125mg/250mg 1ml = 100mg
Cefazolin	50–100 mg/kg/day in 3 divided doses	Parenteral formulation of first generation cephalosporin
Macrolides		
Erythromycin	30–40 mg/kg/day in 4 divided doses	Tablets, dispersible tablets 125mg/250mg/500 mg Oral suspension, powder for suspension, drops 5ml=125mg/250mg 1ml=100mg
Azithromycin	12 mg/kg/day	Tablets 125mg/250mg/500 mg Dispersible tablets 100mg/250mg Oral suspension, powder for suspension, drops 5ml=100mg/200mg 1ml=100mg
Others		
Clindamycin	20-40 mg/kg/day in 3-4 divided doses	Capsules 75mg/150mg/300mg Powder for suspension 5ml=75mg
Co-trimoxazole TMP-SMX	8 mg/kg plus 40 mg/kg/day in 2 divided doses	Tablets; Single strength (40mg (TMP)+200mg(SMX)) double strength (40mg (TMP)+200mg(SMX)) Powder for suspension, Oral suspension 5ml=40mg (TMP)+200mg(SMX)
Doxycycline	2–4 mg/kg/day in 2 divided doses	Capsule 100mg Powder for oral suspension 5ml=25mg/50 mg (not easily available)
Ciprofloxacin	30 mg/kg/day in 2 divided doses	Capsule 100mg Oral suspension 5ml=125mg/250 mg
Linezolid	<5 years old: 10 mg/kg q8 h 5–11 years old: 10 mg/kg q12 h ≥12 years old: 600 mg q12 h	Tablet 300mg/600mg Powder for oral suspension 5ml=100mg

Tips and tricks:

- Compliance with treatment is dependent on the taste of oral antibiotic suspensions and frequency of dosing. Choose an antibiotic that is palatable and has less frequent dosing to optimize adherence.
  - Though palatability has not always been associated with poor compliance it nevertheless makes the experience less unpleasant.
  - Reducing the frequency than that recommended especially for the antibiotics associated with time dependent killing (beta lactams, macrolides) can result in clinical failure.
- Whenever possible, encourage the use of tablets instead of suspensions and guide parents on how to help children swallow pills.
  - Liquid antibiotic preparations are the most flexible to dose, but measuring small volumes can be inaccurate by the parents and hence paediatric doses are prescribed as the smallest volume that can be reliably measured by parents with the provided cups or spoons for practical purposes resulting in medication errors. Balancing against the largest acceptable single dose volume for an unpalatable medicine is also challenging. Hence syringes can be recommended for accurate dispensing than dosing cups or spoons.
  - Liquid formulations need to be refrigerated and are cumbersome to transport and store but are palatable due to addition of sucrose as a sweetening agent.
  - Though dispersible tablets are children friendly due to masking of taste with addition of sweeteners and flavors, they cannot be divided sufficiently to produce exact doses for all children.
- Be cautious of decimal points and dosage units as the dosage varies based on the formulation and the brands. So, it is a good practice to mention the dose in the prescription along with the volume of suspension or number of tablets and to countercheck the dose with the formulation and brand the parent has bought or give appropriate instruction to the pharmacist.
-

Considerations for Antibiotics use in neonates:

- **Individualized Treatment Approach:** Tailoring treatment based on factors such as disease extent, gestational age, weight, renal function, and comorbidities is crucial since evidence-based guidelines specifically for neonates may be lacking. Consulting with a neonatal specialist or infectious disease specialist is recommended when selecting antibiotics for neonates.
- **Pharmacokinetic Considerations:** Maturational and non-maturational factors impact drug distribution and clearance in neonates. These factors include body water composition, protein binding, and renal maturation or impairment, emphasizing the need for careful dosing and monitoring.
- **Topical Treatment Options:** Mupirocin and fusidic acid (fucidin) are recommended for topical treatment of neonatal skin infections. However, systemic treatment may be necessary for cases with systemic symptoms or extensive lesions.
- **Avoidance of Certain Antibiotics:** Caution should be exercised when considering antibiotics like neomycin, gentamicin, polymyxin, and bacitracin in neonates due to the risk of systemic absorption, sensitization, and development of resistance. Similarly, antibiotics like fluoroquinolones, tetracyclines, chloramphenicol, sulphonamides, aminoglycosides, clindamycin and metronidazole should be avoided in neonates due to either limited safety data, known adverse effects, or potential risks to the developing neonatal physiology. It is important for healthcare providers to carefully consider the risks and benefits of antibiotic therapy in neonates and choose agents with established safety profiles whenever possible.
- **Management of Staphylococcal Scalded Skin Syndrome (SSSS):** Hospital admission for intravenous antibiotic therapy is typically required for neonates with SSSS. Careful monitoring for fluid overload and potential excipient toxicity is essential during treatment.
- **Choice of Antibiotics:** The preferred antibiotics for specific infections include penicillin for Streptococcal infections, flucloxacillin for methicillin-sensitive Staphylococcus aureus (MSSA), and vancomycin for methicillin-resistant Staphylococcus aureus (MRSA).
- **Oral Antibiotic Therapy in Neonates:** Oral antibiotics, particularly in drop formulations, can effectively achieve adequate serum levels. However, the lack of robust evidence supporting this practice underscores the need for further research focusing on clinical efficacy and safety.
- **Early Oral Antibiotic Switch Therapy:** Initiating early oral antibiotic switch therapy in neonates can offer benefits for both families and healthcare systems. Encouraging this approach as soon as clinically appropriate may help optimize outcomes.

In summary, while selecting oral antibiotics for children, one must strike a balance between simplicity and accuracy to ensure safe and effective treatment of infections while optimizing compliance and minimizing the risk of adverse effects.

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