Wynnis L. Tom
Editor

Severe Skin Diseases in Children

Beyond Topical Therapy

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Preface

Treating skin disease in children has its challenges, with fewer approved agents and supportive studies, additional time over which risks and side effects must be considered, and variable family dynamics that may affect our approach. Nevertheless, such hurdles must not be left untackled, as many children suffer from severe conditions with a significant impact on daily life and, at times, on growth and development.

The field of pediatric dermatology is moving forward in big strides, utilizing collaborative research efforts to generate advances and a stronger evidence basis for care. But as one author aptly put it, at present our approaches are more art than science, and I greatly thank all the contributors to this text for being willing to share their experience and insights on management. It is by group effort that we have put together a current portrait of systemic and other non-topical treatment options for the conditions we encounter. I myself have learned many pearls in completing this project and hope that you, the reader, experience the same.

San Diego, CA, USA — Wynnis L. Tom

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I am grateful to my mentors in dermatology and pediatric dermatology at the University of California, San Diego; Rady Children's Hospital, San Diego; and Saint Louis University, who fostered my desire and abilities to utilize systemic therapies.

Finally, my family and friends, who are my pillars of support.

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Key Points

- Phototherapy can be considered first in those with diffuse atopic dermatitis (AD) uncontrolled by topical therapies, but it may not always be feasible or effective as well.
- The main systemic agents used at this time for severe, recalcitrant AD are cyclosporine, azathioprine, mycophenolate mofetil, and methotrexate.
- Systemic steroids are limited by their side effects and mainly should be reserved for short courses to bridge to another agent; intravenous immunoglobulin and interferon-gamma are alternatives for those failing the above traditional systemic agents and/or with frequent infections.
- Considerations in choice of agent: efficacy, time to effect, cost, ease of use (i.e., convenience of administration, availability), side effect profile, and impact on other medical treatments.
- Given current therapies are mainly immunosuppressive agents, discussion of risks versus benefits is critical before initiation, and once adequate response is achieved, systemic treatments should be weaned off as tolerated.

Abbreviations

ACD	Allergic contact dermatitis
AD	Atopic dermatitis
HSTCL	Hepatosplenic T-cell lymphoma
IVIg	Intravenous immunoglobulin
MED	Minimal erythema dose
MM	Mycophenolate mofetil
PUVA	Psoralen with ultraviolet A
TPMT	Thiopurine methyltransferase

Atopic dermatitis (AD, commonly called "eczema") has been increasing in prevalence over time and currently affects about 20 % of children in developed countries [1]. While the majority is adequately managed using topical treatment regimens, a small group of patients continue to have severe, persistent disease. Phototherapy is one therapeutic option that can be used, but may not always be feasible or effective as well. Systemic agents may be appropriate for such cases, but

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their use does require careful thought and discussion.

1.1 Phototherapy for Atopic Dermatitis

The observation of clinical improvement during summer months prompted clinicians to utilize phototherapy, the controlled exposure of skin to light, as a potentially viable treatment for AD patients with persistent, widespread disease. Various wavelengths, particularly within the ultraviolet (UV) spectrum, have shown benefit for AD [2]. The presumed mechanism of action is the suppression of pro-inflammatory cytokines and molecules with induction of lymphocyte apoptosis and, additionally, inhibition of Langerhans cells and keratinocytes (in the case of UVB) and dermal fibroblasts, dendritic cells, mast cells, and granulocytes (in the case of UVA, which penetrates more deeply) [3]. With the exception of oral psoralen given with UVA (PUVA), phototherapy has the advantage of being an externally administered treatment, and thus avoids the risk of systemic toxicities. It does need to be dosed carefully to avoid excessive erythema and burning. This is usually based on an individual's minimal erythema dose (MED) and/or Fitzpatrick skin type. The risk of cataract development can be reduced with protective glasses during treatment and regular use of sunglasses that block UV light when outdoors.

Only a small number of randomized controlled trials (RCTs) have been conducted on the use of this treatment modality for atopic dermatitis. In 2007, Meduri et al. [4] systematically reviewed controlled trials in an attempt to establish therapeutic guidelines for UV phototherapy for AD. Due to variability in patient selection parameters, treatment regimens, and clinical response assessments between the nine eligible trials, meaningful conclusions were limited. Phototherapy with UVA1 (340–400 nm) appeared to be more helpful for acute flares, given faster onset and improvement typically observed within several weeks of beginning therapy (about ten treatments). However, the therapeutic response appeared to be short-lived to 2–3 months on discontinuation, suggesting that UVA1 treatment may be best suited as a bridge to another long-term maintenance therapy. The authors concluded that UVB, particularly narrow-band UVB (nbUVB, 311 nm), was more useful in management of chronic AD. nbUVB is less erythemogenic and generally more effective at clearing skin disease relative to broadband UVB (bbUVB, 290–320 nm), although some have found it at times to be more irritating [2, 4]. Two subsequent comparatives studies, however, found that UVA1 was comparable to nbUVB for chronic, moderate to severe AD [5, 6]. Unfortunately, none of the above RCTs included children.

Subsequently, Clayton et al. [7] reported complete clearance or minimal residual activity in 40 % of 50 children age 4–16 years with severe AD who received at least ten exposures of nbUVB. Those with higher MEDs were more likely to clear. More recently, Pavlovsky et al. [8] reported 75 % or greater improvement in 69 % of 36 children with mean age of 13 years treated with nbUVB for an average of 3.3 months. Overall, nbUVB is the preferred phototherapy approach because of its benefit to risk profile and lower cost. Unfortunately, complete clearance rates in AD patients are low, whereas the majority of psoriasis patients get almost complete response [3, 8, 9]. The median duration of remission is shorter with AD as well (3–5 months, compared to 20 months for psoriasis patients) [7, 8].

There are some other disadvantages to phototherapy. Administration requires frequent office visits two to three times weekly, which can be time consuming and financially burdensome for families, especially for those who live a considerable distance from clinics. Home phototherapy units may alleviate some of this burden, when able to be obtained. UVA1 units though are not widely available for home or office use at the current time. Administering phototherapy also requires patient cooperation, which may be problematic for younger children with difficulty standing alone in a confined space and/or complying with eye protection measures. Understandably, many providers are reluctant to use prolonged

courses of UV phototherapy in children, especially in those with lighter skin types, due to concerns of photoaging and future risk of cutaneous malignancies [10]. In darker skin adolescents with severe, refractory AD failing even nbUVB, oral PUVA has sometimes been used but the potential adverse effects that include nausea, vomiting, ocular toxicity, and phototoxic reactions, along with an unclear skin cancer risk, must be weighed against benefits [11]. Evidence-based, standardized guidelines regarding the use of phototherapy in children do not exist at this time.

1.2 Indications for Systemic Therapy and Pretreatment Considerations

No systemic therapy is approved by the United States Food and Drug Administration (USA FDA) for the treatment of AD in children or adults, and the most effective agents at this time are immunosuppressants. As such, patients and parents need to be consented and thoroughly counseled regarding potential side effects, as well as short-term and long-term benefits versus risks. Systemic therapy is understandably reserved for only the most severely affected patients with the greatest burden of disease and morbidity. Such patients continue to have considerable disease despite multiple attempts to optimize topical and adjunctive treatments for epidermal barrier repair and control of the associated inflammation and itch: they suffer from frequent, severe flares despite high-potency topical corticosteroids (Fig. 1.1), have recurrent secondary infections, endure poor sleep and quality of life with constant itch and scratching (Fig. 1.2), and/or experience negative effects on behavior and school performance. Other candidates are those with a chronic need for potent or very potent topical steroids, who have experienced or are at risk for adverse effects from excessive use (i.e., striae, atrophy, dyspigmentation). They may have failed phototherapy or not be able to receive this treatment, as discussed above. Hospitalization may have been necessary to manage severe flares and/or secondary infection. While effective for acute flares [12], prolonged or repeated inpatient management is not feasible as long-term therapy at most centers given the high cost.

Fig. 1.1 12-year-old female with repeated severe flares despite trial of multiple mid- and high-potency topical steroids and adjunctive treatments

Such refractory AD would be unusual before the age of 3 years. Younger children can often be managed with use of techniques such as soaking and immediate smearing of topicals, applying wet wraps to increase penetration of topical agents and provide a physical barrier, and covering of the hands and feet to limit scratching [13]. In older children, however, it becomes more difficult to impede their ability to scratch despite attempts to coach, and they are much more agile at removing coverings and wraps.

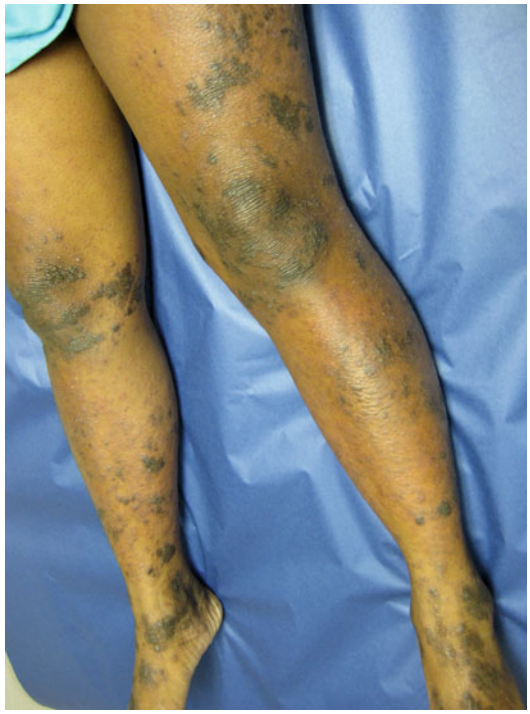

Fig. 1.2 A 10-year-old female with very lichenified plaques due to chronic severe disease

It is important to consider if the diagnosis of AD is correct in cases of refractory disease. Occasionally, a skin biopsy may be indicated to confirm the diagnosis and to rule out other entities such as psoriasis or cutaneous lymphoma. In addition, allergic contact dermatitis (ACD) can be a confounding factor [14]. The compromised barrier allows easier penetration of irritants and allergens, which can cause their own eczematous eruption and/or exacerbate the underlying AD. ACD should be considered if there is worsening disease with increased areas of involvement, lack of response to traditional therapies, lesions at sites more prone to ACD (such as the eyelids, face, neck, and hands), new-onset dermatitis, or presence of dyshidrosis [15]. Common allergens include nickel, neomycin, fragrances, dyes, and lanolin [16, 17]. Some patients become unable to use topical steroids due to the development of contact allergy to one or more topical steroid classes. Cases have been reported of spared use of systemic agents after epicutaneous patch testing revealed significant allergens and their avoidance was successful [18]. Unfortunately, many with severe disease do not have areas of non-inflamed skin to allow accurate patch testing and thus, the suspicion of allergic contact dermatitis as a major component needs to be weighed relative to the severity of the original condition. Options include empiric avoidance of major allergens, including fragrances and formaldehyde, to see if there is improvement [14] or use of a short course of a systemic agent followed quickly by an attempt to patch test, but these are not often easy feats to accomplish.

As provider, patient, and parent can all attest, topical management of atopic dermatitis is time consuming, and parents and children with severe, chronic disease are often understandably frustrated when such efforts are not rewarded with substantial clinical improvement. Many have lost faith in the ability of physicians to control the disease and need re-establishment of the patient-provider relationship. After garnering the agreement of all relevant parties to institute systemic therapy, it is important to set appropriate expectations as to response and need for recurring follow-up evaluations. While the successful use of systemic agents can be a rewarding experience, it is not necessarily easier than topical therapy alone. Patients require frequent blood draws, clinic visits for close monitoring, and will likely need to continue intensive topical therapy, at least initially. Systemic therapy is not a substitute for daily management of disease with topical emollients and other therapies, and should not be considered a "short cut." Because most systemic agents are pregnancy category C, D, or X, discussion of appropriate contraceptive methods and baseline and periodic pregnancy testing are needed for females of childbearing age.

1.3 Available Systemic Agents

Agents that will be discussed here include systemic steroids, cyclosporine, azathioprine, mycophenolate mofetil, methotrexate, intravenous immunoglobulin, interferon-gamma, and biologic agents. The literature regarding the use of these agents in children is limited. Head-to-head

pediatric data is almost nonexistent. To date, providers have relied heavily on personal clinical experience and this is in part reflected here.

1.3.1 Systemic steroids

Systemic steroids are anti-inflammatory agents with broad effects that include inhibition of T-cell proliferation, cytokine production (e.g., interleukin (IL)-1, IL-2, interferon-gamma), antigen processing, eosinophil activity, and mast cell mediator release [19], all of which not surprisingly help alleviate the disease process of AD. One USA study showed oral corticosteroids are prescribed in one in six pediatric outpatient and emergency room visits for AD [20]. Despite their common use, only two randomized controlled trials of systemic steroids for childhood AD have been published to date, with no long-term follow-up after the 2- and 4-week treatment periods, respectively [21, 22]. One case series of seven children with severe disease given intravenous (IV) methylprednisolone (20 mg/kg/day × 3 days) did report significant clinical improvement with a sustained response lasting 3–18 months in five children [23]. No significant adverse events were observed, though two patients developed asymptomatic, transient lymphopenia.

Although short courses are effective in the immediate period, the potential benefits of systemic steroids must be weighed against the well-known adverse effects, including hypertension, mood changes, sleep disturbance, and weight gain. Arrhythmias and hypokalemia may also be seen with IV administration. Extended use is not advised, as they adversely affect linear growth in children and bone density and may lead to cataract formation [24]. Another major concern is the occurrence of a significant rebound flare upon discontinuation of therapy, as has been described in other dermatologic conditions such as psoriasis and which is often noted clinically with AD as well [25]. In general, systemic steroids should be reserved only for "crises" with intent to bridge to another systemic agent or to phototherapy, as they are not likely to allow actual long-term remission.

1.3.2 Cyclosporine

Cyclosporine is the most studied systemic agent for severe AD, including in children. It is a lipophilic cyclic polypeptide that inhibits the transcription of IL-2 and other cytokines, preferentially blocking T-lymphocyte activation. In 2007, Schmitt et al. [26] published a systematic review and meta-analysis of 15 studies (eight of which were randomized controlled trials) that included 602 patients with severe AD. Effectiveness was similar between adults and children. One advantage of cyclosporine is the relative short time of about 2 weeks to note positive effect, with approximately 55 % reduction in mean disease severity after 6–8 weeks of treatment per meta-analysis. More rapid responses were observed in patients who received higher doses (4–5 mg/kg/day). However, the likelihood of adverse effects, such as reversible elevations in creatinine, elevated blood pressure, gastrointestinal symptoms, infections, headaches, and paresthesias, also increased along with dosage increases. Adverse effects were less frequent in children, though not negligible. Some providers report that doses as high as 7 mg/kg/day for a temporary period may be necessary to effectively treat some pediatric AD patients [24, 27] but long-term monitoring data with such regimens are lacking.

Disadvantages of cyclosporine include its known toxicities on end organs, particularly the kidneys. For this reason, continuous therapy for greater than 1 year is typically not recommended by the FDA, while up to 2 years of use is approved in Europe. Additionally, patients may also have return of disease following drug discontinuation. In three studies, relapse rates were 73–86 % after a follow-up period ranging from 6 weeks to 9 months [26]. As a result, some providers have used multiple short courses of treatment instead, although it is not clear if there is increased safety with this method of intermittent dosing compared to continuous use for 1 year [28]. Hypertrichosis and gingival hyperplasia may develop with long-term use. Drug interactions also need to be considered, given cyclosporine is extensively metabolized by cytochrome (CYP) P-450 3A

isoenzymes in the liver and it also inhibits CYP3A4 and the multidrug efflux transporter P-glycoprotein. Plasma concentrations of cyclosporine may be increased or decreased by other medications (e.g., azithromycin, fluconazole, carbamazepine, St. John's wort), and it can affect the levels of other drugs as well.

1.3.3 Azathioprine

Azathioprine is a purine analog and inhibits lymphocytes, predominantly T cells, which rely on *de novo* purine synthesis. Much of the data regarding its utility in dermatology stems from its use as a steroid-sparing agent in the treatment of autoimmune blistering diseases [29]. Prior to the discovery of genetic polymorphisms affecting thiopurine methyltransferase (TPMT) activity, the major catabolic enzyme involved in thiopurine drug metabolism, azathioprine was administered by slow-dose titration with mixed clinical results and sometimes limited effect. The ability to measure TPMT levels has improved initial dosing and decreased the risk of toxic effects, particularly bone marrow suppression. Approximately 1 in 300 individuals are homozygous for low enzyme activity alleles and are not recommended to receive treatment with the drug, while 10 % are heterozygous with intermediate enzyme activity, where lower starting doses are indicated [30].

Several studies of azathioprine for severe childhood AD have been published. One retrospective study of 48 children with severe AD and normal TPMT activity showed "excellent" or "good" response in 41 patients (85 %) after 3 months of treatment [31]. Eight of the most severe cases given prednisolone at the onset of treatment with azathioprine and fifteen additional cases already on oral steroids prior to initiation of azathioprine were all successfully weaned from systemic steroids. Parents noted therapeutic benefit from azathioprine at an average of 4 weeks of treatment. No cases of neutropenia were observed and the authors suggested initiating drug at 2.5–3.5 mg/kg/day. The same authors subsequently reported successful treatment of two severe AD patients with intermediate TPMT activity using azathioprine at 1.0 and 1.25 mg/kg/day [32].

Waxweiler et al. [33] reported their experience using azathioprine and mycophenolate mofetil for 28 children with severe AD. Those with normal TPMT levels were treated with azathioprine at 3 mg/kg/day, while heterozygous individuals were treated at 1 mg/kg/day. Seventeen of 28 (61 %) patients reported "significant improvement" with azathioprine. Responders noted improvement at a mean of 5.3 weeks and were treated for an average of 14.9 months. Seven (25 %) did have lab abnormalities that necessitated an adjustment in dose, most commonly abnormal liver function tests, followed by low hemoglobin and white blood cell count abnormalities. A recent long-term prospective study showed benefit in 11 of 12 children, with only one experiencing mild transaminitis but with good response even after dose decrease [34]. Four responders treated for 13–16.5 months have had prolonged periods of remission (mild to no disease) after discontinuation, ranging from 12–26 months at time of publication.

While dosing of azathioprine according to pretreatment TPMT levels appears to significantly reduce the occurrence of myelosuppression, periodic laboratory monitoring is still required. Changes in TPMT activity can occasionally occur after therapy begins and appear to be inversely related to azathioprine efficacy; repeat assessment may be considered if a patient is not responding or there is a change in response to therapy [34]. Disadvantages of the drug include occasional gastrointestinal side effects such as nausea, indigestion, or vomiting. A hypersensitivity reaction may rarely occur. While immunosuppressants theoretically pose an increased risk of infection, such a phenomenon is difficult to assess as the severe AD population has the inherent propensity for cutaneous secondary infection. Waxweiler et al. [33] found a similar rate of skin infection with azathioprine and mycophenolate treatment. A delay of clinical improvement of 4–6 weeks appears common, making systemic steroid or intensive topical therapy necessary for some patients as they start azathioprine treatment. Finally, the risk of lymphoma and other malignancies associated with long-term use of

the medication must be discussed with families, and will be addressed in more detail below.

1.3.4 Mycophenolate Mofetil

Mycophenolate mofetil (MM) is another inhibitor of *de novo* purine synthesis and works by competitively inhibiting inosine monophosphate dehydrogenase. MM is FDA–approved for the treatment of solid organ transplant rejection in combination with cyclosporine and corticosteroids but has been used off-label by dermatologists, also primarily in the setting of autoimmune blistering diseases. Published literature regarding its use in severe childhood AD is more sparse than with azathioprine. However, the reports that have been published are relatively promising.

Heller et al. [35] reported a retrospective analysis of 14 children with severe AD treated for 2–24 months with MM. Eleven had been treated with systemic corticosteroids previously and four had failed cyclosporine due to lack of response or poor tolerability. Only one patient failed to respond to treatment; eight had greater than 90 % improvement. Improvement was noted in responders at a mean of 4 weeks, with maximal improvement between 8 and 12 weeks. Nine of 13 responders were able to significantly decrease topical corticosteroid use. One had fewer episodes of eczema herpeticum, while two had continued secondary bacterial infections. The most commonly observed side effects (10–35 %) were mild gastrointestinal upset, diarrhea, and abdominal discomfort, which did not require cessation of therapy. No substantial lab abnormalities were observed. The authors noted younger patients needed 40–50 mg/kg/day and older children and adolescents 30–40 mg/kg/day, which were both equivalent to 1,200 mg/m^2/day dosing by body surface area. Only one responder had been weaned off treatment at the time of reporting, with continued control of disease after 10 months using only topical therapy.

Twelve of the 28 patients treated with azathioprine in the retrospective analysis by Waxweiler et al. [33] were eventually transitioned to MM at a dose of 20–40 mg/kg/day. Four transitioned due to azathioprine intolerance, six had failed to respond to this treatment, and two reported a combination of both reasons. Eight of 12 (67 %) reported significant improvement with MM, with initial improvement observed at a mean of 3.9 weeks. Only one patient developed a lab abnormality (anemia) that required a dose adjustment. In general, the medication was well tolerated, with mild gastrointestinal side effects that typically improved with continued treatment. This study shows that failure of one systemic agent may not necessarily preclude the success of another.

Liver function tests and cell counts should be monitored closely, especially for the presence of leukopenia and anemia. Families should be counseled regarding the potential associated risk of lymphoma and other malignancies with use of the drug. However, as with azathioprine, such cases have yet to be described in patients using MM for cutaneous disease. MM can also have a delay in clinical improvement of 4–8 weeks, with initial systemic steroid or intensive topical therapy potentially necessary in those with severe acute disease [33]. In 2008, a warning was released regarding the development of progressive multifocal leukoencephalopathy in patients receiving MM [36]. Confirmed cases of this usually fatal demyelinating disorder due to JC virus infection were in patients with solid organ transplants (six cases) or systemic lupus erythematosus (four cases) who were also taking other immunosuppressants, including steroids, cyclosporine, tacrolimus, azathioprine, or cyclophosphamide. The risk is likely with immunosuppression in general, rather than specific to MM, given reports with other immunosuppressive drugs, although there may be more cases with monoclonal antibodies, including efalizumab and rituximab [37]. Additionally, the FDA recently mandated the Mycophenolate Risk Evaluation and Mitigation Strategy (REMS) for prescribers, pharmacists, and patients to prevent unplanned pregnancy in female patients taking any form of mycophenolate and to minimize fetal exposure to the drug. Postmarketing reports showed that exposure during pregnancy is associated with

increased risk of first trimester pregnancy loss and congenital malformations [38].

1.3.5 Methotrexate

Methotrexate interferes with folic acid metabolism and appears to have anti-inflammatory effects via increased adenosine production. It has a long history of successful use in the pediatric population for skin disease, most notably for psoriasis, as well as for connective tissue disorders. It is inexpensive, fairly well tolerated, and conveniently dosed once weekly. Additionally, while its side effect profile is long, these are well known and well described, including nausea, other gastrointestinal symptoms, glossitis/mouth sores, and the need to monitor for bone marrow, liver, lung, and renal toxicity [39]. However, the risk of malignancy is not necessarily obviated [39, 40] Liver toxicity must also be considered with long-term use, though the risk is thought to be low in otherwise healthy individuals with no underlying risk factors (such as obesity, diabetes, greater than moderate alcohol consumption, and chronic hepatitis) [41].

Unfortunately, despite much experience with methotrexate from other inflammatory dermatoses, published reports demonstrating efficacy in treating AD are few. One randomized controlled trial against azathioprine showed similar benefit for adult AD when using maximum doses of 22.5 mg/week for methotrexate and 2.5 mg/kg/day for azathioprine [42]. In 2008, one center presented a short summary of their experience with oral methotrexate in 30 children age 2–16 years [43]. They reported an effective dose typically between 0.5 and 0.8 mg/kg/week, with 50 % of patients "well controlled," two nonresponders, and the others with partial response. About 2–3 months were needed for positive effect. Overall, the drug was said to be well tolerated with only GI symptoms and transient liver function test abnormalities observed (folic acid supplementation was given). Some providers divide dosing over four consecutive days of the week for AD, but this has not consistently given better responses than weekly dosing [24, 43].

Recently, four centers in Egypt published an open-label, randomized trial comparing 20 children age 8–14 years treated with low-dose methotrexate 7.5 mg weekly to 20 treated with low-dose cyclosporine 2.5 mg/kg/day [44]. Both groups had about a 45 % reduction in disease severity at the end of the 12-week treatment period, with cyclosporine having faster onset of effect (2–3 weeks versus 3–5 weeks for methotrexate). After discontinuation of treatment, there was greater time before relapse in the methotrexate group (average of 20 weeks versus 14 weeks with cyclosporine), although the number of patients with relapse was not given. About 20–35 % experienced gastrointestinal side effects, malaise, or lab abnormalities in both groups, though all resolved by the end of the 12-week posttreatment observation period. Given this was only a short-term study, additional data is needed regarding the use of methotrexate for more extended periods to determine durability of response for severe childhood AD.

1.3.6 Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIg) is a sterile, purified antibody product manufactured from pooled human plasma and typically contains more than 95 % unmodified IgG and only trace amounts of IgA or IgM. It blocks Fc receptors on antigen presenting cells, modulates complement activation, and may downregulate T-cell activation. Indications for IVIg include immune-mediated thrombocytopenia, primary immunodeficiencies, Kawasaki disease, and HIV infection in children. Use for AD has mainly been in small case series and with mixed results [45, 46]. Most have tried 0.4–2 g/kg given monthly over 1–5 days. One RCT of administration of 2 g/kg/month for 3 months in 40 children showed significant reduction in severity during treatment and for 3 months after stopping, but unfortunately, disease relapse was observed by 6 months after discontinuation [47]. Turner et al. [48] reviewed their ten pediatric cases on long-term monthly IVIg treatment (average of 24 months, range of 6–52 months). Most had "very good" to complete response and needed

3–6 months for response. In five children, the IVIg was ceased after 18 ± 10 months without relapse and with follow-up to 4 years. One child experienced an initial clinical response but deteriorated after 2 years of ongoing treatment and subsequently responded to a higher dose of IVIg at g/kg/month (from 0.4 g/kg/month).

While Turner et al. did not note any side effects among their cases, IVIg can cause symptoms such as headache, flushing, and tachycardia, especially during infusion, along with hypo- or hypertension, serum sickness-like reaction, and transient creatinine increases [45]. Those with IgA deficiency need IgA-depleted IVIg given the rare risk of anaphylaxis. At this time, given the small amount of data and the expense of this treatment including the need for intravenous administration and close monitoring, IVIg should mainly be considered if the above more traditional systemic drugs fail or are contraindicated.

1.3.7 Interferon-gamma

Interferon-gamma (IFN-γ) is a Th1 cytokine used to reduce infection rates in patients with chronic granulomatous disease. Mononuclear cells from patients with AD have been shown to produce reduced amounts of IFN-γ *in vitro*. This observation, coupled with the known suppression of interleukin (IL)-4 by IFN-γ, prompted therapeutic trials in AD patients [49].

In a double-blind, placebo-controlled multicenter 12-week trial of 83 children and adults with severe, unremitting AD, 45 % of 40 patients receiving daily subcutaneous recombinant IFN-γ at 50 μg/m^2 achieved >50 % improvement versus 21 % of placebo-treated patients. Headache, myalgias, and chills were reported in 30–60 % of patients but seemed to improve with acetaminophen and bedtime dosing [50]. Five patients developed transient granulocytopenia, and mildly elevated LFTs were observed in seven patients. Twenty-four of an eligible 32 patients from this study subsequently were followed for 12–24 months with open-label maintenance therapy and clinical improvement was maintained in these patients [51]. In a second study, 51 patients randomized to high-dose IFN-γ (1.5 × 10^6 IU/m^2), low-dose IFN-γ (0.5 × 10^6 IU/m^2), or placebo three times per week showed decreased disease severity in both IFN-γ groups but more quickly in the high-dose group [52]. By 8 weeks, however, disease severity between the two doses was similar. Only three patients from both treatment groups discontinued therapy, two due to disease flare and one who developed transaminase elevation. Over half (54 %), however, experienced adverse effects, including lactate dehydrogenase elevation, myalgia, and mild respiratory difficulty, though effects were transient and not dose-limiting.

Some have suggested utility of IFN-γ in the setting of severe AD with frequent secondary infections, particularly with herpes simplex virus (HSV) infection or eczema herpeticum (EH) where its production is decreased [53]. In a recently published case series of five children, one treated with IFN-γ and prophylactic acyclovir had improvement in her severe skin disease and relapse on discontinuation, although EH was only demonstrated once previously [54]. A second child with frequent EH had improvement in the skin disease but continued herpes labialis; testing showed HSV resistant to acyclovir, foscarnet, and ganciclovir. The authors suggested prophylactic antivirals as the first step in management of such cases, followed by IFN-γ or IVIg in the case of failure given these are immunomodulators rather than immunosuppressants.

Disadvantages of IFN-γ include the flu-like symptoms which appear to be common. Myelosuppression and neurotoxicity are occasionally observed and require close monitoring. Hypotension and tachycardia have also been reported, though usually at higher doses. Finally, access to the drug is limited by its high cost and thus, use is rare at this time, but additional evaluation of it and IVIg would be of benefit for those with infection-complicated AD.

1.3.8 Other Biologics

As outlined above, the use of traditional systemic agents is limited by potential toxicities and

their more broad immunosuppressive effects. Theoretically, biologic agents offer a more targeted approach to systemic therapy. But agents as well as studies on their use for atopic dermatitis have been limited.

Tumor necrosis factor-alpha (TNF-α) and Th1 responses are thought to play a role in chronic atopic dermatitis, and coupled with the accessibility of TNF-α inhibitors for adult psoriasis and pediatric rheumatoid arthritis and Crohn's disease, these inhibitors have been attempted for the treatment of severe AD. Unfortunately, published case series and reports of their use for AD have been mostly disappointing [55, 56]. Furthermore, AD-like eruptions have occasionally been reported with TNF-α inhibitors for other conditions [57].

Omalizumab is a monoclonal antibody that targets the Fc portion of the IgE molecule and it is FDA approved for the treatment of refractory asthma. While elevated IgE levels are commonly observed in AD patients, some suggest the role of IgE in AD pathogenesis may be more an epiphenomenon, and clinical response to treatment does not necessarily correlate with IgE levels [49, 58]. Results of multiple case series and a prospective adult study have yielded mixed results [55, 59, 60] and with these less than promising reports, omalizumab generally cannot be recommended for AD patients at this time.

Efalizumab, a monoclonal antibody that binds CD-11a and inhibits T-cell function, was tried for 14 cases, including in one child [55]. Early reports were promising but rebound disease noted on stopping, similar to that seen with psoriasis, along with two cases of thrombocytopenia. Furthermore, the drug was removed from the US market in 2009 due to four reports of progressive multifocal leukoencephalopathy in psoriasis patients on long-term therapy. In an RCT of 43 subjects, a greater number in the mepolizumab (an anti-IL-5 monoclonal antibody) group had improvement compared to placebo, although only 22 % had over 50 % improvement by physician global assessment [61]. Rituximab (an anti-CD20 antibody affecting B cells) and tocilizumab (an IL-6 receptor antagonist) have also shown some benefit in several small series of adults with refractory disease, but tocilizumab may increase the risk of infections [62, 63]. None of these three agents have been used in children with AD.

In short, the use of biologic agents in the management of severe AD is in its infancy and nearly all tried were originally developed for other indications. New biologics specifically targeted toward the AD population are needed.

1.3.9 Other Therapies

Oral forms of the calcineurin inhibitors, tacrolimus and pimecrolimus, have been tested in two adult trials [64, 65]. Though short courses appear helpful for AD, whether long-term use has renal or other adverse effects similar to cyclosporine has not been determined. Other anti-inflammatory agents tried include peroxisome proliferator-activated receptor (PPARs) agonists and phosphodiesterase inhibitors [66, 67]. None, however, have pediatric data to support their use at this time.

1.4 Administration and Monitoring

Given experience with their use for other dermatologic conditions and available data to date specific to AD, the major drugs utilized at this time are the traditional systemic agents: cyclosporine, azathioprine, mycophenolate mofetil, and methotrexate. Recommended dosing, monitoring labs, and common adverse effects for these four drugs are in Table 1.1.

When determining the choice of medication for the patient with severe AD, one must consider the agent's efficacy, time to effect, cost, ease of use (i.e., convenience, availability), side effect profile, and impact on other medical treatments. As reviewed, the risks with long-term use and rebound flare with systemic steroids make them mainly short-term bridging agents to other therapies. For the severe, acutely flaring patient, cyclosporine can provide fast onset of effect, but there may also be return of disease after courses with need to plan for a second agent or phototherapy. Azathioprine and MM allow longer courses of

Table 1.1 Recommendations on the use of cyclosporine, azathioprine, mycophenolate mofetil, and methotrexate for atopic dermatitis in children

Drug	Recommended dosage	Recommended monitoring[a]	Major side effects
Cyclosporine	4–5 mg/kg/day to start	CBC with diff, liver function tests, BUN, creatinine, potassium, magnesium, uric acid, fasting lipids at baseline and weeks 4, 8, and 12, then every 8 weeks (resume every 4 weeks with dose increases)	GI upset, vomiting, headache, paresthesia, myalgia, elevated blood pressure, hypertrichosis, gingival hyperplasia, renal dysfunction, myelosuppression
	Maximum: 7 mg/kg/day (not for prolonged periods)	Blood pressure weekly for the first month, then every 4 weeks	
Azathioprine	If normal TPMT: 2.5–3.0 mg/kg/day to start	Red blood cell TPMT activity at baseline, consider repeat if non-response or change in response [34]	GI upset, vomiting, diarrhea, fatigue, myalgia, hypersensitivity reaction, pancreatitis, pneumonitis, myelosuppression
	If intermediate TPMT activity:1 mg/kg/day to start	CBC with diff, liver function tests, BUN, creatinine at baseline and weeks 2, 4, 8, and 12, then every 8 weeks (resume every 4 weeks with dose increases)	
	Maximum: 4 mg/kg/day		
Mycophenolate mofetil	30–40 mg/kg/day to start	CBC with diff at baseline and weeks 2, 4, 8, and 12, then every 8 weeks (resume every 4 weeks with dose increases)	GI upset, diarrhea, fatigue, headache, possible increased risk of viral infections, myelosuppression
	Maximum: 1,200 mg/m^2 body surface area	Liver function tests every 4 weeks × 3, then every 12 weeks	
Methotrexate	0.5 mg/kg/week up to 15 mg/week to start	CBC w/diff, liver function tests at baseline and weeks 4, 8, and 12, then every 8 weeks (resume every 4 weeks with dose increases)	GI upset, diarrhea, fatigue, stomatitis, hepatotoxicity, pneumonitis, pulmonary fibrosis, myelosuppression, teratogenicity (category X)
	Maximum: 0.7 mg/kg/week up to 25 mg/week (generally not more effective to go higher)	BUN, creatinine at baseline	
	Folic acid can reduce GI side effects, subcutaneous dosing sometimes helpful		
Patients should have recent negative tuberculosis testing prior to starting systemic therapy and testing repeated periodically during treatment			
Live vaccines should be avoided during treatment			
Females of childbearing age should have baseline and periodic pregnancy testing and appropriate contraceptive counseling			

CBC complete blood count, *diff* differential, *BUN* blood urea nitrogen, *TPMT* thiopurine methyltransferase, *GI* gastrointestinal

[a]Based in part on the protocol of an ongoing observational study by the Pediatric Dermatology Research Alliance Inflammatory Skin Disease Collaborative [80] (ClinicalTrials.gov, study NCT01447381; author is a PI/member)

treatment and potentially, more prolonged control. But they do have slower onset, and severely flaring patients may need prednisone or cyclosporine as an initial agent to provide some relief while awaiting their effect. Methotrexate may even be a little slower to provide clinical improvement and there is less supportive information for its utility for AD, but practitioners often have the most comfort with administering this drug in children.

When the mutual decision is made to start any of these systemic agents, it is important to inform

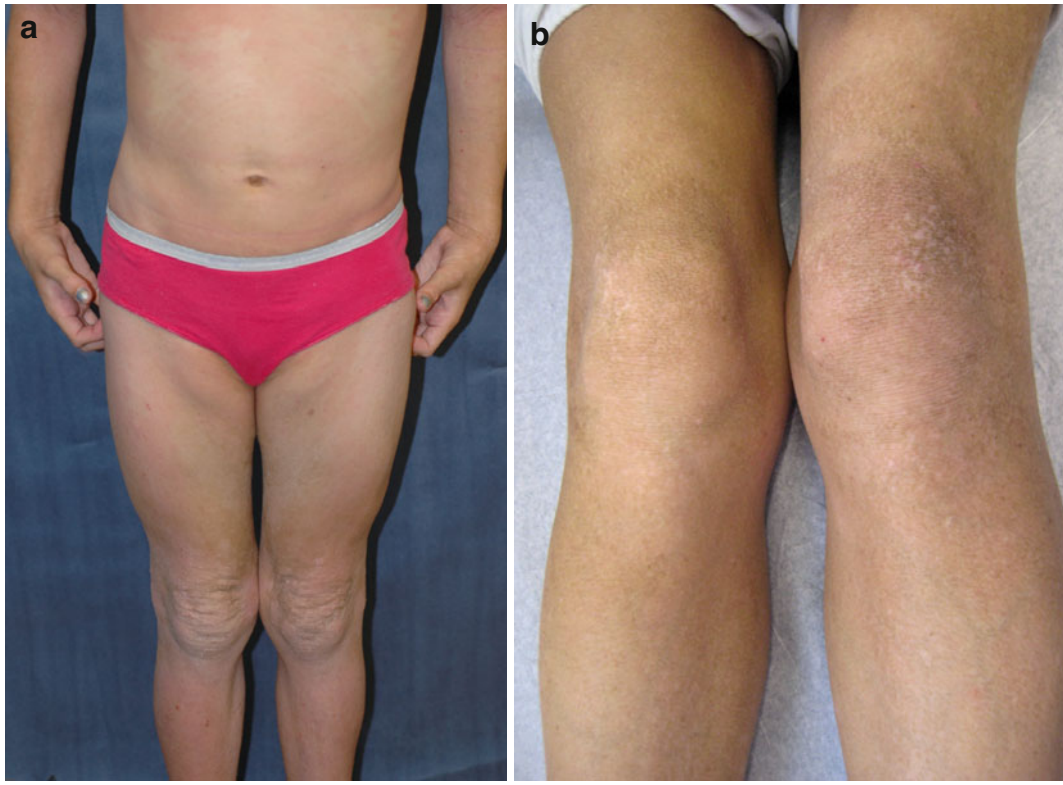

Fig. 1.3 Improvement of the 12-year-old, (**a**) first in part with azathioprine and then (**b**) subsequent mycophenolate (with mainly post-inflammatory changes, some residual scarring, and mild lichenification). She was treated for 2.5 years total with minimal disease 12 months after discontinuation

the patient's primary care and other providers, as this may impact their treatment of other conditions and adds the need to consider drug interactions. Vaccinations should be completed in advance of starting systemic therapy, and all live vaccines avoided during the treatment period. Those with a history of herpes simplex virus infections may need consideration of concomitant suppressive therapy. While systemic immunosuppressive agents theoretically pose an overall increased risk of infection, this is difficult to separate from rates due to the disease itself, and cutaneous infections may also lessen once the underlying skin condition is well controlled [30, 34, 53]. But for those failing the traditional systemic agents or with frequent infections, IVIg or IFN-γ may be alternative therapies to consider.

1.5 Duration of Therapy and Risk of Malignancy

The hope in using systemic agents in patients with severe AD is to induce a lasting remission, especially in cases where disease appears non-resolving. This appears possible based on case reports and series (Figs. 1.3 and 1.4 show additional examples) [31, 34, 54], though difficult to prove definitively as long-term comparative studies to natural course are not very feasible.

Duration of treatment is based on patient response, drug tolerability, and the risk of potential side effects associated with long-term use. Of these, the possibility for an increased risk of malignancy due to therapy is the greatest concern for both providers and parents. The cancers most

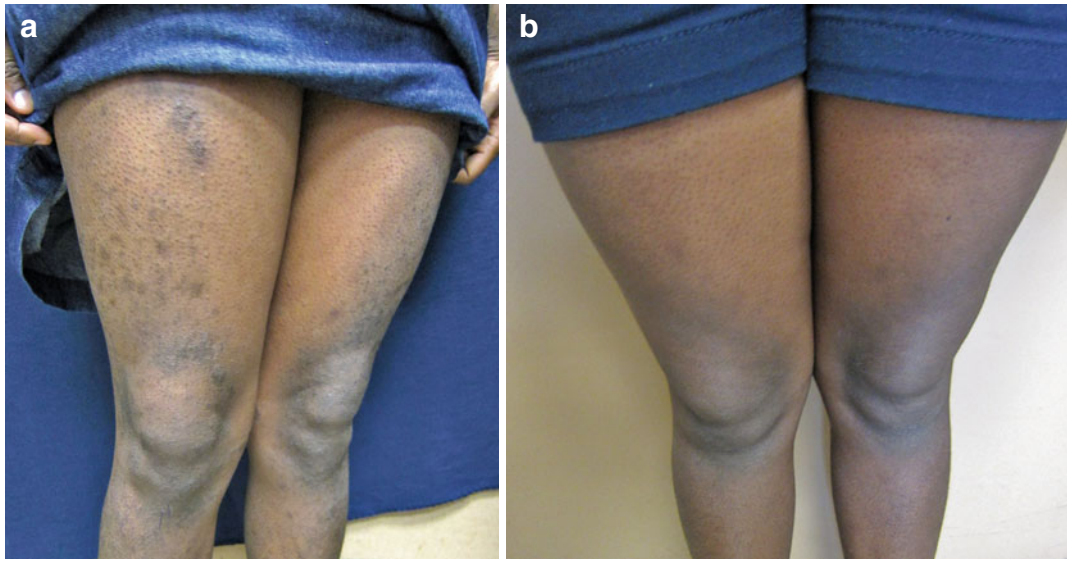

Fig. 1.4 The 10-year-old patient had much improvement (**a**) by 8 months of azathioprine therapy and (**b**) with near reversal of lichenification at the end of 19-month course. Now with very mild disease 5 months posttreatment

associated with chronic immunosuppression due to these drugs are lymphomas and lymphoproliferative disorders, along with skin cancer. Risk is related to dose and duration of immunosuppressive treatment, along with skin type and sun exposure for cutaneous carcinomas [68]. As mentioned earlier, systemic steroids and cyclosporine have other adverse effects that typically self-limit their duration of use. The risk for malignancy is therefore more applicable to the other three traditional systemic agents – azathioprine, mycophenolate, and methotrexate – as they can be administered for longer periods, although use of cyclosporine still carries these concerns, particularly if used beyond the recommended period [69].

Data from treatment of rheumatoid arthritis and connective tissue disorders suggest a greater risk of post-transplant type (usually Epstein-Barr virus-associated B cell) lymphoma after 5–6 years of treatment with azathioprine [29, 68]. This type of lymphoma has been associated with mycophenolate use for lupus and other autoimmune conditions, methotrexate use for rheumatoid arthritis, and several cases have been reported in psoriasis patients treated with methotrexate [68, 70–72]. While difficult to extrapolate from one disease population to another, these are all inflammatory/immune conditions that appear to themselves confer a mildly increased risk of lymphoma. A retrospective cohort study from the UK indicated an increased incidence of cancer overall, and lymphoma specifically, in patients with AD due to having the skin disease [73], but there is no information regarding the effect of systemic treatments.

A recent warning has also been released for azathioprine and TNF-α inhibitors due to cases of a rare but often lethal type of non-Hodgkin's lymphoma called hepatosplenic T-cell lymphoma (HSTCL). Most cases (73 %) of HSTCL occur *de novo* in otherwise healthy individuals. But some have developed post-transplant and in patients with inflammatory bowel disease [74]. Crohn's disease patients with severe disease co-treated with TNF-α inhibitors and azathioprine appear to be most at risk (median duration of treatment at time of lymphoma was 5.5 years, range 1–13.5 years). Sixteen cases have been reported with azathioprine or 6-mercaptopurine without concomitant TNF-α inhibitors, but all were after at least 3 years of therapy (median duration of treatment 6 years, range 3–17 years) [75]. Also,

two cases of HSTCL have been reported with methotrexate in conjunction with TNF-α inhibitors for rheumatoid arthritis and one with systemic steroids and methotrexate given for Sjögren's disease [76, 77]. No cases of HSTCL have been reported thus far with the use of azathioprine or methotrexate for AD, nor with psoriasis where methotrexate is sometimes prescribed in combination with TNF-α inhibitors. While similar reports of this particular type of lymphoma have not been documented with mycophenolate, use of this agent for Crohn's disease has been more limited to date and may influence the absence of cases. At least in the transplant population, mycophenolate shows similar to a slightly decreased overall malignancy risk relative to azathioprine, depending on the study [78, 79].

Based on the above, it is prudent to say that once adequate control of AD is reached over several months to a year, systemic treatments should be weaned off as tolerated. Patients and parents should be counseled about the theoretic risk of developing a malignancy, but that the slight risk is probably even smaller than with other reported patient populations where continued and often higher doses of therapy are needed. Vigilant sun protective methods and sunscreen use should be made routine. Overall, to minimize risk, the use of azathioprine, mycophenolate, and methotrexate should be limited to 2–3 years in duration, although concrete evidence to support these recommendations is needed.

Conclusion

Systemic therapies can be helpful for severe, refractory cases of AD, but much more information is needed on their appropriate utilization and long-term benefits and risks. Other than the 12-week trial by El-Khalawany et al. [44] on low-dose methotrexate versus low-dose cyclosporine, there is little head-to-head information by which to compare current agents. A multicenter observational study is underway to assess dosing, response, and long-term safety of cyclosporine, azathioprine, mycophenolate, and methotrexate [80], but controlled drug trials are sorely needed. Even in adults, only several RCTs have been performed and were also short term. Ultimately, the goals should be to develop more specific therapies based on the growing knowledge of AD pathogenesis, followed by rigorous, controlled studies on their usefulness for severely affected children.

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Psoriasis and Pityriasis Rubra Pilaris

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Key Points

- Psoriasis and pityriasis rubra pilaris (PRP) are both characterized by thick, well-demarcated, scaly plaques on the skin and may range from localized to diffuse disease.
- While a more rare condition, PRP is no less a burden on affected individuals than psoriasis.
- Several critical factors should govern clinical decision-making with respect to treatment, including the age of the patient, severity and extent of disease, impact on quality of life, presence of joint involvement (with psoriasis), and patient or caregiver preferences for therapy.
- When needed, treatment options include topical therapy, phototherapy, systemic agents including nonbiologic traditional agents and biologics, and a combination of these modalities; benefits, risks, and side effects need to be considered in choice of therapy.

The pathologies of psoriasis vulgaris (PV) and pityriasis rubra pilaris (PRP) are characterized by hyperplasia, hyperkeratosis, parakeratosis, and acanthosis of the epidermis, yet these are two distinct clinical entities [1]. Psoriasis has greater prevalence, affecting approximately 2 % of the world's population. The prevalence varies widely across ethnic groups, affecting only 0.45–0.7% of African-Americans but 1.4–4.6 % of the rest of the United States (USA) population [2]. Approximately one-third of cases have onset in childhood and among affected children, the median age of psoriasis onset is between 10 and 11 years, with males and females affected about equally [3, 4]. By contrast, pityriasis rubra pilaris is much rarer, affecting somewhere from 1 in 5,000 to 1 in 50,000, depending on the ethnic population [5]. The median age of onset of the most common form of childhood PRP is between 5 and 10 years, and males are more commonly affected than females in a 3:2 ratio [6]. The two conditions, their features, and management will be discussed here.

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2.1 Psoriasis

Psoriatic lesions commonly present as well-demarcated, erythematous plaques covered by silvery white scales. Lesions in children tend to be more pruritic, thinner, softer, and less scaly relative to those in adults [7]. Widespread teardrop-shaped guttate lesions on the torso, limbs, and face are another common initial pediatric presentation [2]. Key features of psoriasis include the Koebner phenomenon, in which lesions appear in an area affected by trauma; altered pigmentation with lesional clearance; and the Auspitz sign or the presence of pinpoint bleeding at the base of removed scales [4]. Although subjective, the Psoriasis Area Severity Index (PASI) employed in clinical trials, with numeration ranging from 0 to 72, attempts to standardize evaluation of the degree of erythema, thickness, and scaling of psoriatic plaques, with each summed category ranked in severity from 0 to 4, and the proportion of skin involvement in each of four body regions of head, arms, trunk, and legs ranked 0–6 [8]. The proportion of patients who experience a 75 % reduction in PASI scores (PASI 75) under a treatment regimen in question is often reported by researchers as a benchmark of effectiveness in clinical trials. Pitting of the nails, onycholysis, and subungual debris are other clinical signs of psoriasis and can aid in diagnosis [9].

2.1.1 Etiology

While it is known that psoriasis skin manifestations are mediated by episodic, autoimmune T-lymphocyte inflammation, there are multiple possible factors for the disease etiology, and no one trigger has been identified. Predisposition to the disease is largely presumed to be genetic, as up to 71 % of pediatric psoriasis cases have a familial history of the disease [10]. The psoriasis susceptibility 1 (PSORS1) locus in the major histocompatibility complex (MHC) region of chromosome six has been identified as the culprit in conveying susceptibility in up to half of all psoriasis cases, with HLA-Cw6 being the major disease allele at the PSORS1 locus that confers susceptibility to early-onset disease [2]. Other susceptibility genes have been identified, though mainly in studies of affected adult populations [11]. Among pediatric patients, the most common environmental trigger of disease onset is a *Streptococcus*-induced upper respiratory infection; potential disease exacerbation can be due to *Staphylococcus aureus* infection, but stress, trauma, and drugs, such as lithium, corticosteroids, antimalarials, trimethoprim, and sulfamethoxazole, can also be contributing factors [12]. Sunlight exposure has been shown to reduce inflammation of psoriatic skin lesions, while both the winter season and environmental and/or daily stressors exacerbate the pathology [3].

2.1.2 Subtypes

Psoriasis can affect pediatric patients in three major forms: self-limited infantile psoriasis, early-onset psoriasis, and pediatric psoriasis with psoriatic arthritis (PsA) [7]. The principal subtypes of pediatric psoriasis based on clinical manifestations include plaque-type, napkin, guttate, erythrodermic, pustular (including palmoplantar pustular), nail-based, inverse, and linear psoriasis [4, 10].

Chronic plaque-type psoriasis is the most common form, consisting of large, well-demarcated, symmetrical, erythematous lesions with thick micaceous scale [4] (Fig. 2.1a). Based on a population-based incidence cohort study of patients under 18 years of age in the Midwestern United States, plaque-type psoriasis accounts for 73.7 % of pediatric cases, and the most commonly affected sites are the extremities (59.9 %), scalp (46.8 %), and trunk (35 %) [13]. Other specifically affected areas include the elbows, knees, umbilical region, and buttocks [4].

The subtype most common among infants under 2 years of age is psoriasis affecting the diaper area, which can be particularly severe and be localized or with disseminated lesions elsewhere. These clinical findings may precede later plaque-type or other forms of psoriasis in children [10]. Napkin psoriasis in the diaper region of infants is characterized by bright- to dull-red, smooth or minimally scaly erythema [9].

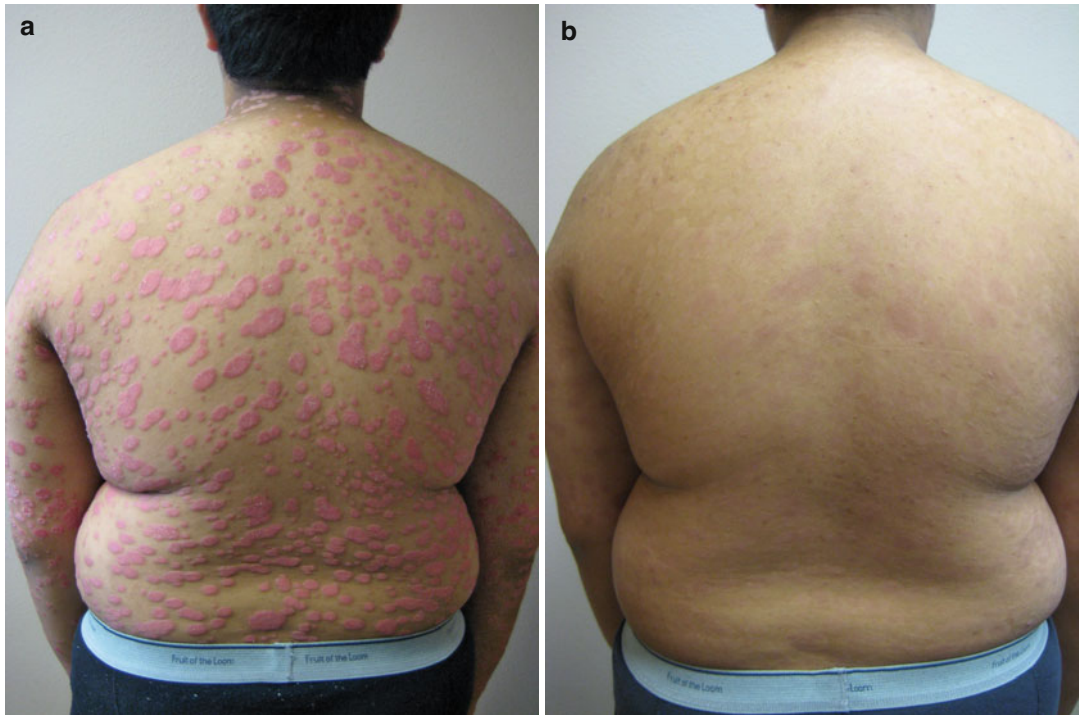

Fig. 2.1 A 14-year-old male who developed (**a**) widespread plaque psoriasis over 3 months. Given continued progression during a trial of topical therapy, methotrexate was started at 15 mg Qweek (0.15 mg/kg/week). (**b**) The patient had excellent response after increase to 20 mg Qweek (0.2 mg/kg/week), with mainly residual hyperpigmentation and only a few small plaques at 4 months of therapy. He was then tapered off methotrexate and transitioned to phototherapy for the lesions that returned (though less severe)

Much more prevalent among children than adults, guttate psoriasis presents as multiple small (up to 0.5 cm), eruptive round lesions, erythematous to salmon in color and located on the trunk, limbs, and face [10]. Guttate psoriasis in children, which accounts for between 13.7 and 28.9 % of pediatric psoriasis cases according to the Midwestern USA cohort [13] and a Chinese survey of 277 children with psoriasis [12], is frequently associated with recent pharyngitis caused by *Streptococcus* infection [10]. A 2012 Korean epidemiological study of 358 pediatric psoriasis patients showed that children under 13 years of age manifest more severe guttate and pustular lesions and with greater frequency than adolescents between 13 and 18 years of age [3].

Infrequently, children can be affected by erythrodermic psoriasis, marked by hyperemia-induced redness, edema, desquamation, skin thickening, and systemic pathology, including fever, malaise, and resultant dehydration and toxicity [9, 14]. Similar systemic symptoms accompany the rare pediatric cases of von Zumbusch generalized pustular psoriasis (GPP), in which the child is covered with widespread annular plaques studded with pustules [15]. In other cases, pustules may be localized to extremities or palmoplantar regions [10]. Nail-based psoriasis is marked by nail pitting, oil spots, and subungual hyperkeratosis and is noted as trachyonychia in some studies when psoriatic lesions do not disseminate beyond the nails [4]. Pediatric patients with inverse psoriasis possess erythematous, occasionally macerated thick plaques occurring in skin folds, including the postauricular region, lips, axillae, inframammary folds, naval, intergluteal crease, groin, and/or genital region [4]. Finally, in exceptionally rare instances, children may present with Blaschko line-distributed lesions along the arms and trunk, characteristic of linear psoriasis [10].

One severe complication of psoriasis is psoriatic arthritis (PsA), which is arthritis concurrent with psoriasis or at least in the presence of nail pits, onycholysis, or dactylitis and a history of psoriasis in a first-degree family member [16]. Pediatric PsA is heterogeneous in its presentation, such that early-onset PsA peaks between ages 2 and 3 years and resembles other subtypes of ANA-positive early-onset juvenile idiopathic arthritis (JIA) and late-onset PsA peaks between ages 10 and 12 years, resembling spondyloarthritis [16]. While early-onset PsA likely has an autoimmune etiology, it is hypothesized that late-onset PsA involves autoinflammatory activation at the synovial-entheseal complex. The entheses are subjected to chronic biomechanical stressors, which cause small injuries and subsequent release of damaged extracellular matrix fragments that activate macrophage-derived inflammation of the synovium and local arthritis [16]. While PsA is less common in children relative to adulthood populations, this diagnosis should be considered in the differential diagnosis of pediatric arthritis and requires non-topical, relatively powerful systemic therapy such as methotrexate or biologics [4, 17].

2.1.3 Treatment

Several critical factors should govern clinical decision-making with respect to psoriasis treatment, including the age of the patient, factors pertaining to his or her quality of life, disease severity/PASI score, and patient or caregiver preferences for therapy [18]. Current options for the treatment of pediatric patients with psoriasis include topical therapy, phototherapy, and, for moderate to severe cases, nonbiologic systemic therapy, biologic systemic therapy, or a combination of the aforementioned treatments. Systemic therapy is required for patients with severe or refractory plaque, pustular, or erythrodermic psoriasis and PsA [9, 17]. Both topical and systemic therapies are used across all age groups among pediatric psoriasis patients. However, UVB light therapy and biological therapy are most commonly prescribed for psoriasis patients over the age of 5 years [19].

2.1.3.1 Phototherapy

There are three major options for therapeutic light use in a physician's office, including broadband ultraviolet B (BB-UVB, 290–320 nm), narrowband ultraviolet B (NB-UVB 312 nm), and ultraviolet A (UVA) [9]. For nearly two decades, BB-UVB or NB-UVB radiation therapy has been utilized in psoriasis management, particularly in cases of plaque-type or guttate psoriasis disseminated over the body and unresponsive to coal tar, topical steroids, other topical agents, or antibiotics [4, 20]. Focal, debilitating palmoplantar disease may also benefit from phototherapy. Clearance of cutaneous disease can only be achieved with multiple, short exposure treatments, but phototherapy can be administered with success even in those as young as 14 months [20], though older children are better able to comply. A combination of topical therapies and NB-UVB phototherapy is often effective and reduces the risk of skin cancer development relative to other types of phototherapy [18].

2.1.3.2 Nonbiologic Systemics

Systemic treatment is generally utilized for cases of moderate to severe psoriasis, particularly when comorbid with pediatric PsA [19]. Current knowledge regarding the efficacy, risks, and benefits of the use of nonbiologic systemic agents stems from the long-term use of these drugs to treat other pathologies, including ichthyoses (acitretin), juvenile rheumatoid arthritis (methotrexate), and tissue rejection in organ transplantation (cyclosporine) [9]. Standardized, universal treatment guidelines for the use of nonbiologic systemic agents in pediatric psoriasis do not exist, and clinical indications for the use of these drugs are based largely on experience and anecdotal evidence rather than FDA-sanctioned indications [9]. The agents will be mentioned here in regard to situations of use, with recommended dosing and adverse effects discussed later in greater detail.

Antibiotics

Streptococcus-induced infections of the pharynx or perianal regions may trigger acute onset of severe forms of psoriasis, including the guttate and pustular subtypes, therefore antibiotics are

often an appropriate course of systemic treatment necessary to eradicate the underlying initial pathology or to treat relapses of guttate disease [18]. However, there is a lack of consensus and evidence on the effectiveness of antibiotic treatment for psoriasis [21].

Oral Retinoids

While often used for adult psoriasis given its lack of immunosuppression, acitretin is utilized to varying degrees to treat pediatric patients for cutaneous disease. When warranted, such as in cases of severe plaque, pustular, or erythrodermic psoriasis, acitretin can be used alone or in combination with topical treatment, PUVA (psoralen and UV light therapeutic combination, mainly for adolescents or adults), and/or NB-UVB or UVB phototherapy. It can be used for maintenance of lesion clearance or in emergency flare-ups [19]. Some have concerns about a negative effect on bone maturation and limit its use to older children (>10 years of age), though there is not a clear risk with the low doses administered for psoriasis [19, 22]. While in the United States, acitretin for pediatric patients is considered "second line," in Korea it was the most commonly used systemic agent at a tertiary referral center for severe cases of psoriasis in children [3].

Methotrexate

Following failure of lesion clearance with topical treatment and/or phototherapy, methotrexate can be used therapeutically in children with severe plaque, guttate, pustular, or erythrodermic psoriasis with disseminated lesions, as well as in cases of PsA [19, 22] (Fig. 2.1b). Methotrexate is a folic acid antagonist, so the standard recommendation is to administer a concurrent folate supplement to decrease gastrointestinal and hematologic side effects. Methotrexate use among children is not commonly employed in mild cases given the multisystem adverse effects that may be incurred and the need for close monitoring, including blood cell counts and the liver [18].

Cyclosporine

An immunosuppressant, cyclosporine can also be administered to pediatric patients to treat severe plaque or guttate psoriasis, for maintenance of lesion clearance, or in emergency flare-ups [19]. Some studies have questioned the efficacy of cyclosporine in rare or unusual presentations of pediatric psoriasis, including neonatal erythrodermic psoriasis, acral pustular psoriasis, generalized pustular psoriasis, PsA, and very severe erythrodermic psoriasis [23]. Cyclosporine does have the advantage of relative rapid onset of effect, but as will be further discussed, use is generally not recommended to exceed 1–2 years [22].

Fumarates

Although oral fumarates are not currently used for the treatment of psoriasis in the United States, they have been legally used in Germany and some other European countries since 1994 [24, 25]. They are mentioned here given recent clinical trials examining their use for the treatment of autoimmune diseases, such as multiple sclerosis and rheumatic arthritis.

2.1.3.3 Biologic Systemics

Biologic therapies, including antibodies and cytokine-targeted fusion proteins, constitute the preferred therapeutic agents for many autoimmune inflammatory illnesses in children. These agents, which include the tumor necrosis factor alpha (TNF-α) inhibitors etanercept, infliximab, and adalimumab, are currently most frequently employed for pediatric patients with severe plaque psoriasis but have demonstrated remarkable efficacy in treating both cutaneous and joint disease. Both risks and benefits must be considered in selection of these expensive biologics for treatment in children, as there have been only a few pediatric trials and serious adverse events have been reported, including opportunistic infections [9]. None of the currently available biologic agents for adults with psoriasis have an FDA-approved indication for childhood psoriasis.

Etanercept

Administered as a subcutaneous injection, this recombinant DNA-derived protein inhibits the pro-inflammatory TNF-α cytokine that normally promotes keratinocyte proliferation and synthesis of other pro-inflammatory cytokines, endothelial

growth factors, and adhesion molecules [26]. Of the biologic agents, etanercept has the most published literature to support its use in children [21]. A European survey of experts noted that it is the most used biologic agent for plaque, guttate, pustular, and erythrodermic psoriasis in pediatric patients and, for the majority, the first-line systemic therapy for chronic, moderate to severe plaque psoriasis, despite its European license indication for use only in patients unresponsive to or intolerant of other systemic therapies [19]. Proponent dermatologists in Europe cited the efficacy, tolerability, and safety of etanercept, relative to nonbiologic systemic treatments [19]. Etanercept is also approved by the FDA for treatment of juvenile idiopathic arthritis (JIA) in children ages 2–17 years, of which PsA is a debatable subtype [26]. One aspect of etanercept contributing to its efficacy appears to be the lack of neutralizing antibodies to this biologic, thus preventing hindrance to TNF-α binding [27]. As in adults, intermittent etanercept therapy among pediatric patients with moderate to severe plaque psoriasis appears to be effective, as demonstrated in a study of 138 participants between the ages of 4 and 17, in which no patient experienced any serious adverse effects [28]. Patient compliance to the etanercept treatment regimen is critical to long-term remission [27].

Infliximab

Administered through intravenous infusion, infliximab is a chimeric monoclonal antibody that binds and prevents action of TNF-α, suppressing inflammation in a manner not unlike etanercept [26]. Some clinicians opt to use infliximab in cases of pustular or erythrodermic psoriasis before etanercept [19]. Patients with comorbid PsA are frequently treated with a combination therapy of infliximab and methotrexate, which has been reported to be more effective and less risky in children than either treatment alone [19]. The potential for relapse of lesions following infliximab-induced remission has been documented [26]. Maintenance of PASI 75 is more common in patients negative for infliximab antibodies, suggesting that loss of the PASI 75 response may be due to the formation of neutralizing infliximab antibodies or changes in the serum infliximab concentrations [27]. In all, definitive conclusions about infliximab in children cannot be drawn based on isolated case reports, and clinical studies must be conducted prior to widespread adoption of infliximab for use in the pediatric psoriasis population [26].

Adalimumab

Provided as a subcutaneous injection, adalimumab was the first completely human anti-TNF-α monoclonal antibody developed, which blocks the interaction of TNF-α with its specific cell-surface receptors [26]. Although there are no published reports on the use of adalimumab in pediatric psoriasis, it has demonstrated rapid efficacy (relative to etanercept) and longer induction of remission (relative to infliximab) in adults with moderate to severe psoriasis, as demonstrated in randomized, controlled phase III trials [29], and it is FDA-approved for plaque-type psoriasis in adults. Finally, adalimumab is both effective and FDA-approved for children with JIA age 4 years and older [26]. These studies and case reports all suggest the promising nature of adalimumab for future use in children with severe psoriasis such as the generalized pustular form, especially with concurrent PsA.

2.2 Pityriasis Rubra Pilaris

Pityriasis rubra pilaris (PRP) is characterized by circumscribed, papulosquamous plaques, which are follicular or perifollicular and salmon in coloration, with interspersed, well-defined "islands" or "nappes claires" of clear skin [1] (Fig. 2.2). In children, PRP normally starts and persists more commonly on the lower half of the body, whereas in adults the initial presentation is often on the upper half [5]. In addition, while follicular involvement can occur in some cases of psoriasis, follicular plugging followed by development of hyperkeratotic follicular papules is more characteristic of PRP [30]. Like other areas of the body marked by PRP lesions, the patient's palms and

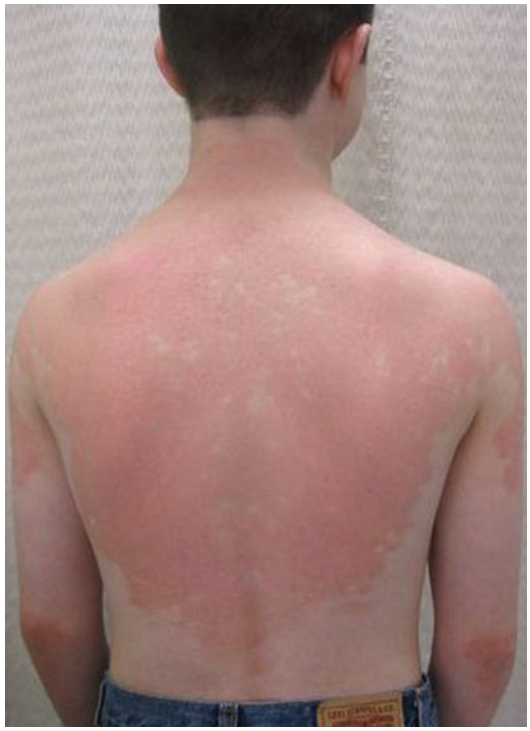

Fig. 2.2 Teenage male with typical salmon-colored plaques of PRP, with interspersed islands or "nappes claires" of clear skin

soles are frequently yellow orange in coloration and exhibit hyperkeratinization. The nails of PRP patients exhibit subungual debris but are also rough, thick, and yellow brown in coloration, sometimes with distal crumbling [1].

2.2.1 Etiology

More remains to be discovered regarding the underlying cause of PRP, though various studies have linked autoimmune diseases and infections as potential inciting factors for disease development in children [31]. Due to the dermal infiltration of eosinophils and plasma cells noted on skin biopsy, PRP may represent an inappropriate delayed-type hypersensitivity reaction in response to antigenic triggers [1]. T-suppressor spontaneous activity with diminished T-helper cell activity has been noted in children with PRP, along with hypogammaglobulinemia and isolated IgA deficiency [31]. Other common theories for the etiology of PRP involve abnormal keratins or abnormal vitamin A metabolism, specifically improper transmission through the retinol signaling pathway [30]. Evidence supporting the vitamin A theory includes the finding of PRP among patients with autoimmune hypothyroidism, in whom the transformation of carotene to vitamin A is deficient secondary to thyroid hormone deficits [1]. In addition, systemic or topical vitamin A administration has ameliorated hyperkeratotic lesions in PRP, both with and without follicular involvement [31].

2.2.2 Histologic Discrimination from Psoriasis

From an overall clinical perspective, the physical presentations of psoriasis and PRP are very similar, but histomorphologic features, as assessed from skin biopsies, can facilitate more definitive discrimination in the differential diagnosis. Almost universally, PRP uniquely exhibits acantholysis and the absence of three characteristic features of psoriasis—very tortuous, dilated dermal papillae capillaries oriented in opposition to the suprapapillary plates of the epidermis, Munro microabscesses, and polymorphonuclear neutrophils within the parakeratotic scale [30]. PRP also often has an acanthotic epidermis with alternating orthokeratosis and parakeratosis in both vertical and horizontal directions and follicular plugging. Additional notable features, but which can be seen with psoriasis as well and therefore not helpful in discrimination, include atrophy of epithelial cells, extensive inflammation of the dermis involving infiltration of lymphocytes and plasma cells, an abnormal stratum granulosum, and hyperkeratosis of the epidermis.

2.2.3 Subtypes

As in psoriasis, a variety of clinical manifestations of PRP exists, and subtyping of the disease should be approached as being a continuum, without strict adherence to categories of clinical

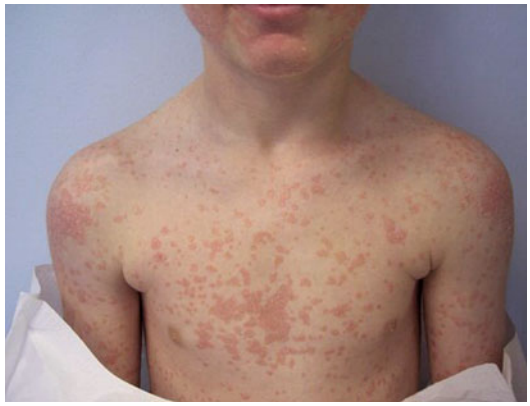

Fig. 2.3 Multiple papules with central keratotic plugs in another patient with PRP

presentation in all cases. Three main subtypes of PRP affect the pediatric population, including type III, type IV, and type V [5].

Almost identical to adult type I PRP in appearance and sharing its prognosis of 80 % spontaneous remission in 1–3 years, type III PRP usually presents initially with a single erythematous macule on the lower half of the body in children between 5 and 10 years of age [1]. As additional macules arise, these develop into papules associated with hair follicles or immediately adjacent to follicles, and a central keratotic plug can be observed [31]. Coalescence of the papules forms sheets of erythematous, acuminate papules (Fig. 2.3), and palmoplantar hyperkeratinization and scalp scaling also result in this most common, "classical" juvenile form of PRP.

Type IV PRP is also commonly observed among children, with well-circumscribed, erythematosquamous plaques localized to elbows and knees and interspersed with follicular and/or nonfollicular papules [31]. Circumscribed type IV PRP among children and young adults does not morph into a type III presentation (or type I, in the case of adults), which suggests a different pathological development; however, the reverse development has been documented [5]. Like classical type III PRP, the typical age of onset of type IV is in the later part of the first decade of a patient's life and keratotic plugging, and eventual palmoplantar hyperkeratosis is evident [31]. Scaly macular and papular involvement of the trunk and scalp may arise in a minority of cases. Patients with type IV circumscribed PRP often experience frequent remissions and relapses of lesions, with possible permanent resolution in the late teens [31].

More rarely, children can exhibit type V atypical PRP with chronic ichthyosiform lesions and occasional development of sclerodermatous changes of the fingers [5]. Typical onset occurs at birth or in the first few years of life and is marked by mild to severe erythema, follicular plugging, and keratoderma. This uncommon form of juvenile PRP likely has a genetic basis, as there is a strong familial correlation [31].

2.2.4 Treatment

Type III PRP, the most prevalent subtype of the disease among children, is acute, self-limited, and frequently resolves within a few months to a few years without intervention, suggesting that potentially detrimental drugs should not be employed in many cases of pediatric PRP [32]. However, if patients and their physicians opt for therapy, topical treatments such as topical steroids and calcineurin inhibitors, tazarotene, and keratolytics can be utilized. Systemic treatment is usually required if involvement is extensive or disease is erythrodermic or disabling [33]. Of note, there is a relative lack of both controlled clinical trials and standardized assessment of PRP severity, contributing to the variability of treatment for this disorder among clinicians [34].

2.2.4.1 Phototherapy

The alleged efficacy of phototherapy in PRP treatment is diminished relative to that in psoriasis. UVB treatment alone may be ineffective in lesion clearance, and NB-UVB may cause lesional blisters, but the combination of acitretin and NB-UVB has had documented efficacy in pediatric patients [34].

2.2.4.2 Nonbiologic Systemics

Antibiotics

The association of previous infection in some affected patients, including Group A Streptococcus infection in at least two pediatric cases, has led to speculation that perhaps focal infection plays the

role of a superantigen that triggers PRP [35]. But the evidence for use of antibiotics is limited to a few cases, and more cases are associated with viral infection, particularly HIV infection. Most do not list antibiotics as a major systemic treatment for PRP [1, 5], but cases with actual bacterial infection should be appropriately treated.

Oral Retinoids

Among PRP patients, systemic vitamin A has been employed effectively to clear lesions, reinforcing the plausibility that PRP etiology involves abnormal vitamin A metabolism [34]. However, since the development of synthetic retinoids, drugs such as isotretinoin (13-cis-retinoic acid) and acitretin have largely replaced systemic vitamin A therapy [34]. Oral retinoids are typically the first-line systemic agent for juvenile PRP [1, 31]. A Taiwanese case study of 28 patients found acitretin to be more effective in cases of circumscribed type IV PRP than the classical presentation of generalized type III PRP [33].

Methotrexate

While methotrexate alone or in combination with acitretin or etretinate for the treatment of moderate to severe cases of adult PRP has been documented as an effective second-line therapy after synthetic retinoids [34], other studies have suggested the relative inefficacy of methotrexate in PRP pediatric patients. Of 30 pediatric patients with PRP treated at the Mayo Clinic, five received methotrexate and one received azathioprine, a purine analogue and immunosuppressant, without improvement using either drug [6].

Cyclosporine

Although cyclosporine has been used in adult-onset PRP with varying success, a few reports suggest the usefulness of cyclosporine in pediatric PRP patients. A 2003 case report noted the clearance of lesions after 5 weeks in a child with type III PRP when short-term cyclosporine treatment was utilized [36].

Fumarates

Some reports note that fumarates can have a therapeutic effect on pediatric PRP. Theories on mechanism of action include that fumarates shift a Th1-like cytokine profile to that of a Th2 profile, thus suppressing inflammatory cytokines and leukocyte migration into subendothelium and promoting apoptosis among activated T-cells [25]. A 15-year-old male with a 14-year history of intractable PRP experienced marked clearance of lesions with only a few discrete lesions on his arms and legs remaining after fumarate treatment for 2 years [25]. Following withdrawal of fumarate treatment in exchange for retinoid treatment for acne vulgaris, PRP lesions reappeared quickly. Thus, fumaric acids and their ester variants may hold promise for future therapeutic developments in PRP treatment.

2.2.4.3 Biologic Systemics

As with psoriasis, both risks and benefits must be considered in selection of biologic agents for the treatment of PRP in children, and data is mainly limited to case reports.

Etanercept

While most cases of use of etanercept for PRP have been in adult patients, at least one case of use for a 16-year-old girl with nonspecified juvenile PRP demonstrated almost complete clearance with 50 mg given twice weekly and had recurrence when tapered off [37, 38]. She has since been maintained at 50 mg weekly for 4 years with a large plaque on each anterior leg, but without diffuse disease (personal communication). Another 10-year-old boy did not respond to etanercept but did respond to efalizumab (drug no longer available) [39].

Infliximab

Few reports exist regarding the efficacy of infliximab in PRP in children, but success has been documented in the treatment of adults with PRP and in one case of a 33-year-old with a 25-year history of type III PRP refractory to other therapies [38, 40].

Adalimumab

Although there are no published reports on the use of adalimumab in the pediatric PRP population, it has been successfully used in adults with PRP in isolated case reports [38, 41]. As it is FDA-approved for children with JIA [26], it is

another TNF-alpha inhibitor that could be considered for severe, refractory cases of PRP in children.

2.3 Dosing and Potential Adverse Effects of Above Therapies

2.3.1 Phototherapy

Historically, UVB lamps used for phototherapeutic treatment of psoriasis patients have used an emission spectra of 270–385 nm, peaking at about 312 nm [20]. Fitzpatrick skin-type classification should be used in determining the initial dose used in phototherapy (ranging from 0.015 J/cm^2 for type I skin to 0.04 J/cm^2 for type VI skin) and subsequent dose increments (up to 0.02 J/cm^2 for type I and up to 0.04 J/cm^2 for type VI). In Tay et al.'s [20] landmark study of 20 pediatric patients with photoresponsive dermatoses, UVB phototreatments were administered three times weekly for 6–20 weeks depending on progress of lesional clearance, followed by maintenance therapy (once weekly for 1 month, then once biweekly for 1 month, then once monthly) at the level of the last clearance dose of UVB. Cessation of phototherapy followed 90 % body surface clearance of psoriasis or PRP lesions.

In general, UVB treatment is safe and effective in many cases of psoriasis and some cases of PRP and does not incur serious side effects; however, generalized erythema with or without blistering or desquamation can occur in patients with very fair skin if treatment is not given in appropriate dosages [20]. UVB treatment should be pursued judiciously, as it may increase risk of malignant transformation in fairer-skinned patients, although the risk is lower with NB-UVB. This risk should not preclude the utilization of phototherapy, provided that precautions are taken, such as the use of protective eyewear and limiting exposure to the minimum needed [19].

Psoralens (methoxsalen) in oral, lotion, or bath salt form, in combination with UVA phototherapy (PUVA), should be reserved for exceptional cases in young children due to the increased risk of cataract and skin cancer development, although PUVA has been shown to increase photosensitivity and clear psoriatic lesions in adults [19]. At the discretion of the physician, PUVA therapy can be pursued in adolescents, again with caution, employing the use of topical psoralens rather than oral psoralens to avoid both adverse gastrointestinal effects and the need to wear protective eye gear for 1 day following treatment [18]. In summary, NB-UVB is often the optimal choice in phototherapy as its efficacy mirrors that of PUVA, but it is has a more favorable benefit-risk ratio [18].

2.3.2 Nonbiologic Systemics

2.3.2.1 Oral Retinoids

For appropriate cases of psoriasis or PRP in older children, acitretin can be administered at a dose of 0.5 mg/kg per day for at least 2 months of treatment, or in maintenance or emergencies [19]. However, generalized pustular psoriasis in early infancy has been treated successfully with a higher dose of acitretin, 1 mg/kg daily, with the dose tapered following skin desquamation and gradual clearance [15]. Finally, if clinically indicated in PRP patients, isotretinoin (13-cis-retinoic acid) should be administered at a slightly higher dose of 1–2.2 mg/kg for 3–5 months to provide benefit, though clearing may not be achieved as rapidly as with acitretin [34].

Vitamin A derivatives, including oral retinoids, have been linked to congenital anomalies of the fetus when exposed in utero. Oral contraceptives should be given to female pediatric patients of child-bearing age from 1 month prior to 1 month after isotretinoin therapy. Etretinate, the metabolite of acitretin, exhibits increased lipid solubility relative to the original compound and can be retained in fat depots for multiple months, which should be of consideration by physicians considering prescribing acitretin for postpubescent girls [19]. The biometabolic properties necessitate the concurrent prescription of oral contraceptives and for 3 years following therapy [18]. Cheilitis, pruritus, and hair loss are among the potential adverse effects associated with systemic retinoid treatment. In addition,

they have been associated with increased blood triglycerides and premature epiphyseal bone closure; thus, blood lipid panels, close monitoring of growth, and bone X-rays (long bones and spine) must be acquired by physicians who choose to prescribe oral retinoids for long-term use in pediatric patients [19, 22]. For these reasons, they are to be judiciously used in children.

2.3.2.2 Methotrexate

In children with severe, unresponsive psoriasis, a 0.3 mg/kg per week dose of methotrexate for 6–10 weeks can be administered regardless of age, with further titration upward as needed. Dosing should generally not exceed 22.5 mg per week [19].

Folic acid supplements should be administered concurrently with methotrexate treatment to ameliorate side effects that may include nausea, vomiting, headache, and gastrointestinal distress [42]. Periodic blood cell counts and liver function tests should also be performed to monitor potential blood or liver toxicity [18].

2.3.2.3 Cyclosporine

Also regardless of age, cyclosporine can be administered at 1–5 mg/kg daily for 2–6 weeks for treatment of severe psoriasis or PRP in children, for maintenance, or in emergencies [19]. To avoid renal impairment in obese children, dosing of this immunosuppressant should be based on ideal, rather than actual, body weight. The potential toxicity of cyclosporine, necessitates that the dose be tapered to the minimum yielding acceptable therapeutic benefit [18]. While a case of type III juvenile PRP refractory to other treatments exhibited clearance with 3 mg/kg/day of oral cyclosporine, a dosage as high as 10 mg/kg/day has been used successfully to treat severe psoriasis unresponsive to other treatments [36]. Pharmacokinetic reactions differ between adults and children, therefore extrapolation of adult dosing schedules to pediatric patients does not always provide for commensurate clinical response. Oral absorption may be lower, clearance more rapid, and steady state volume distribution greater among children relative to adults [23]. As a result of dose-dependent effects, pediatric psoriasis patients may require higher dosages of cyclosporine, or the doses should be administered three times daily [23].

Careful attention to blood pressure and kidney function is critical during anything other than short-term cyclosporine therapy due to the substantial risks of hypertension and renal impairment over time [36]. These risks limit the use of cyclosporine to not more than 1–2 years [22]. Carcinogenesis is another risk of prolonged use of cyclosporine, though short-term therapy as above appears to be safe [36].

2.3.2.4 Fumarates

Although currently limited to use in Europe, fumarates, marketed as Fumaderm® , have been utilized in adolescents and adults starting at 30 mg daily (one low-strength tablet), with weekly escalation up to a dose providing therapeutic benefit, with a maximum of 720 mg daily (six high-strength tablets) [25]. The 15-year-old male with PRP treated with this drug experienced clearance with a maximum of five tablets daily for 2 years [25].

In terms of potential side effects incurred, during the use of fumarates as therapy, patients experienced abdominal distension, diarrhea, or flushing, which spontaneously resolved following discontinuation [25]. Short-lived, reversible lymphopenia and eosinophilia may also result, but did not warrant withdrawal of fumarate therapy as used by Klein et al. [25].

2.3.3 Biologic Systemics

Though biologics have exhibited relative safety and efficacy aside from reports of serious opportunistic infections in some isolated cases, there is a need for longer-term studies of their effects, particularly in children [9].

2.3.3.1 Etanercept

As determined in a double-blind trial of 211 psoriasis patients between the ages of four and 17 years, 3 months of once-weekly subcutaneous injections of 0.8 mg/kg etanercept, not to exceed 50 mg weekly, followed by 6 months of

once-weekly open-label etanercept, achieved PASI 75 in significantly more patients (57 %) relative to controls (11 %) [17]. Etanercept dosed at 50 mg weekly has also been used effectively among pediatric patients with unspecified juvenile PRP [43].

Frequently self-resolving side effects of etanercept are usually localized to the site of injection [44]. However, the documented development of concurrent, selective IgA deficiency during etanercept treatment of psoriatic arthritis in an adult suggests a possible reason for the occasional occurrence of opportunistic infections with various TNF-α blocker therapies and necessitates the evaluation of the immunologic status of patients prior to beginning treatment with biologics [45]. While etanercept may be associated with an increased risk for active tuberculosis and other infections, malignancy, neurological effects of demyelination, and worsening of congestive heart failure, patients discontinue etanercept due to adverse effects less frequently than with other biologic treatments [44]. In addition, among pediatric patients, the likelihood of cancer development following etanercept treatment appears to be diminished relative to treatment with other biologics [44].

2.3.3.2 Infliximab

Among adults with psoriasis, the majority of clinical trial patients achieved PASI 75 when 5 mg/kg IV infusion of infliximab was administered at weeks 0, 2, and 6 and then every 8 weeks for maintenance therapy [27]. Case reports of children with psoriasis suggest that 3.5 and 5 mg/kg with the same dosing schedule as in adults have been used successfully in instances of recalcitrant plaque, generalized pustular, and erythrodermic psoriasis unresponsive to other treatments [26].

This chimeric monoclonal anti-TNF-α drug has demonstrated a higher incidence of and more serious adverse effects than etanercept [26]. Infliximab increases the risk of reactivation tuberculosis, congestive heart failure, and lymphoma, necessitating careful prescreening of a patient's immunologic status prior to starting treatment [26]. More thorough analysis of the effects of infliximab used for other clinical indications, such as Crohn's disease, has been conducted. In such contexts, the rare incidence of hepatosplenic T-cell lymphoma, which is usually fatal, has been documented, but all such reports have indicated the concurrent use of azathioprine or 6-mercaptopurine immunosuppressants during therapy to diminish infliximab antibody formation and infusion reactions [26]. In any case, close monitoring for potential malignancy is critical.

2.3.3.3 Adalimumab

The results of phase II and III clinical trials demonstrate that subcutaneous injections of adalimumab starting with an 80 mg loading dose and 40 mg every 2 weeks thereafter for a year are very effective among adult patients with moderate to severe plaque-type psoriasis [27]. Weight-based dosing injected every other week for 16 weeks was effective in trials with children with JIA, between the ages of 4 and 17 [26].

With a risk profile similar to those of other anti-TNF-α biologics, adalimumab can lead to local injection site reactions and positive antinuclear antibodies [26]. A double-blind phase III trial using adalimumab (with and without methotrexate) among children with JIA between the ages of 4 and 17 found infection and pain at injection site to be the most common adverse effects [26]. No deaths, malignancies, demyelinating diseases, opportunistic infections, or lupus-like symptoms were documented—the absence of which has been echoed in other larger-scale studies of children with JIA and suggests that adalimumab may be a safe, promising therapy for children with psoriasis or PRP [26].

Table 2.1 summarizes the aforementioned treatments, their uses for psoriasis, PRP, or both pathologies in the pediatric population, a suggested starting dose, and the approximate duration of therapy necessary to achieve PASI 75 in the case of psoriasis. Data for some of the biologics is largely based on extrapolated data from adult trials.

Table 2.1 Approximate dose schedule and clinical indication (psoriasis, PRP, or both clinical entities in pediatric patients) for various systemic treatments beyond topical therapy

Treatment	Initial dose	Minimum duration to PASI 75	Clinical indication
Phototherapy (UVB)	0.015–0.04 J/cm^2 3×/week (Depending on skin type)	6–20 weeks	Both
Acitretin	0.5–1 mg/kg daily	2 months	Both
Etretinate	0.5–1 mg/kg daily	3–5 months	Both
Isotretinoin	1–2.2 mg/kg daily	3–5 months	PRP
Methotrexate	0.3 mg/kg/week	6–10 weeks	Both
Cyclosporine	1–5 mg/kg daily	2–6 weeks	Psoriasis
Fumaderm®	30 mg daily[a]	3 months to 2 years	Both (not yet in the USA)
Etanercept	0.8 mg/kg weekly, up to 50 mg weekly	3 months	Both
Infliximab	3.5–5 mg/kg weeks 0, 2, and 6	10 weeks	Both
Adalimumab	80 mg then 40 mg QOW[b]	Not available	Both

[a]Adolescents only, Fumaderm® consists of dimethylfumarate and salts of monoethylfumarate
[b]Only adult dosage data available

Conclusion

A 2010 cohort study of pediatric psoriasis patients found that the overall annual incidence of the disease increased from 29.6 psoriasis cases per 100,000 children between the years 1970 and 1974 to 42.7 per 100,000 between 1985 and 1989 to 62.7 per 100,000 between 1995 and 1999 [13]. This trend suggests the increasing prevalence of psoriasis in the pediatric population, a disease with more serious ramifications for the quality of life of children than diabetes or epilepsy [3]. As in adults with psoriasis, comorbidities such as Crohn's disease, obesity, diabetes mellitus, and rheumatoid arthritis are also significantly higher in pediatric patients with psoriasis relative to the normal population [3]. The psychological implications are revealed in a 2012 cohort study where 7,404 psoriasis patients under age eighteen were compared with 37,020 control subjects of equivalent age and sex ratios. These patients were followed from diagnosis of psoriasis to first diagnosis of a psychiatric disorder [46]. This study suggested that children with psoriasis are associated with an increased risk of depression, anxiety, and bipolar disorder by 23, 32, and 55 %, respectively [47]. Although less common, less studied, and often shorter lived, PRP likely places a similar psychological burden on patients. Far-reaching consequences of psoriasis and PRP for quality of life and the potential impact of early treatment on disease course make it incumbent upon pediatricians and dermatologists to seek improved, safe, targeted therapies both to provide relief for and protect the future health and development of these patients.

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Acne: Vulgaris and Variants

3

Marissa J. Perman and Anne W. Lucky

Key Points

- There are many variants of acne which can be treated with similar types of systemic therapy.
- Acne vulgaris (AV) is responsive to several systemic agents, including oral antibiotics, hormonal therapies, isotretinoin, and occasionally, systemic corticosteroids. Most patients with AV or with hormone-related acne do not have evidence of hyperandrogenism and do not require laboratory evaluation.
- Acne conglobata and/or acne fulminans may present as distinct entities or as part of a syndrome such as SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) or PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome.
- Several systemic hormonal agents, including combined oral contraceptives and antiandrogens, are available to treat hormone-related acne; these decrease levels of local and circulating androgens, oppose their effects on sebaceous glands, and may play a role in regulation of inflammatory mediators of acne.
- Isotretinoin is potentially curative for acne vulgaris and is an important medication in managing other severe forms of acne including acne rosacea, acne conglobata, acne fulminans, and SAPHO syndrome.
- Considerations in using systemic therapy for acne: age and sex of the patient, comorbidities (e.g., inflammatory bowel disease, depression), acne as a component of a systemic disease (e.g., acne fulminans, SAPHO syndrome, PAPA syndrome), and polypharmacy (e.g., tetracyclines and isotretinoin).

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Abbreviations

AC	Acne conglobata
AF	Acne fulminans
AR	Acne rosacea
AV	Acne vulgaris
COC	Combined oral contraceptives
CPA	Cyproterone acetate

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DHEAS	Dehydroepiandrosterone sulfate
HA	Hormone-related acne
OCP	Oral contraceptive
PAPA	Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome
PCOS	Polycystic ovarian syndrome
PF	Pyoderma faciale
SAPHO	Synovitis acne, pustulosis, hyperostosis, and osteitis syndrome

Although the term "acne" often brings to mind the common form of acne known as acne vulgaris, acne can have several other variants, with different courses and thus management approaches. In addition to recognizing the type of acne, assessing the degree of severity is critical to providing the best possible treatment. With more severe presentations, topical therapy may be inadequate. Many systemic therapies are available for various forms of acne – some provide control of the disease, while others may actually provide a cure. They may, however, also give unwanted side effects and complications, of which the prescriber should be cognizant and have comfort in managing. This chapter provides a review of the presentation of various forms of acne requiring systemic therapy, candidate systemic agents, when and how to use these medications, and various pitfalls associated with their administration.

3.1 Acne Variants

3.1.1 Acne Vulgaris

Acne vulgaris (AV) is a common skin condition, most often developing around puberty and involving the face, chest, back, and shoulders. Occasionally, neonates and infants can have acne as well. The underlying pathogenesis of AV is a combination of bacterial infection of the pilosebaceous unit (predominantly by *Propionibacterium acnes or P. acnes*), abnormalities of keratinization (resulting in comedo formation), increased sebum production (mediated by systemic and local androgens), and inflammation (genetically directed towards *P. acnes*). Thus, treatment comprises a multitude of approaches and medications, often in combination.

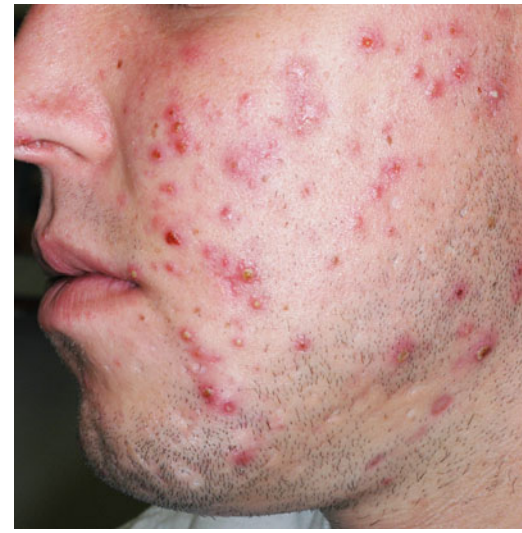

Fig. 3.1 Extensive papular and pustular acne in patient prior to therapy

Most people experience AV at some time during adolescence. Occasionally, AV may be more severe in nature and can progress to scarring and even permanent disfigurement. AV can also have a profound psychosocial impact on patients when left untreated or treated inadequately. In cases of moderate to severe AV or AV with scarring, systemic therapy may be warranted. Moderate to severe AV is composed of inflammatory lesions consisting of variably sized papules, pustules, nodules, and cysts (Fig. 3.1), as well as open and closed comedones. Post-inflammatory hyperpigmentation may last for several months but is not permanent. Scarring may be seen subsequent to inflammatory lesions and often presents as pits or atrophic papules and plaques. Occasionally, patients will develop keloidal or hypertrophic scars.

Time of AV onset may determine the clinical severity of acne, particularly in females, as females who develop AV prior to the onset of menses have a higher risk of developing severe acne later in life compared to females with AV occurring later in adolescence [1]. In most cases, patients with AV have normal androgen levels, and routine testing is not recommended unless the history and/or physical examination suggests

hyperandrogenism or the patient is refractory to conventional therapy [2]. In a study by Lucky et al. assessing predictors of acne severity in young adolescent females, only 29 % of girls with severe acne had dehydroepiandrosterone sulfate (DHEAS) levels above the 90th percentile, although mean levels of DHEAS were higher in this group [1].

3.1.2 Hormone-Related Acne

Hormone-related acne (HA) should be suspected in patients with evidence of hyperandrogenism (i.e., hirsutism, androgenetic alopecia, irregular menses, clitoromegaly), a lack of response to conventional therapy, acne flares prior to menses, and females with deep-seated inflammatory nodules located on the lower face and jawline [3].

Children with hyperandrogenism tend to have early-onset acne along with axillary and pubic hair, body odor, advanced bone age, and clitoromegaly. Hyperandrogenism in adult females may present with a constellation of findings including late-onset or difficult-to-treat acne, as well as irregular menses, male or female pattern alopecia, hirsutism, infertility, acanthosis nigricans, and/or truncal obesity. Elevated serum androgens may be due to disorders such as premature adrenarche, late-onset congenital adrenal hyperplasia, or an adrenal or gonadal tumor. But the most common underlying cause of hormone imbalance in females is polycystic ovarian syndrome (PCOS). Often in PCOS, serum androgens are not elevated above normal values until later in adolescence. Many of these patients also have features of the metabolic syndrome. Female patients with concern for hyperandrogenism should be screened for hormone dysregulation with laboratory tests including DHEAS, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and free testosterone (T). Screening is not necessary in patients for acne without findings suggestive of hyperandrogenism [2]. If PCOS is confirmed or highly suspected, inclusion of a lipid panel, fasting glucose, and insulin level are appropriate to assess for the metabolic syndrome [4].

3.1.3 Acne Rosacea and Periorificial Dermatitis

Acne rosacea (AR) can present in four different patterns and seems to be due to a combination of vasomotor instability and inflammation [5, 6]. Clinically, this leads to flushing and erythema along the convexities of the face. AR is uncommon in children and adolescents but may be underreported. The four classic patterns of rosacea include erythematotelangiectatic, papulopustular, phymatous, and ocular [5]. Additionally, granulomatous rosacea and idiopathic facial aseptic granuloma may be distinct subtypes and along the same spectrum [7]. Periorificial dermatitis (PD) is a separate but related entity that is seen commonly in childhood. PD may be associated with topical corticosteroid exposure, either applied or via nebulizers used for asthma, but its underlying cause is still obscure [8–10].

Patients with moderate to severe AR who have extensive inflammatory papules and pustules or more persistent eruptions may not be responsive to topical therapies and require systemic therapy. In addition, ocular involvement often can be difficult to treat topically, especially when it involves the lid margins. Therefore, systemic therapy may be indicated to help prevent ocular complications of AR including keratitis, blepharoconjunctivitis, chalazia, meibomitis, and rarely corneal ulcers [5].

3.1.4 Pyoderma Faciale

Pyoderma faciale (PF) is considered to be a variant of rosacea by many and is sometimes referred to as rosacea fulminans to reflect its analogous presentation to acne fulminans (described below) [11]. It represents an extreme manifestation of the inflammatory component of rosacea and occurs almost exclusively in females. PF presents on the faces of young women with the sudden onset of deep, coalescing nodules; draining sinuses with tract formation; and inflammatory cysts. Localization to the chin, nose, cheeks, forehead, and temples is common, and a background of blushing and flushing is required

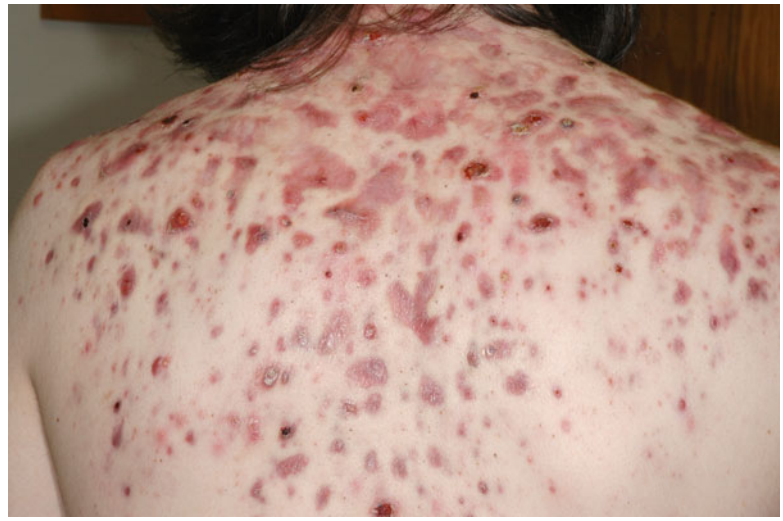

Fig. 3.2 Acne conglobata and fulminans in a teenage boy

(consistent with rosacea). Systemic signs and symptoms may be present and include fever, leukocytosis, and elevated erythrocyte sedimentation rate [11, 12]. Due to the rapid onset and inflammatory nature, patients require systemic therapy for several months.

3.1.5 Acne Conglobata

Acne conglobata (AC) is an uncommon but severe, chronic, nodulocystic form of acne that involves the chest, back, and buttocks. AC is more common in males and starts in adolescence or adulthood. AC typically presents with papules, pustules, nodules, abscesses, and draining sinuses, and it often heals with disfiguring scarring and keloid formation. There can be deep open and closed comedones and true cysts. AC may be associated with systemic syndromes such as SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome or PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome discussed below. The disfiguring and often chronic nature makes AC difficult to manage medically as well as psychosocially.

3.1.6 Acne Fulminans

Acne fulminans (AF) presents as a severe, sudden-onset, inflammatory acneiform condition that is characterized by fever, polyarthralgia, and severe ulcerative nodules involving the face, chest, and back, unresponsive to conventional acne therapy such as antibiotics (Fig. 3.2). Other associated cutaneous and systemic symptoms include weight loss, fatigue, aseptic bone osteolysis, hepatosplenomegaly, myositis, and erythema nodosum. It is most common in adolescent males and often presents in patients with a prior history of mild AV. AF may be the presenting cutaneous manifestation of SAPHO syndrome (described below). Due to the severe nature of the condition and lack of response to antibiotics, AF requires aggressive systemic therapy [13].

3.1.7 SAPHO Syndrome

Synovitis, acne, pustulosis, hyperostosis, and osteitis, also known as SAPHO syndrome, is a rare, chronic, relapsing, and remitting inflammatory syndrome found in pediatric and adult patients with a constellation of findings including osteoarticular and dermatological manifestations, specifically anterior chest wall hyperostosis, multifocal aseptic osteomyelitis, synovitis, along with severe acne in the form of AC, AF, and/or hidradenitis suppurativa, and palmoplantar pustulosis [14, 15]. The pathogenesis and genetics are not well understood and treatment has not been standardized [14]. *P. acnes* has been found in osteitis lesions of SAPHO and is believed to

cause a persistent, low-grade infection leading to innate and T-cell-mediated immune dysfunction in genetically predisposed patients [14, 16, 17]. Many systemic therapies have been utilized to treat the condition including TNF-α blockers.

3.1.8 PAPA Syndrome

Pyogenic arthritis, pyoderma gangrenosum, and acne, also known as PAPA syndrome, is a familial neutrophilic dermatosis that begins in adolescence and consists of sterile pyogenic arthritis, pyoderma gangrenosum, and cystic acne often consistent with acne conglobata. PAPA syndrome is due to autosomal-dominant mutations in the *PSTPIP1* gene, encoding proline/serine/threonine phosphatase-interacting protein 1. PSTP1P1 binds to the pyrin protein; therefore, patients with PAPA syndrome may also demonstrate symptoms found in patients with periodic fever syndromes [18, 19]. The arthritis usually precedes the acne and pyoderma gangrenosum. PAPA syndrome is managed systemically and may be treated similarly to other autoinflammatory conditions associated with pyrin defects (see Chap. 7). A similar but distinct entity comprised of pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH) has been recently described [20].

3.1.9 Apert Syndrome

Apert syndrome is an autosomal-dominant genetic disorder of craniosynostosis, developmental delay, and severe nodular acne. It is due to gain-of-function mutations in the fibroblast growth factor receptor (*FGFR2)* gene. Systemic treatment, often with isotretinoin, is usually required because of the severity of the acne. The role of FGFR2 in the pathogenesis of acne is being investigated [21].

3.2 Principles of Management

The management of acne must be tailored to each individual. The type of acne, its severity, predominant lesion type, the number of lesions, associated comorbidities, age of the patient, previous medications, concomitant medications, and other factors each play a role in the decision of how to best treat. A certain regimen might work well for one patient while failing another. The following sections will review commonly used systemic therapies available for acne, how to best use these medications based on the type of acne they have, potential side effects, pitfalls, and the need for caution when appropriate. It should be noted that recent studies are elucidating the importance of inflammatory mediators in the pathogenesis of acne. Not only does this knowledge provide potential for new drugs in the treatment of acne, it has shown that many of the medications we now use, including antibiotics, retinoids, and hormones, actually do have significant effects on inflammation [22].

3.3 Antibiotics

3.3.1 Tetracyclines

For patients who fail topical therapy, systemic antibiotics are the standard of care for many types of acne, especially AV. The tetracyclines are typically first line in acne systemic therapy and work by decreasing *P. acnes* counts as well as by reducing inflammation [23]. The expert panel that developed guidelines for AV management for the American Academy of Dermatology in 2007 believes that doxycycline and minocycline are superior to tetracycline. In addition, there is some evidence that minocycline is superior to doxycycline in decreasing *P. acnes* and may have a lower rate of resistance [2, 23]. Recommended doses and common side effects are included in Table 3.1 and are generally based on acne severity and medication dose, respectively. The tetracyclines should not be used in children age eight and under as they can have a detrimental impact on dental enamel and bone growth. In addition, females should be aware that vaginal candidiasis may develop in all age groups. Tetracyclines are pregnancy category D and are excreted into breast milk.

Moderate to severe AR and perioral dermatitis not responsive to topical therapy are usually treated with oral antibiotics, most commonly

Table 3.1 The tetracyclines: recommended dosing and common side effects

Drug	Recommended dosage	Common and serious side effects
Tetracycline	250–500 mg PO QD-BID	Phototoxicity, gastrointestinal upset, benign intracranial hypertension
Doxycycline hyclate or monohydrate	50–100 mg PO QD-BID	Phototoxicity, nausea/vomiting, pill esophagitis, headaches, benign intracranial hypertension
Doxycycline hyclate (enteric coated)	100 mg QD-BID	
Minocycline	50–100 mg PO QD-BID	Dizziness, skin pigmentation, autoimmune hepatitis, lupus-like syndrome, urticaria, drug reaction with eosinophilia and systemic symptoms (DRESS), benign intracranial hypertension
Minocycline HCl (extended release)	1 mg/kg QD	

QD every day, *BID* twice daily

tetracyclines (age-permitting), although definitive data implicating a specific microbial pathogen is lacking. Tetracyclines and macrolides at standard AV doses are used, mainly for their anti-inflammatory properties. In addition, subantimicrobial doses of doxycycline (Oracea®) have been FDA approved for AR [24]. Oral antibiotics may also be considered for management in certain cases of pyoderma faciale when prednisone and/or isotretinoin are not an option [12].

Tetracycline is relatively inexpensive and effective for AV and AR, but its use is limited by the need to take it on an empty stomach and without any calcium-containing products that impair absorption [23]. This may be particularly difficult for adolescents. Second-generation doxycycline and minocycline have increased gastrointestinal (GI) absorption and require lower dosages, allowing for better tolerability than tetracycline [25]. There are only a few reports comparing the efficacy of doxycycline and minocycline, but most have shown comparable efficacy for AV [26, 27]. Doxycycline tends to be associated with more phototoxicity and GI upset, especially esophagitis; it can be taken with food to help decrease associated nausea and vomiting as dairy and other foods do not significantly impede its absorption. It is imperative that patients take their medication with ample fluids to avoid esophagitis and ulcer formation. Doxycycline is usually prescribed in the hyclate or monohydrate form or may be prescribed in enteric-coated tablets (Doryx®) to help increase tolerability [25]. Doxycycline and minocycline have both been associated with benign intracranial hypertension (BIH, pseudotumor cerebri) [24].

Minocycline has a higher risk of central nervous system side effects, including dizziness and vertigo, that may be mitigated with extended-release formulations (Solodyn®), although these formulations can be prohibitively expensive. Other concerns include pigment deposition in the skin with longer treatment or higher doses, specifically blue-gray pigmentation on the anterior shins, blue-black pigmentation in acne or other scars, and brown pigmentation in sun-exposed areas [2, 25]. Minocycline has also been associated with autoimmune hepatitis as well as drug-induced lupus and minocycline-induced autoimmunity (MIA). If patients were to develop serum sickness-like symptoms and urticaria, these findings are commonly seen in the first few weeks of therapy. Drug reaction with eosinophilia and systemic symptoms (DRESS) is a drug hypersensitivity syndrome also reported with minocycline, with significant morbidity and potential mortality [25]. According to the FDA's MedWatch adverse event (AE) program, AEs were five times more likely with minocycline than doxycycline for the period between August 1998 and August 2003, despite doxycycline being prescribed more than three times as frequently [28]. Therefore, careful patient selection, awareness of potential adverse events, and limited duration of therapy play an important role in the use of tetracyclines, particularly minocycline.

3.3.2 Other Antibiotics

Oral antibiotics other than tetracyclines have proven benefit in AV and work similarly to

Table 3.2 Other commonly used antibiotics for AV, AR, and periorificial dermatitis, recommended dosages, and common side effects

Drug	Recommended dosage	Common side effects
Erythromycin base	250–500 mg Q6hours	Nausea, abdominal pain, diarrhea, cytochrome-P 450 inhibitor drug interactions
Azithromycin	[a]500 mg TIW × 8–12 weeks [a]500 mg QD × 4 days/monthly for 3 months	Rash, abdominal pain
Clindamycin	150–300 mg TID	Nausea, vomiting, diarrhea, *Clostridium difficile* colitis
Trimethoprim-sulfamethoxazole	80/400–160/800 mg (DS) QD	Nausea, vomiting, anorexia, rash, phototoxicity
Trimethoprim	100 mg TID 300 mg BID	Nausea, vomiting, anorexia, rash

Q6hours every 6 h, *TIW* three times weekly, *TID* three times daily
[a]There is no standard AV dosing for azithromycin. These are two suggested dosing regimens based on prior literature [24, 29]

tetracyclines. These antibiotics include oral erythromycin, azithromycin, clindamycin, trimethoprim, and trimethoprim-sulfamethoxazole (see Table 3.2). Most of the medications are dosed once or twice daily and are generally well tolerated. However, many of these antibiotics are useful for other infectious conditions, and the longer-term use required for acne may predispose other resident bacterial flora to develop antimicrobial resistance; thus, these should be used with caution and assessment of necessity. *P. acnes* may have increasing resistance to erythromycin and clindamycin, and these should not be considered first-line therapy. Azithromycin is thought to have less resistance and appears well tolerated with fewer GI side effects as compared to the tetracyclines. In addition, it is pregnancy class B and safe with breastfeeding. There is no standard dosing regimen for azithromycin. Several studies report success with pulse dosing, i.e., three times weekly or daily for 3–4 days every week or month for 8–12 weeks [24].

Trimethoprim-sulfamethoxazole has been shown to be effective against *P. acnes* but should be reserved for more recalcitrant cases of AV to avoid emerging antibiotic resistance and to minimize the risk of rare but serious side effects that include severe drug hypersensitivity reactions, Stevens-Johnson Syndrome/toxic epidermal necrolysis, hematologic abnormalities including pancytopenia, and hyperkalemia [30]. It also increases sun sensitivity. Other antibiotics occasionally used in AV with limited data include cephalexin and levofloxacin [24].

3.3.3 General Antibiotic Pitfalls

In order to avoid resistance to *P. acnes* and other bacteria sensitive to these antibiotics including coagulase-negative *Staphylococci*, *Staphylococcus aureus,* and group A *Streptococcus*, systemic antimicrobial therapy should be used for the shortest duration possible to treat AV and at the lowest effective dose. In addition, monotherapy with oral antibiotics should generally be avoided, and instead antibiotics should be combined with topical benzoyl peroxide and/or retinoids. Once the acne is well controlled, ideally in 3–6 months, the antibiotics should be tapered and topical therapies instituted or continued in order to maintain results [31]. If acne flares with taper, other modalities, such as isotretinoin in males and combined oral contraceptives and/or isotretinoin in females, should be considered.

Gram-negative folliculitis may also occur with long-term oral antibiotic use and is reported most commonly with tetracyclines. The gram-negative bacteria seen include *Escherichia coli*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Proteus mirabilis*, and *Klebsiella* and should be suspected in patients not responding or flaring

while on appropriate doses of oral antibiotics after 3–6 months. Gram-negative folliculitis is often treated with isotretinoin, though some cases may respond to appropriate antibiotics for gram-negative organisms [32].

There is some literature to suggest a risk of inflammatory bowel disease, particularly Crohn's disease, with certain antibiotics, especially tetracyclines. A true causal association has not been established, and many of the studies lack details on important potential confounders including the severity of acne, dosing and duration of antibiotics, and compliance. Two possible explanations for the association include a potential association between more severe AV and IBD, and patients receiving long-term antibiotics see their physicians more frequently and may be more likely to be diagnosed with other medical conditions [33, 34].

Finally, the association of antibiotics with oral contraceptive (OCP) failure, which is in the literature and the package insert of OCPs, is controversial. The general OCP failure rate ranges from 1 to 3 %, and more recent larger studies support a similar failure rate among patients on concomitant antibiotics. The most common mechanism believed to cause OCP failure involves decreased enterohepatic recirculation of the OCPs when taking concomitant antibiotics [35, 36]. Rifampin specifically has been shown to interfere with OCP effectiveness by decreasing levels of ethinyl estradiol (EE) and norethindrone due to induction of hepatic microsomal enzyme activity leading to an increased rate of metabolism [37]. Currently, the evidence for OCP failure with concomitant antibiotics remains equivocal, and further prospective studies are needed.

3.4 Hormonal Agents

There are several hormonal agents available to treat AV and hormone-related acne, although many have not been tested for Food and Drug Administration (FDA) approval. In general, the ameliorating effects of hormones are due to estrogens. They act by decreasing levels of local and circulating androgens, increasing sex hormone-binding globulin (SHBG), and opposing androgenic effects on sebaceous glands [38, 39]. This section will focus on the three most commonly used hormonal therapies for acne: ovarian androgen blockers (oral contraceptive pills or OCPs), androgen receptor blockers (spironolactone and cyproterone acetate), and adrenal androgen production blockers (corticosteroids), which are summarized in Table 3.3.

3.4.1 Oral Contraceptive Pills

It is now well established that estrogen-containing oral contraceptives are effective in the treatment of acne vulgaris [40]. Combined OCPs (COCs) contain an estrogen (usually ethinyl estradiol or EE)

Table 3.3 Medications for hormone-related acne vulgaris

Drug	Recommended dosage	Common side effects
Oral contraceptive pills (see text for details)	1 tab PO QD	Breakthrough bleeding, nausea, vomiting, breast tenderness
Spironolactone	50–100 mg PO QD-BID	Breast tenderness, menstrual irregularities, dizziness, headache, orthostatic hypotension, decreased libido, hyperkalemia
Cyproterone acetate	50–100 mg QD	Menstrual irregularities, nausea, vomiting, breast tenderness, fluid retention, headaches
Cyproterone acetate combined with ethinyl estradiol (EE) (Diane-35® or Dianette®)	2 mg + 35 μg of EE QD	
Systemic corticosteroids		Weight gain, sleep disturbance, hyperglycemia, osteopenia/osteoporosis, hypertension, striae
Inflammatory AV	Prednisone: 0.5–1 mg/kg/day	
Congenital adrenal hyperplasia	Prednisone: 5–10 mg PO QD Dexamethasone: 0.25–0.75 mg PO QD	

and a progestin. The estrogen suppresses ovarian production of androgens by suppressing pituitary gonadotropin release, and the progestin is added to prevent the risk of endometrial cancer from unopposed estrogen [41]. All COCs should improve HA based on the above mechanism, but certain COCs are FDA-approved for acne. These include: Estrostep® (EE20/30/35 μg and norethindrone 1 mg), Ortho Tri-Cyclen® (EE 35 μg and norgestimate 0.18/0.215/0.25 mg), and Yaz® (EE 20 and drospirenone 3 mg). Yaz® was approved by the FDA in 2007 but, along with its sister pill, Yasmin®, which also contains drospirenone, was reviewed by an FDA advisory panel in 2011 following findings suggesting an increased risk of thromboembolic events as compared with three other OCPs [42]. Other forms of estrogen-containing contraceptives such as the NuvaRing® and transdermal patches like Ortho Evra® have not been evaluated for use in AV [2]. It should be noted that progesterone-only contraceptives (injected, implanted, and oral) can actually exacerbate acne via the intrinsic androgenic properties of many progestins [41, 43].

COCs can be prescribed by physicians comfortable selecting appropriate patients and providing proper counseling. Otherwise, patients should be referred to an adolescent medicine physician or gynecologist for initiation and follow-up while on COCs. The pills can be started on the Sunday after the start of a menstrual period, at the beginning of the menstrual period, or the same day the pill is prescribed, known as the "quick start" method. The first and third methods require backup birth control [38].

Common side effects include breakthrough bleeding, nausea, vomiting, and breast tenderness. Although weight gain is often quoted as a potential side effect, a recent meta-analysis concluded that there are no data to support this concern [44]. Other less common side effects include melasma, mood changes, and decreased libido. Side effects tend to improve after two to three cycles. The risk of potential serious complications is more likely in patients with a personal history of thromboembolic disorders or a familial tendency to form blood clots, a history of diabetes, cardiovascular disease, hypertension, migraines, and in cigarette smokers.

Table 3.4 Contraindications to COCs

Personal history of clotting disorders or familial tendency to develop blood clots
History of cardiovascular disease
History of cerebrovascular disease
Known or suspected estrogen-dependent tumors including breast cancer, endometrial cancer, and hepatic adenomas or carcinomas
Abnormal uterine bleeding
Abnormal liver function
Long-standing diabetes or diabetes with end-organ damage
Smokers over the age of 35

Therefore, there are several contraindications to COCs, including being over age 35 years and one who smokes, a history of clotting disorders, a history of cardiovascular or cerebrovascular disease, individuals with known or suspected breast cancer, endometrial cancer, hepatic adenomas or carcinomas or other estrogen-dependent tumors, abnormal uterine bleeding, abnormal liver function, and long-standing diabetes or diabetes with evidence of end-organ damage [38]. Contraindications to COCs are summarized in Table 3.4. These side effects remain rare in adolescents and young women who are otherwise healthy and remain an excellent choice in females with HA, including the majority of patients with HA who do not have laboratory evidence of hyperandrogenism. Patients should be counseled that COC therapy for HA may take 3 months to work. Finally, contraceptive failure while on antibiotics is addressed in the section on antibiotics above.

3.4.2 Antiandrogens

3.4.2.1 Spironolactone

Spironolactone is an androgen receptor blocker and acts by competing with testosterone (T) for androgen receptors, thus inhibiting androgen biosynthesis. It is also an inhibitor of 5α-reductase which converts T to the more potent dihydrotestosterone (DHT). The resultant increased estrogen effect may in part be due to suppressed androgen action as well as increased production of SHBG. Suppression of

androgens is known to decrease sebum excretion. Patients will note a decrease in oiliness of their skin and hair. In addition, more recent studies have shown hormonal effects on the underlying inflammatory cascade important in acne pathogenesis [45].

Spironolactone is not FDA-approved to treat AV and should be used as a second-line agent in patients with HA resistant to other therapies. Doses range from 50 to 200 mg and can be divided once or twice daily. Acne, as opposed to hirsutism and androgenic alopecia, tends to respond to relatively low doses (i.e., 25 mg BID). Common side effects are dose-dependent and include breast tenderness, menstrual irregularities including breakthrough bleeding, central nervous system effects such as dizziness and headache, orthostatic hypotension, decreased libido, and hyperkalemia. Hyperkalemia is more likely in patients on higher doses or a history of cardiac or renal compromise. Monitoring for hyperkalemia is optional but should be considered in patients at risk for hyperkalemia and in patients on concomitant therapy with Yasmin® or Yaz® in which the drospirenone antiandrogen effect is equivalent to about 25 mg of spironolactone [38]. Spironolactone has been used with caution in patients at increased risk for breast cancer, although these concerns have not been verified. Spironolactone also theoretically could cause birth defects and feminization of the male fetal genitalia; thus, patients must be counseled accordingly [38].

Similar to COCs, spironolactone takes about 3 months to work. Lower doses of spironolactone may allow for improved tolerability with fewer side effects in patients taking an OCP in combination with spironolactone [46].

3.4.2.2 Cyproterone Acetate

Cyproterone acetate (CPA) is also a progesterone derivative that provides antiandrogen function via blockade of the androgen receptor blocker. It decreases adrenal androgens and reduces 5-alpha reductase activity. CPA is not available in the USA but is used in other countries for refractory AV. It is prescribed most commonly as a 2 mg dose combined with 35 μg of EE (Diane-35® or Dianette®) or less commonly as a single agent in doses ranging from 50 to 100 mg daily. Common side effects are similar to other antiandrogenic agents. More serious side effects include hepatotoxicity and thromboembolic events [38].

3.4.2.3 Corticosteroids

Corticosteroids serve as adrenal androgen production blockers and may be used short term in high doses to control severe inflammatory AV or in low doses for patients with adrenal hyperactivity, most commonly late-onset congenital adrenal hyperplasia (CAH) [2, 38]. Corticosteroids are also used as adjunctive treatment to prevent flares when starting isotretinoin in patients with severe inflammatory or nodular AV and may serve as primary therapy in AF, AC, PF, SAPHO, and PAPA syndromes.

DHEAS levels are typically increased in patients with late-onset CAH between 4,000 and 8,000 ng/dL. Treatments with corticosteroids for CAH include prednisone 2.5–5 mg/day or dexamethasone 0.25–0.75 mg/day, taken orally at night. Dexamethasone has a higher risk of adrenal suppression. DHEAS levels can be monitored while on therapy to assess response. An adrenocorticotropin hormone stimulation test can be used to assess adrenal suppression 2–3 months after starting therapy [38, 47].

Corticosteroids in higher doses can be used as primary therapy in certain forms of inflammatory acne as mentioned above. In most cases, prednisone is used in ranges from 0.5 to 1 mg/kg/day and occasionally as high as 2 mg/kg/day for disease control for several weeks then tapered slowly. In many cases, isotretinoin is then added once the initial flare has subsided (for details on isotretinoin, see below). The two therapies may be combined for ongoing therapy if needed [11, 13, 48]. A common pitfall involves tapering steroids too quickly, leading to rebound flares.

The most common side effects of corticosteroids are well known and include weight gain, Cushingoid facies, sleep disturbance, hyperglycemia, osteopenia/osteoporosis, hypertension, and striae. Long-term use can paradoxically result in steroid-induced acne; this type of acne is primarily inflammatory and may later become comedonal. Side effects can be minimized by

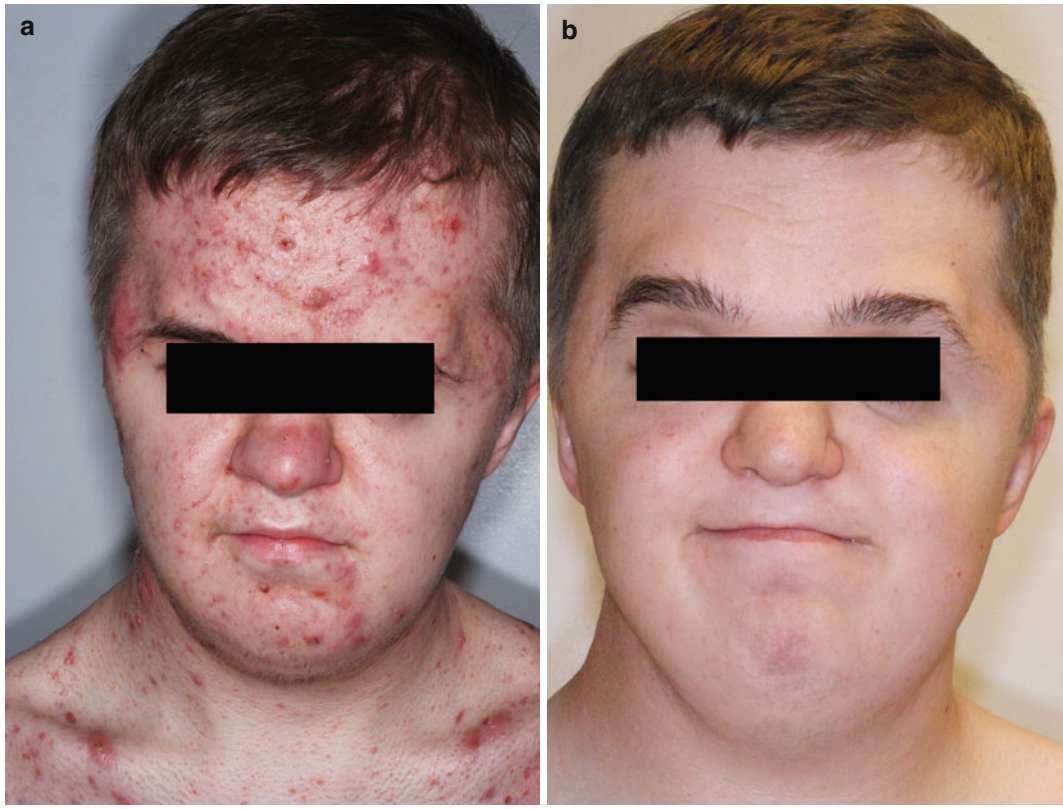

Fig. 3.3 (**a**) The face of an 18-year-old boy with Apert syndrome before isotretinoin. (**b**) The same 18-year-old boy after isotretinoin

limiting the treatment length of time and dosage as well as taking the medication in the morning to lessen adrenal suppression.

3.5 Isotretinoin

Isotretinoin (13-cis-retinoic acid) stands in a class by itself. No other medication used in the management of acne has had as much success. Isotretinoin is a retinoid, which is a vitamin A derivative that is not fat soluble and thus does not remain permanently fixed to tissues, unlike vitamin A. It acts to decrease sebaceous gland size and secretions as well as modify keratinocyte maturation [49]. Isotretinoin also plays a role in downregulating the *P. acnes* – induced cytokine inflammatory cascade thought to be important in acne pathogenesis [50]. Unlike other therapies, it is considered a potential cure for AV. Long-term remission rates range from 70 to 89 % in the literature [51]. Isotretinoin is highly regulated in the USA through the iPLEDGE program and has many possible side effects, limiting its use to certain candidates as well as prescribers familiar with the medication and its side effects.

Isotretinoin is approved for severe nodular AV (Figs. 3.3a, b). It is also used in moderate AV that has proven treatment resistant, AV leading to physical or psychological scarring, gram-negative folliculitis, and other severe variants of acne including AC, AF, AR, PF, and SAPHO syndrome [2, 11, 48, 49, 51, 52].

Isotretinoin is used in doses ranging from 0.5 to 2 mg/kg/day divided once or twice daily depending on disease severity. Absorption is improved when it is taken with food. Patients are usually treated for 4–6 months and on average for 20 weeks. Occasionally, providers will use lower doses of isotretinoin for longer periods of time.

The overall cumulative goal dose is 120–150 mg/kg total [2]. Lower doses have been reported useful in AR, PF, and SAPHO syndrome [11, 48, 49, 52]. The risk of flaring in cases of severe inflammatory acne may be lessened by starting with lower doses of isotretinoin (i.e., 0.5 mg/kg/day for the first month) or pretreatment with corticosteroids as discussed above [2]. Isotretinoin may rarely precipitate a form of AF and thus should be started carefully following systemic corticosteroids for this condition [13].

Common side effects of isotretinoin are similar to signs and symptoms of hypervitaminosis A. Mucocutaneous side effects include cheilitis, xerophthalmia, epistaxis, xerosis or irritant dermatitis, alopecia, and worsening night vision. Moisturization of the mucosa with petrolatum-based products and emollients for the skin will help. Patients may require topical steroids to improve their dermatitis. Saline eye drops can be used for conjunctival symptoms, and occasionally patients may need to switch from contacts to glasses if the discomfort is severe [2, 51].

Musculoskeletal symptoms include myalgias and arthralgias, which usually improve with nonsteroidal anti-inflammatory drugs [51]. Hyperostosis, bone demineralization, and premature epiphyseal closure have been reported with the use of isotretinoin. Such conditions are more likely to occur with long-term use of high-dose retinoids, such as that used in disorders of keratinization. In the case of AV where the course is limited, these findings are less of a concern [53]. General guidelines do not recommend routine screening for bony changes associated with isotretinoin when used for AV in this manner [2].

Central nervous system effects include headaches and less commonly benign intracranial hypertension (BIH). Severe headaches and headaches associated with vision changes should be evaluated for BIH [2, 51]. Patients on concomitant tetracycline antibiotics are at higher risk for BIH. In most cases, these side effects are temporary and improve after termination of therapy.

One of the most serious and consequential side effects of isotretinoin is teratogenicity. In order to prevent unplanned pregnancies in females while taking isotretinoin, the medication is highly regulated in the USA through the iPLEDGE system (see www.ipledgeprogram.com for details). iPLEDGE was created by the FDA in 2006 as a pregnancy prevention program for isotretinoin. The limited data to date, however, suggest no further reduction in unplanned pregnancies as compared to prior regulatory systems [54, 55]. Physicians prescribing isotretinoin in the USA must be preapproved and comply with iPLEDGE and its pregnancy monitoring guidelines, as well as be able to appropriately counsel female patients on the use of two forms of contraception or abstinence. Physicians not comfortable with prescribing contraception should refer patients to the appropriate provider for contraception management prior to starting isotretinoin.

Mood disorders, depression, and suicide are also of concern for patients on isotretinoin. Adolescence and AV may be independent risk factors for depression [56]. Therefore, establishing a true causal association between isotretinoin and mood disorders has proven difficult [2, 57]. In fact, several studies have shown improved mood following acne treatment with isotretinoin [58]. Nevertheless, patients and their families should be counseled and monitored for any signs or symptoms of depressive symptoms or suicidal ideation as there may be a subgroup of patients who indeed do have negative reactions [59]. History of a psychiatric disorder is not an absolute contraindication to using isotretinoin. However, such patients should be in the care of a psychiatrist or therapist who can continue to manage their underlying psychiatric condition [57].

Recently, a potential association between inflammatory bowel disease (IBD) and isotretinoin has come to medical and public attention. Several case reports and a few case–control studies have suggested a possible association between Crohn's disease, but not ulcerative colitis, and isotretinoin [60]. However, a clear causal association is lacking [34, 61]. Confounders to these studies include possible long-term antibiotic use preceding isotretinoin (which may be associated with IBD), as well as a possible relationship between nodular AV and IBD. Although a clear relationship is currently lacking, inquiry into a personal and/or family history of IBD is important,

Table 3.5 Common and serious side effects of isotretinoin by system (see text for details)

System	Potential side effects
Mucocutaneous	Cheilitis, xerophthalmia, epistaxis, xerosis, irritant dermatitis, alopecia, worsening night vision
Musculoskeletal	Myalgias, arthralgias, hyperostosis, bone demineralization, premature epiphyseal closure
Central nervous system	Headaches, benign intracranial hypertension
Reproductive	Potent teratogen
Psychiatric	Mood changes, depression, suicidal ideation, suicide
Gastrointestinal	Nausea, vomiting, questionable risk for Crohn's Disease

as well as education of all isotretinoin candidates about the risk, albeit low, of the development of IBD symptoms while on therapy [34]. Side effects of isotretinoin are summarized in Table 3.5.

The most common laboratory abnormalities include elevated lipid levels, particularly triglycerides, transaminitis, and less commonly leukopenia. Hypertriglyceridemia and hypercholesterolemia are seen in up to 25 % of patients on therapy but usually resolve once therapy is completed. Transaminitis is seen in up to 15 % of patients, is mild in most cases, reversible, and often improves in 2–4 weeks despite ongoing therapy [51, 57]. In some cases, elevated levels (particularly of aspartate aminotransferase) may be due to muscle rather than liver transaminase in adolescents who perform strenuous exercise. Monthly laboratory evaluation while taking isotretinoin should include monitoring of transaminases, total cholesterol and triglycerides, and complete blood counts, along with pregnancy testing in females of childbearing potential [2].

3.6 Biologic Therapy

Finally, there is little literature and experience on the use of biologic agents for acne variants. Biologic therapy with agents such as adalimumab, etanercept, and infliximab are generally reserved for severe systemic disorders; they may be useful in inflammatory acne variants not responsive to conventional systemic therapies such as antibiotics, corticosteroids, isotretinoin, or other immune modulating agents. These disorders include SAPHO syndrome, PAPA syndrome, hidradenitis suppurativa (addressed in Chap. 4), and severe, treatment-resistant cases of AV, AC, and AF. Currently, standard dosing regimens for these conditions are not available. Accepted dosages for other autoimmune conditions for which the biologic agents are approved, such as Crohn's disease or psoriasis, are commonly employed in these cases. A more detailed discussion of biologic therapy including dosing, side effects, and other concerns are addressed in the chapter on psoriasis (Chap. 2) [62–68]. It remains to be seen whether anakinra, an IL-1 inhibitor successfully used in some of the anti-inflammatory conditions mentioned, will be useful for accompanying severe acne.

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Hidradenitis Suppurativa

4

Melinda Jen and Mary Wu Chang

Key Points

- Hidradenitis suppurativa (HS) is a chronic disorder due to follicular occlusion and secondary inflammation of the apocrine glands.
- Although some have mild disease, others progress to having numerous painful nodules with draining ulcers, sinus tracts, and scarring.
- Treatment goals are to limit disease activity and psychosocial impact and to postpone higher-risk procedures such as surgery. Systemic agents (e.g., oral antibiotics, hormonal therapy, immunosuppressants, and biologics) along with laser treatments may be utilized for moderate to severe cases.
- Most data for therapies are extrapolated from adult disease, and pediatric HS needs further attention and study.

Abbreviations

FDA	Food and Drug Administration
HS	Hidradenitis suppurativa
Kg	Kilogram
Mg	Milligram
Nd:YAG	Neodymium:yttrium-aluminum-garnet
PUVA	Psoralen plus ultraviolet A

Hidradenitis suppurativa (HS), also known as acne inversa, is an inflammatory disease of the apocrine-bearing areas of the skin. HS is chronic, recurrent, difficult to treat, and potentially debilitating. Onset of HS typically occurs after puberty, but rare prepubertal cases have been reported [1]. Females are three times more likely to be affected than males. The prevalence is estimated to be 1–2 % in the general population [2]. It appears to be less prevalent among individuals 55 years and older, but more common among young adults, in which one study noted a prevalence of 4 % [3, 4].

Verneuil first coined the term "hidradenitis suppurativa" in 1854 from the Greek words *hidros* for sweat and *adne* for gland, believing that the disease was caused primarily by purulent inflammation of apocrine glands. Since that time, the cause remains elusive, but histologic studies demonstrate that HS is a disease of the hair follicle. Follicular occlusion and dilation of the pilosebaceous unit lead to rupture and result in secondary inflammation of the apocrine glands. Along with acne conglobata, dissecting cellulitis,

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Table 4.1 Hurley staging system

Stage	Clinical disease
I	Single or multiple abscesses without sinus tracts or scarring
II	One or more widely separated recurrent abscesses with sinus tract formation and scarring
III	Multiple interconnected sinus tracts and abscesses. Diffuse or nearly diffuse involvement of the affected region

and pilonidal sinuses, HS is considered part of the follicular occlusion tetrad. Smoking, obesity, and mechanical friction are associated with HS and are exacerbating factors for some patients. HS commonly occurs in the intertriginous areas, typically the axillae, inguinal, anogenital, mammary, and inframammary regions, but other apocrine-prominent areas can be affected, such as the scalp, retroauricular skin, and chest. Double comedones and tender subcutaneous nodules are characteristic. The nodules are deeper than and lack the superficial purulent appearance of furuncles. Nodules often rupture, draining a foul-smelling purulent discharge, or become painful, deep dermal abscesses. As the disease progresses, sinus tracts, hypertrophic fibrotic scars, and dermal contractures can develop. Complications include infection, anemia, lymphedema, and fistulae to the urethra, bladder, or rectum in HS of the perineum.

Two methods of clinical staging for HS have been proposed. The Hurley staging system divides HS into three stages depending on the presence of sinus tracts and scars [5] (Table 4.1 and Figs. 4.1, 4.2, and 4.3). In contrast, the Sartorius system was developed to better assess treatment efficacy in clinical studies. This system scores regional and total disease severity based on involved anatomic regions, number and type of lesions, distance between lesions, and presence of normal skin between lesions.

The psychosocial impact of HS can be profound. The chronic serous, bloody, and purulent exudate, pain, and physical deformity of private or hidden areas of the body are a tremendous psychological burden [2]. HS can disrupt school attendance, self-image, and employment. Patients lose an average of 2.7 workdays per year because of the disease, with women losing more days than males [6]. Patients with HS report a quality of life worse than those with alopecia, mild to moderate psoriasis, vascular anomalies of the face, and atopic dermatitis [7]. Younger patients

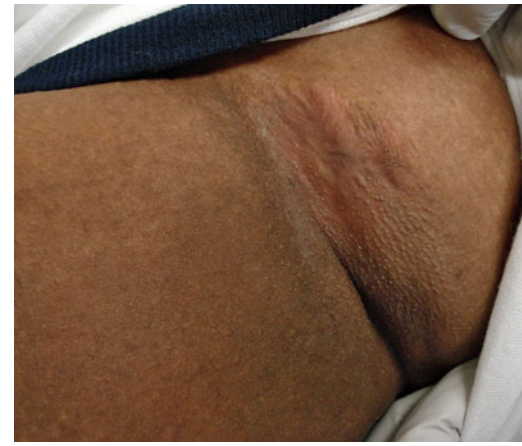

Fig. 4.1 Hidradenitis suppurativa, Hurley stage I. 14-year-old male with two inflammatory nodules in the axilla without scarring or sinus tract formation. He was treated with topical benzoyl peroxide wash and topical clindamycin solution with subsequent disease remission

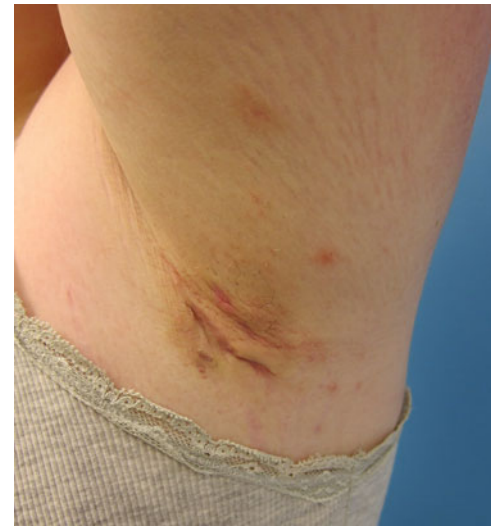

Fig. 4.2 Hidradenitis suppurativa, Hurley stage II. 16-year-old female with recurrent inflammatory nodules, abscesses, and scarring in the axillae (shown here) and groin, treated with topical chlorhexidine wash and oral doxycycline

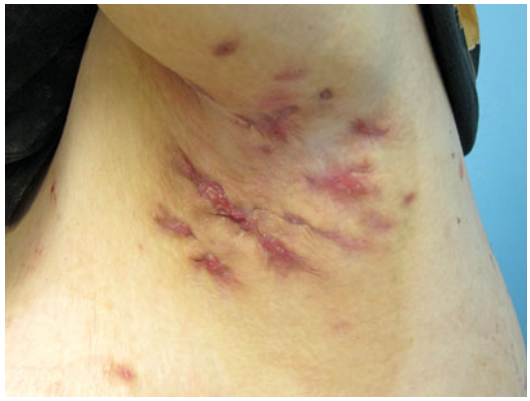

Fig. 4.3 Hidradenitis suppurativa, Hurley stage III. 16-year-old female with multiple inflammatory papules and nodules, chronically draining abscesses, and sinus tracts with exuberant granulation tissue in the axillae (shown here), inframammary region, and groin. Multiple systemic therapies, including doxycycline, minocycline, clindamycin and rifampin, and infliximab, have been unsuccessful. Because of coexistent medical conditions, dapsone, hormonal therapy, and oral retinoids were contraindicated

are more likely to feel depressed, unworthy, and unlovable than older individuals, and this may explain the greater tendency for recall of alcohol abuse, suicidal ideation, and/or suicide attempts during adolescence [8]. In many cases, patients are told by medical professionals that nothing can be done for them, leading to more isolation and despair.

4.1 Management

There are few randomized controlled trials of therapy for HS and less data for pediatric patients. Treatment is guided by the severity and progression of disease. Patients must understand that as there is no cure for HS, the goals of therapy are to alleviate pain, minimize inflammation and scarring, maintain the disease at the early stages, and postpone the need for extensive surgery.

Treatment of localized, mild HS (Hurley I) consists of topical therapies and lifestyle changes. Smokers should be counseled on smoking cessation, and if obese, healthy weight loss strategies should be emphasized. Decreasing mechanical irritation through loose-fitting cotton clothing and avoidance of shaving, depilation, deodorants, heat, and humidity should be initiated early. Warm compresses or soaking baths can soothe inflamed lesions, and topical antibiotic/antiseptic or benzoyl peroxide soaps are appropriate. Topical clindamycin is a commonly used topical antibiotic agent to treat HS and can be effective in reducing the number of abscesses and pustules [9]. Combination topical therapies for acne, such as clindamycin-benzoyl peroxide preparations, are also useful. If these conservative measures are not enough, intralesional steroids are very helpful in alleviating painful nodules and halting progression to purulent, draining nodules. Other systemic therapy can be added, including oral antibiotics, if needed.

4.2 Systemic Antibiotics

Patients and physicians often view the purulent discharge from HS lesions as evidence of bacterial infection, but half of HS lesions are culture negative [10]. In culture-positive lesions, *Staphylococcus epidermidis*, *Staphylococcus aureus*, and coagulase-negative Staphylococci are most commonly isolated [10–12]. Often cultures are polymicrobial, with both gram-positive and gram-negative organisms. Gram-negative organisms such as *Klebsiella*, *Proteus*, and *Escherichia coli* may be frequently cultured from perineal HS [13]. Bacteria cultured from HS typically arise from secondary bacterial superinfection or represent colonization. Systemic antibiotics having anti-inflammatory and antibacterial properties can target the inflammation and bacterial superinfection that arise following follicular occlusion.

The tetracycline family (e.g., doxycycline and minocycline) and clindamycin are commonly used oral antibiotics for the treatment of HS and appear to be clinically helpful, though large studies supporting their efficacy are lacking. Tetracyclines are selected because of their anti-inflammatory and antibacterial properties and known efficacy in acne vulgaris. However, in one study comparing topical clindamycin to

tetracycline 500 mg twice daily for at least 3 months, there was no significant difference in disease improvement between the two treatment arms [14]. Combination antibiotic therapy with clindamycin and rifampin has also been used in HS. Although there are no randomized controlled trials, there have been several case series of its efficacy in HS. Clindamycin 300 mg twice daily with rifampin 300 mg twice daily for at least 10 weeks decreased clinical severity, but diarrhea was a major side effect and can limit its use [15–17].

Combination antibiotic therapy with rifampin, moxifloxacin, and metronidazole has also been reportedly effective for HS. A series of 28 patients with severe HS were treated with rifampin 10 mg/kg/day, moxifloxacin 400 mg daily, and metronidazole 500 mg three times a day for 6 weeks, followed by rifampin and moxifloxacin therapy for 12 weeks [18]. Sixteen patients (57 %) had complete remission, with no active lesions at the end of the 18-week treatment course. Individuals with less severe disease (Hurley stage I and II) were more likely to achieve complete remission. Despite these promising results, the adverse effects were significant. Sixty-four percent of patients reported gastrointestinal side effects, predominantly nausea and diarrhea; 35 % of females reported vaginal candidiasis; and 14 % had moxifloxacin-associated tendonitis, which resulted in treatment termination.

Dapsone is an antibiotic effective in the treatment of neutrophilic dermatoses. Since HS has a prominent neutrophilic infiltrate, dapsone has been used as a treatment option, but the results have been mixed. A series of five patients responded to 25–150 mg of dapsone within 4–12 weeks of starting the medication [19]. A subsequent series of 24 patients treated with 50–200 mg of dapsone daily showed that only 38 % of patients had improvement, while 62 % had none. After cessation of treatment, the patients who responded reported a rapid recurrence of disease [20]. Prior to starting treatment with dapsone, patients should be screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency and monitored for anemia during therapy.

4.3 Retinoids

Because early lesions of HS show follicular occlusion, acne therapies are commonly utilized for the treatment of HS. Unfortunately, the responsiveness of HS to such therapies often differs from acne vulgaris or nodulocystic acne. Isotretinoin has often been used to treat HS, but with very variable results. Early, small case reports were promising [21–24]. More recently, a retrospective review of 68 patients with moderate and severe HS treated with low-dose isotretinoin (mean dose 0.56 mg/kg/day) for 4–6 months demonstrated only 23.5 % of patients with clearance; an additional 20.6 % had marked improvement. Twenty-nine percent of patients dropped out before completing 4 months of treatment because of side effects and poor response to therapy [25]. Another review of 88 HS patients treated with isotretinoin showed that 77 % of them felt they had no improvement, and 6.9 % felt there was worsening of their disease following treatment [26].

Acitretin (mean dose 0.59 mg/kg/day) for 9–12 months was efficacious for severe HS in one small study [27]. The re-esterification of acitretin to etretinate in the presence of alcohol limits its use in the adolescent and adult populations, particularly in females, as both compounds are teratogens. Etretinate has an 80- to 160-day half-life, so if females of childbearing potential receive this drug, contraception is required not only during acitretin use but also for 3 years after discontinuation of treatment.

4.4 Hormones

Although the onset of HS usually corresponds with puberty, HS patients have normal androgen profiles and no difference in levels compared to age-, weight-, and hirsute-matched controls [28]. Altered end-organ sensitivity to androgens is postulated in HS, and antiandrogen treatments have been investigated as therapeutic options. Finasteride is a selective type II 5α-reductase inhibitor used for the treatment of

benign prostatic hyperplasia and androgenetic alopecia in adult men. Finasteride has been tried in a small number of male and female patients with HS. A 5 mg daily dose produced significant clinical improvement in six of seven patients, with three having complete healing [29]. The multiple side effects of this medication, however, including breast tenderness, gynecomastia, irreversible sexual dysfunction, depression, anxiety, increased risk of prostate cancer in men, and teratogenicity limit the use of this medication.

Cyproterone acetate is an antiandrogen agent that has been used in female HS patients, but it is not available in the United States. Cyproterone acetate 50 mg/ethinyloestradiol 50 μg daily and cyproterone acetate 100 mg daily have both produced improvement in disease activity in females. [30, 31]

Several combination oral contraceptives with lower androgenic activity have gained FDA labeling for acne vulgaris. While quite effective for many female patients with resistant acne, oral contraceptives appear to have mixed efficacy in the treatment of HS in females. There are no controlled trials for this off-label use of oral contraceptives.

4.5 Immunosuppressants

Although HS has long been categorized as a form of acne, the lack of consistent improvement with acne therapies including isotretinoin argues that HS may be a different disease. More recently, HS has been considered to be an inflammatory disorder. The efficacy of intralesional steroid therapy to the inflamed sterile nodules of HS is supportive of this view. Systemic corticosteroids can provide temporary relief, but the multiple side effects of systemic steroids preclude long-term therapy. Several case reports have described improvement with cyclosporine of 3–6 mg/kg/day, but disease often recurs after treatment discontinuation, [32, 33] and long-term therapy is limited by the increased risk for hypertension and nephrotoxicity. Methotrexate at 12.5–15 mg weekly resulted in no clinical improvement of HS in one series of three patients [34]. Colchicine failed to reduce the severity of HS in patients treated with 0.5 mg twice daily for up to 4 months [35].

4.6 Biologics

Elevated tumor necrosis factor-alpha (TNFα) and interleukin(IL)-1β levels are noted in HS lesional and normal perilesional skin. Biologic agents that target the TNFα and IL-1β pathways have been used with promising results [36]. None of the biologics are approved by the Food and Drug Administration for the treatment of adult or pediatric HS. Of the few studies using biologics to treat HS, only a handful of patients under 18 years of age have been included [37, 38]. However, they have been used for other pediatric diseases: infliximab is approved for the treatment of pediatric inflammatory bowel disease in those age 6 years and older, etanercept is approved for the treatment of juvenile idiopathic arthritis in those age 2 years and older, and adalimumab is approved for the treatment of juvenile idiopathic arthritis in those age 4 years and older.

Infliximab, a chimeric monoclonal antibody to TNFα, has been the most studied of all the biologics in the treatment of HS. Several case reports and case series demonstrated that infliximab decreases clinical severity, but the long-term efficacy remains in question [37, 39–49]. Treatment regimens varied widely. Most studies utilized 5 mg/kg infusions at week 0, 2, and 6, with a variable number of infusions every 8 weeks thereafter. Some patients were given concurrent low-dose methotrexate to decrease the likelihood of developing neutralizing antibodies. Long-term disease control varied, with two studies reporting disease relapse 6 weeks to 4 months after stopping therapy [44, 45], while another showed no relapse in ten patients with follow-up of 4–24 months [46]. Reported adverse effects include an eczema-like eruption [47], abscess [47], abdominal pain caused by colon cancer [48], multifocal motor neuropathy with conduction block [48], severe allergic reaction with bronchospasm and urticaria [48], infliximab-induced lupus reaction [49], and hypersensitivity reaction to infliximab [49]. An 8-week randomized, placebo-controlled, crossover

trial of 30 patients showed that a greater, though not statistically significant, number of patients treated with infliximab achieved at least a 50 % decrease in disease severity, but there was a significant improvement in patient-reported quality of life and visual analog scale scores [50].

Uncontrolled studies and case reports of etanercept showed that it was efficacious and well tolerated for HS, given at 50 mg weekly for at least 12 weeks [38, 51–53]. One study decreased dosing to 25 mg weekly after the initial treatment period [54], whereas another study started at 50 mg twice weekly for 24 weeks before decreasing to 25 mg twice weekly for another 24 weeks [55]. In contrast, a 12-week randomized, placebo-controlled trial of 20 patients found no significant difference between etanercept and placebo-treated patients in disease severity or quality of life [56]. No significant adverse effects from etanercept were reported in these studies.

After several case reports of successful control of HS with adalimumab were published [57–62], a 12-week randomized, placebo-controlled trial in 21 patients was performed. The dosing was based on standard psoriasis treatment: an initial dose of 80 mg, followed by 40 mg every other week. Compared to placebo, there was a significant decrease in clinical severity based on the Sartorius score, but nonsignificant decreases in quality of life and pain. Adalimumab was generally well tolerated, but the treatment group had a higher number of infections. As with etanercept, there was poor long-term control, as all patients relapsed by the 3-month follow-up [63].

Ustekinumab is a newer biologic agent that targets IL-12 and IL-23 cytokines in the Th1 immune pathway. A handful of HS cases successfully treated with ustekinumab have been reported [64, 65], but further larger-scale and placebo-controlled studies are needed to better assess safety and efficacy in treating HS.

4.7 Other Therapies

Cryotherapy has been reported for the treatment of individual inflammatory nodules. One study described ten patients with persistent, painful nodules treated with one freeze-thaw cycle of cryotherapy. Eight of the ten patients reported improvement in the treated nodules, but also had significant pain with treatment and long, painful healing complicated by infections and ulcerations [66].

Photodynamic therapy has shown mixed results in case reports. Some patients have noted complete clearance [67–70], but an equal number of patients saw no improvement [69, 71, 72]. A series of 13 patients treated with psoralen plus ultraviolet A (PUVA) therapy demonstrated that 38 % of patients cleared and 31 % had moderate clearance [73].

A single case report of botulinum toxin A injection for axillary HS showed complete remission of symptoms for 10 months [74]. The authors proposed that toxin inhibition of acetylcholine release decreases apocrine gland secretion, and with decreased accumulation of these secretions in an occluded follicle, the risk of follicular rupture and inflammation is decreased.

4.8 Laser Surgery

Ablative and nonablative laser therapy have been utilized as an alternative to surgical excision for HS. Several reports have shown successful localized treatment with carbon dioxide lasers. One of the first reports described the treatment of 24 patients with a stepwise horizontal vaporization technique with second-intention healing. Healing time was 4 weeks, and after a mean follow-up of 27 weeks, 92 % of patients reported no recurrence of disease in the treated areas [75]. Another early study treated seven patients with axillary and inguinoperineal disease with carbon dioxide laser and second-intention healing. After the 4- to 8-week healing time, patients were left with flat and linear scars, with only one patient experiencing a recurrence [76]. Three subsequent studies have shown similar positive responses [77–79]. Reported complications included axillary scar contracture [76, 79], hypertrophic granulation tissue [78], cellulitis [78], Sweet's syndrome [78], and candidal wound infection [76].

Long-pulse neodymium:yttrium-aluminum-garnet (Nd:YAG) laser has shown some promise as a nonablative laser therapy for HS. As the

chromophore for the Nd:YAG laser is the hair follicle, laser surgery might selectively halt the primary follicular occlusion process of early HS. A randomized controlled trial treated 17 patients with topical benzoyl peroxide wash 10 % and clindamycin 1 % lotion only versus these topical treatments plus Nd:YAG (using 4 monthly laser sessions). The entire affected area was treated with one pass, and inflammatory nodules, abscesses, and fistulae were treated with three stacked pulses. There was significantly more improvement in disease severity with adding Nd:YAG treatment and no reported adverse effects, [80] but more studies are needed to determine safety and efficacy.

4.9 Surgery

Patients with debilitating HS unresponsive to the therapies above should consider consultation for surgical treatment by a surgeon experienced in HS care. The best approach has yet to be determined, but surgical procedures can be divided into incision and drainage, unroofing of sinus tracts, and excision. Incision and drainage is often unsatisfactory. One study demonstrated 100 % recurrence after an average of 3 months [81].

Deroofing of sinus tracts can aid in tract healing. After the surgeon determines the extent of the tracts by exploring nodules and sinus tracts with a blunt probe, the roof of the tracts is surgically removed. The open tracts are allowed to heal by second intention; healing time averages 2 weeks. Two studies have shown this method to have a low recurrence rate and low complication rate, with the most common complication being postoperative bleeding [82, 83].

Wide excision is generally recommended over local excision for severe disease, because the recurrence rate is almost two times higher with local excision [81]. Several studies have shown that complete radical excision of the affected areas offers a low recurrence rate, with the inframammary, inguinogenital, and buttock being more likely to have recurrent disease [81, 84–86]. Complications include contractures [84, 85], suture dehiscence [87], bleeding or hematoma [85, 87], wound infection [85, 87], and pain [85]. Evidence also suggests that split-thickness skin grafts or flaps lead to lower recurrence rates compared to primary closure. A review of 72 patients who had excision demonstrated disease recurrence in 13 % of those closed with split-thickness grafts, 19 % of those closed with flaps, and 54 % of those with primary closure [88]. A subsequent review of 106 patients after excision showed no recurrence for those closed with flaps or split-thickness skin grafts versus 70 % recurrence in patients who had primary closure [89].

4.10 Approach to Managing Pediatric Hidradenitis Suppurativa

HS is a chronic, inflammatory, scarring disease that has no cure. There are no FDA-approved treatments, and formal guidelines do not exist for the treatment of HS. Although some pediatric patients have mild disease that remits with minimal intervention, many patients suffer from recurring painful nodules, ulcers, and scars. HS can have a significant impact on quality of life, lifestyle, and self-esteem. Many do not seek medical attention due to embarrassment or lack of past treatment efficacy. Moreover, painful lesions can limit activity and exercise, contributing to obesity, which in turn can exacerbate HS.

Management of HS is challenging because the data for treatment is limited and even more so in children, with few randomized controlled trials and with most treatment modalities having mixed results. Currently, the treatment of HS is as much art as science, and therapy should be selected bearing in mind the age of the patient, the disease activity, and risk-benefit ratio of the intervention, with the goal being to limit disease activity and postpone higher-risk procedures such as surgery. Multimodal management is often needed. Table 4.2 reviews the dosing and side effects of selected systemic medications.

Mild HS (Hurley Stage I) may be treated with antimicrobial washes (e.g., benzoyl peroxide cleansers) and topical clindamycin. Combination

Table 4.2 Dosing and side effects of select systemic medications

Medication	Dosing	Side effects
Doxycycline	50–100 mg twice daily	GI discomfort (nausea, vomiting, epigastric burning), phototoxicity, pseudotumor cerebri
Minocycline	100 mg daily to twice daily	Dizziness, pseudotumor cerebri, drug-induced lupus, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, serum sickness-like reaction, blue-black pigmentation of the nails, skin, scars, teeth, and sclera
Clindamycin and rifampin	300 mg clindamycin twice daily and 300 mg rifampin twice daily	Pseudomembranous colitis (clindamycin), discoloration of body fluids (rifampin), vulvovaginal candidiasis
Dapsone	25–200 mg daily	Hemolytic anemia, methemoglobinemia, peripheral neuropathy, agranulocytosis, hepatitis, hypersensitivity reaction
Isotretinoin	0.2–1 mg/kg/day	Teratogenicity, dry mucous membranes, xerosis, transaminitis, pseudotumor cerebri, myalgias, depression, and other side effects
Cyclosporine	3–6 mg/kg/day	Nephrotoxicity, hypertension, hypertrichosis, gingival hyperplasia, GI discomfort (nausea, diarrhea), immunosuppression, hyperkalemia
Infliximab	5 mg/kg at week 0, 2, 6, and every 8 weeks thereafter	Infusion reaction, reactivation of latent tuberculosis, immunosuppression, exacerbation of demyelinating disease, lupus-like reaction, serum sickness-like reaction, neutralizing antibody formation
Etanercept	25–50 mg weekly, up to 25–50 mg twice weekly	Reactivation of latent tuberculosis, immunosuppression, exacerbation of demyelinating disease, lupus-like reaction, injection site pain

products such as benzoyl peroxide-clindamycin gel have less impact on microbial resistance and may provide beneficial comedolytic effects. Clindamycin-tretinoin gel is another off-label option. Tender inflammatory nodules often respond well to low-strength intralesional steroid injections, particularly if early lesions are injected. If multiple nodules frequently recur, oral tetracycline antibiotics can be added to the regimen, such as doxycycline or minocycline 100 mg twice daily or sustained release minocycline, which is expensive but well tolerated and convenient with single daily dosing. If inadequate response is seen after 10–12 weeks, or if progression to Stage II disease occurs, clindamycin 300 mg and rifampin 300 mg twice daily for at least 10 weeks should be considered. Dapsone and isotretinoin are helpful in some patients, but data for these agents is less convincing. Surgical deroofing of sinus tracts can supplement systemic therapy as well.

If the above treatments are insufficient or if the disease progresses to Hurley Stage III, surgical consultation for partial or complete excision or ablative or nonablative laser treatment may be considered. Alternatively, systemic biologics can be considered, with infliximab being the most studied therapy for HS at this time.

For women who have flares of HS with their menstrual cycle, a trial of an oral contraceptive can be helpful. The oral contraceptives with FDA labeling for acne vulgaris are preferable as they are low in androgenic activity. As discussed earlier, patients who are obese should be counseled on healthy weight loss, and smokers should be directed to cessation strategies. Support groups or professional counseling can be very helpful for patients living with chronic HS. Lastly, teratogenic medications, such as isotretinoin and acitretin, should be used with extreme caution in the adolescent female population, with concomitant reliable contraception and serial pregnancy tests.

Pediatric HS remains an orphan disease and a therapeutic challenge needing further investigation.

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Part II

Immune-Mediated/Autoimmune Diseases

Autoimmune Bullous Diseases of Childhood

5

Nicole A. Weitz, Emily M. Mintz, and Kimberly D. Morel

Key Points

- Though uncommon in children relative to adults, autoimmune bullous diseases are important as blistering can lead to significant pain, impact on function, scarring, mucosal ulceration, and, very rarely, death.
- Accurate diagnosis of the specific disorder, utilizing histopathology and immunofluorescence studies, is important for determination of prognosis and selection of the most appropriate treatment.
- Other than in mild or localized cases, systemic therapy is usually needed but should be used with caution and appropriate monitoring.
- Specific considerations for each drug:

Systemic corticosteroids	Watch for HPA axis suppression with long-term treatment. Avoid live or live-attenuated vaccines for 1 month after treatment if treated >14 days with dose ≥2 mg/kg/day. Consider PPI or H2 blocker if treated >3–4 weeks or with high doses. Consider PCP prophylaxis.
Dapsone	Check G6PD level prior to treatment.
Azathioprine	Check TPMT level prior to treatment; adjust dose according to enzyme activity.
MMF	Discontinue treatment or decrease dose for WBC <3,500–4,000 cells/mm^3. Avoid live or live-attenuated vaccines during treatment.
Cyclophosphamide	Discontinue treatment or decrease dose for WBC <4,000–4,500 cells/mm^3 or platelets <100,000 cells/mm^3, or RBCs in urine. Refer to urologist for persistent hematuria.
IVIg	Check IgA level prior to treatment.
Rituximab	Black box warnings: Fatal infusion reaction, tumor lysis syndrome, severe mucocutaneous reactions, progressive multifocal leukoencephalopathy.

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Abbreviations

ABDC	Autoimmune bullous diseases of childhood
ACE	Angiotensin converting enzyme
BM	Basement membrane
BP	Bullous pemphigoid
CBDC	Chronic bullous disease of childhood
DH	Dermatitis herpetiformis
DRESS	Drug reaction with eosinophilia and systemic symptoms
EBA	Epidermolysis bullosa acquisita
ECP	Extracorporeal photopheresis
G6PD	Glucose-6-phosphate dehydrogenase
HPA	Hypothalamic-pituitary-adrenal
Ig	Immunoglobulin
INID	Intraepidermal neutrophilic IgA dermatosis
IVIg	Intravenous immune globulin
MMF	Mycophenolate mofetil
MMP	Mucous membrane pemphigoid
PCP	Pneumocystis pneumonia
PF	Pemphigus foliaceous
PPI	Proton pump inhibitor
PV	Pemphigus vulgaris
REMS	Risk evaluation and mitigation strategy
SJS	Stevens-Johnson syndrome
SLE	Systemic lupus erythematosus
SPD	Subcorneal pustular dermatosis
TEN	Toxic epidermal necrolysis
TMP-SMX	Trimethroprim-sulfamethoxazole
TPMT	Thiopurine methyltransferase

Autoimmune bullous diseases of childhood (ABDC) are a heterogeneous group of disorders that are characterized by vesicle and bulla formation (Table 5.1). Autoantibodies directed at structures responsible for integrity of the skin, desmosomes and hemidesmosomes, lead to cleavage of the skin and the clinical phenotype. These diseases are rare in childhood and their true incidence remains unknown.

The most common ABDC are chronic bullous disease of childhood (CBDC) and dermatitis herpetiformis (DH). Pemphigus, epidermolysis bullosa acquisita (EBA), bullous pemphigoid (BP), bullous systemic lupus erythematosus (SLE), and mucous membrane pemphigoid (MMP) are less commonly encountered in children. As clinical diagnosis is difficult, histopathologic evaluation and immunofluorescence studies must be utilized to establish an exact diagnosis. Accurate differentiation among the various ABDC is important for selection of the most appropriate treatment.

Depending on the severity and localization of disease, ABDC have significant potential for morbidity and mortality. Some of these diseases may heal with fibrosis, thereby compromising form and function. Mucosal lesions can be acutely devastating. Oral involvement may lead to poor oral intake, dehydration, and failure to thrive. Involvement of the gastrointestinal mucosa may result in a protein-losing enteropathy.

In addition to topical wound care measures, which are pivotal to the management of all bullous diseases, pharmacologic interventions are often needed to control disease activity. Whereas topical corticosteroid treatment may suffice for mild, localized disease, systemic treatment is the mainstay of therapy for most ABDC. Systemic intervention is indicated for patients with large body surface areas involved, painful lesions, lesions threatening function, lack of an identifiable disease trigger that can be removed, and in patients who have failed topical treatment. Patients must not have any contraindication to a given systemic medication. The goals of treatment are to decrease new blister formation and promote healing of existing lesions with the minimal dose of medication possible. No controlled or comparative studies of treatment of ABDC exist and data is limited based on the rarity of these diseases. Approaches are often based on anecdotal reports, case series, and extrapolation of data from treatment of adults with autoimmune bullous diseases. All treatments discussed herein are off-label in children.

5.1 Systemic Therapy

Similar systemic therapies are common to the management of the various ABDC. These treatment modalities all function via several

Table 5.1 Clinical and histopathologic features of ABDC subtypes

Disease	Age of onset/ triggers	Clinical features	Cutaneous distribution	Mucosal involvement	Histopathologic features	Immunofluorescence	Antibody target	Prognosis
Chronic bullous disease of childhood (CBDC)	First decade, usually preschool; may be triggered by drugs, especially antibiotics	"String of pearls"; large, tense, clear and/or hemorrhagic bullae on normal or erythematous skin	Face, scalp, lower trunk, genital area, buttocks, legs, dorsal feet	Occasional oral	Subepidermal bullae with edema of dermal papillae; dermal infiltrate of PMN>eosinophils and mononuclear cells	Linear IgA deposits in lamina lucida	97-kDa or 120-kDa soluble ectodomain of BP 180	Most resolve in months to 5 years, nearly all by puberty; may be chronic
Dermatitis herpetiformis (DH)	People of Northern European descent; males>females; as young as infancy	Pruritic papulovesicular and bullous eruption; clear tense vesicles that rupture easily	Extensor surfaces, buttocks, shoulders>face, eyelids, hairline, nape of neck, scalp; symmetric	Very rare	Dermal papillary microabscesses with PMN and eosinophils	Granular IgA at tips of dermal papillae (perilesional)	Epidermal transglutaminase	Chronic course with exacerbations and remissions; ultimate remission requires gluten-free diet
Pemphigus vulgaris (PV)	Any age	Painful oral lesions, flaccid bullae on normal-appearing skin and mucosa, positive Nikolsky sign	Seborrheic areas, pressure areas of feet and back	95 % with oral involvement	Intercellular edema, suprabasal clefts, "row of tombstones"	Intercellular IgG and C3	Desmoglein 3 and 1	Prognosis better than in adults; may be life-threatening if untreated
Pemphigus foliaceus (PF)	More common in prepubertal children than PV	Superficial, flaccid vesicles and bullae, rupture easily, leave erosions, arcuate configuration; may present with crusted plaques	Scalp, face, upper chest, abdomen, back	Rare oral involvement	Epidermal bullae and intercellular acantholysis, subcorneal clefts	Intercellular IgG and C3	Desmoglein 1	Milder course than PV
Drug-induced pemphigus	After several months of exposure to medications	Nonspecific morbilliform, annular, or urticarial eruption evolves into bullae after latency period	May resemble PF or PV	Rare oral involvement	Intraepidermal acantholysis	Intercellular IgG and C3	Sulfhydryl groups modify desmogleins 1 and 3	Similar to PF

(continued)

Table 5.1 (continued)

Disease	Age of onset/ triggers	Clinical features	Cutaneous distribution	Mucosal involvement	Histopathologic features	Immunofluorescence	Antibody target	Prognosis
IgA pemphigus	As young as 1 month of age	(1) subcorneal pustular dermatosis (SPD), (2) intraepidermal neutrophilic IgA dermatosis (INID); small vesicles, bullae, pustules over well-circumscribed erythema	Abdomen, axillae, groin	Very rare	Subcorneal or intraepidermal bullae with PMN	Intercellular IgA	(1) SPD: desmocollin 1 (2) INID: desmoglein 1 or 3, some without identified antigen	Remissions and exacerbations for 5–8 years
Paraneoplastic pemphigus	Associated with Castleman's disease or malignancy	Intractable stomatitis, conjunctival involvement; bullae, EM- or lichen planus-like pattern	Lips, palms/ soles, nails	Labial, tracheal-bronchial (may lead to bronchiolitis obliterans)	Intraepidermal acantholysis, keratinocyte dyskeratosis, basal cell vacuolar changes	Often negative	Plakin family of proteins	Poor
Epidermolysis bullosa acquisita (EBA)	Any age	Hemorrhagic or serous blisters at sites of trauma or pressure; may be associated with scarring alopecia and nail dystrophy	Extensor surfaces; sites of pressure or trauma	Oropharyngeal; conjunctival; esophageal; anogenital	Subepidermal bullae	Linear IgG (± C3) in lower lamina densa or sublamina densa of BM	Type VII collagen; IgG>IgA	Chronic course with flares; better course in children than adults
Bullous systemic lupus erythematosus (Bullous SLE)	African-American adolescent females; mean age 22 years	Pruritic vesicles, tense bullae, erythematous macules and papules	Sun-exposed areas, flexor and extensor surfaces	Oral mucosa	Subepidermal bullae with PMN	Granular, linear or mixed; IgG>IgM, IgA, C3 at BM and upper dermis	Type VII collagen	Determined by course of associated systemic SLE

Mucous membrane pemphigoid (MMP)	Females > males; as young as 20 months; mean age 10.3 years	Desquamative gingivitis often initial presentation; ocular involvement may be delayed	Only 25 % have cutaneous lesions; face, neck, upper chest	Oral mucosa, conjunctiva more commonly than nasopharynx, esophagus, larynx, anogenital	Subepidermal bullae	Linear IgG (± C3) in lamina lucida of BM	(1) BP antigens (BP 180, BP 230) (2) Laminin 332 (laminin 5 or antiepiligrin) (3) β4-integrin (ocular MMP)	Chronic disease, remains active into adulthood
Bullous pemphigoid (BP)	As young as 2 months	Pruritus, urticarial plaques evolve into large, tense bullae over weeks to months; over normal or erythematous skin; negative Nikolsky sign	Lower abdomen, anogenital, flexors, occasionally face; palms and soles in infants; penile blisters in older males	25 % have oral lesions; especially older children	Subepidermal bullae; eosinophilia	C3 and IgG at lamina lucida of BM	BP180 > BP230	Remits in most children within 1 year; resolves without scarring

PMN polymorphonuclear leukocytes, *Ig* immunoglobulin, *BM* basement membrane

mechanisms: (1) suppression of the inflammatory process, (2) suppression of antibody production, and (3) removal of circulating antibodies.

5.1.1 Systemic Corticosteroids

Systemic corticosteroids are the mainstay of treatment for many of the ABDC, including pemphigus, BP, EBA, and MMP. Treatment is most often initiated with oral prednisone at 1 mg/kg/day and may be increased to 2 mg/kg/day in divided doses (maximum dose 80 mg/day) [1, 2]. Once the disease is controlled, the steroids should be consolidated to a single morning dose and then tapered to alternate-day therapy. The addition of a steroid-sparing agent should always be considered given the significant potential for adverse effects.

These adverse effects are well documented. Suppression of the hypothalamic-pituitary-adrenal (HPA) axis is one of the most important consequences of steroid therapy. HPA axis suppression is a dose- and duration-dependent complication, the risk of which increases with (1) the use of an agent with an intermediate to long half-life, (2) the use of divided-dose therapy, and (3) the administration of steroids at any time other than early morning. While laboratory evidence may occur sooner, clinically significant HPA suppression occurs after 3–4 weeks of treatment with physiologic or supraphysiologic doses of steroids. The increased vulnerability to stress from adrenal suppression lasts 12–16 months after discontinuation of long-term treatment. Adrenal crisis is the potentially fatal manifestation of this suppression, which can be prevented by appropriate dose tapering and administration of stress dose steroids, when indicated, after discontinuation [1].

Other complications of steroid therapy include behavioral changes (fussiness/sleep disturbance), pseudotumor cerebri, metabolic alterations (hyperglycemia, hyperlipidemia, hyperphagia, and weight gain leading to a cushingoid appearance), hypertension, congestive heart failure, gastrointestinal irritation, glaucoma, cataracts, osteoporosis, myopathy, aseptic necrosis of bone, menstrual irregularities, hematologic abnormalities, and immunosuppression [1, 3]. Cutaneous adverse effects include delayed wound healing, striae, and hypertrichosis [4].

Of particular importance in children is the potential for impairment of normal growth and development that may accompany steroid therapy. Corticosteroids slow the growth of long bones and retard bone aging, which can cause significant linear growth suppression in pediatric patients. In a review of patients younger than 13 years of age undergoing treatment with oral steroids for pemphigus, 50 % developed growth retardation [5]. Catch-up growth has been noted within a few months of therapy cessation [6, 7]. Though the data have been conflicting, it has also been suggested that systemic steroid use in neonates and ex-preterm infants may adversely impact neurodevelopment [8–10].

Steroid-induced immunosuppression may lead to life-threatening opportunistic infections in addition to compromising the child's ability to obtain and respond adequately to routine immunizations. While the dose and duration of systemic steroids necessary to cause immunosuppression in a child are not clearly defined, the Committee on Infectious Diseases of the American Academy of Pediatrics recommends that children receiving a dose equivalent to 2 mg/kg/day or greater of prednisone (or 20 mg/day or greater in those weighing over 10 kg) for more than 14 days should be considered immunosuppressed and immunization with live-attenuated vaccines avoided for at least 1 month after treatment cessation. Patients treated for fewer than 14 days may receive their immunizations immediately upon drug cessation [11]. There is recent evidence that systemic corticosteroid therapy may prevent the development of protective immunoglobulin titers to acellular immunizations [12]. As a result, Kelly et al [12] have suggested that all pediatric patients treated with systemic corticosteroids during the immunization period have antibody titers to diphtheria and pertussis checked after treatment cessation, with the possible need for additional booster immunizations.

Given the myriad of potential adverse effects of corticosteroids, patients must be monitored closely (Table 5.2). Pretreatment evaluation

Table 5.2 Monitoring guidelines for systemic drug therapy*

Drug	Baseline	Follow-up
Systemic corticosteroids	Blood pressure	Blood pressure
	Height/weight (plot on growth chart)	Height/weight (growth chart) at 1 month, then q2–3 months
	Ophthalmologic exam	Ophthalmologic exam q6–12 months
	TB screen	Annual TB screen
	Fasting glucose, K+, triglycerides	Fasting glucose, K+, triglyceride at 1 month, then q3–4 months
		AM cortisol prior to drug cessation
		Antibody titers after cessation if immunized during treatment
Dapsone	CBC + differential	CBC + differential q1 week × 4 weeks, then q2 weeks until week 12, then q3–4 months
	LFTs	
	BUN/Cr	Consider reticulocyte count PRN to assess response to hemolysis
	Urinalysis	LFTs, BUN/Cr, urinalysis q3–4 months
	G6PD enzyme level	Methemoglobin level, if clinically indicated
	Pregnancy test in females of childbearing potential	
Azathioprine	CBC + differential	CBC + differential, LFTs q2 weeks × 2 months, then q2–3 months
	BMP	BMP, urinalysis in high-risk patients or if abnormal baseline labs
	LFTs	
	Urinalysis	
	TB screen	
	TPMT level	
	Pregnancy test in females of childbearing potential	
Mycophenolate mofetil	CBC + differential	CBC + differential q2 weeks × 2–3 months, then q1 month up to first year, then decrease frequency
	BMP	
	LFTs	LFTs at 1 month, then q3 months
	Pregnancy test in females of childbearing potential	
Methotrexate	CBC	CBC, LFTs 5–6 days after "test dose," then q 1–2 weeks × 2–4 weeks and after dose escalation, then taper to q3–4 months
	LFTs	
	BMP	BMP q6–12 months
	Hepatitis serologies	Consider liver biopsy in patients on long-term therapy or with high cumulative dose or repeatedly elevated LFTs
	HIV test in at risk patients	
	Pregnancy test in females of childbearing potential	
Cyclophosphamide	CBC + differential	CBC + differential, urinalysis q1 week × 2–3 months, then decrease frequency
	BMP	BMP, LFTs q month × 3–6 months, then q3 months
	LFTs	Chest X-ray q6 months
	Urinalysis	Consider urine cytology when cumulative dose >50 g or hemorrhagic cystitis
	Pregnancy test in females of childbearing potential	Pap smear (for women) and stool guaiac q6 months

(continued)

Table 5.2 (continued)

Drug	Baseline	Follow-up
Cyclosporine	Blood pressure CBC LFTs BMP Urinalysis Fasting lipid profile Magnesium Uric acid Pregnancy test in females of childbearing potential	Blood pressure, CBC, LFTs, BMP, fasting lipid profile, magnesium, uric acid q2 weeks × 2 months, then q1 month Consider checking trough levels
Colchicine	CBC LFTs BMP Urinalysis Pregnancy test in females of childbearing potential	CBC, LFTs, BMP, urinalysis q3 months

TB tuberculosis, *K+* potassium, *CBC* blood cell count, *LFTs* liver function tests, *BUN/Cr* blood urea nitrogen/creatinine, *BMP* basic metabolic/chemistry panel, *q* every, *G6PD* glucose-6-phosphate dehydrogenase, *TPMT* thiopurine methyltransferase

*More frequent evaluation if clinically indicated or in patients at high risk for adverse events

should include blood pressure, height and weight plotted on a growth curve, an ophthalmologic exam, and screening for tuberculosis (TB) in high-risk patients [1]. Subsequently, blood pressure, height, and weight should be reassessed every 1–2 months in addition to obtaining a thorough history for any adverse effects. Patients should undergo an ophthalmologic exam every 6–12 months. Laboratory evaluation (potassium, fasting glucose, fasting triglycerides) should be obtained 1 month after treatment initiation and then every 3–4 months. Several authors recommended prophylaxis against pneumocystis pneumonia with trimethroprim-sulfamethoxazole (TMP-SMX) while treating children with systemic steroids [12]. It is recommended to prophylactically protect the gastric mucosa with a proton pump inhibitor or H2 channel blocker in children undergoing treatment for at least 3–4 weeks or for shorter periods of time using high drug doses [4]. When nearing treatment cessation, it is reasonable to check a morning cortisol level to assess for HPA axis suppression [1]. Patients should be aware of the need for stress dose steroids for accidents, illnesses, or procedures. Pediatric endocrinology consultation may be useful to assist with management of tapering long-term steroid treatment.

5.1.2 Dapsone

Dapsone is a sulfone antimicrobial agent that is the standard treatment for several ABDC, including CBDC, DH, and bullous SLE. The presence of a predominantly neutrophilic infiltrate in bullae indicates a higher likelihood of successful treatment with dapsone [13], as it exerts its anti-inflammatory effects by interfering with neutrophil chemotaxis and adherence [14, 15]. When indicated, dapsone should be started at a dose of less than 0.5 mg/kg/day and increased slowly over weeks to months to achieve response, up to 2 mg/kg/day (maximum dose 100 mg/day) [2].

Dose-related adverse effects include hemolysis [especially in the setting of glucose-6-phosphate dehydrogenase (G6PD) deficiency, which is a contraindication to the use of this medication] and methemoglobinemia, which manifests as cyanosis, dyspnea, lethargy, and headache. A benign hemolysis is expected, and a compensatory reticulocytosis occurs [16, 17].

Idiosyncratic adverse reactions include agranulocytosis, peripheral neuropathy, hepatitis, gastrointestinal (GI) upset, liver necrosis, psychosis, tachycardia, and cutaneous hypersensitivity reactions. The dapsone hypersensitivity syndrome, characterized by lymphadenopathy, eosinophilia, hepatitis, and rash, is a rare and severe reaction that occurs early in treatment. Most complications occur within the first 3 months of treatment [18].

Initial laboratory evaluation should include a complete blood count (CBC) with differential, liver function tests (LFTs), renal function tests including urinalysis, and a G6PD level (Table 5.2). In females of childbearing age, a baseline pregnancy test is also indicated as dapsone is a pregnancy category C drug. In addition to a detailed history and physical exam to assess for signs and symptoms of adverse effects, a CBC with differential should be monitored frequently during the first 3 months of treatment (every week for 4 weeks, then every 2 weeks until week 12, and then every 3–4 months). Liver function tests and renal function tests/urinalysis should be checked every 3–4 months [13]. When patients are well controlled with few, if any, active lesions, the dose should be gradually tapered to minimize adverse effects.

5.1.3 Sulfonamides

Other members of the sulfonamide class may also be used to treat ABDC, in combination with or as an alternative for patients who cannot tolerate dapsone. Sulfapyridine is the most commonly used member of this class. Although it is not currently available in the USA, sulfapyridine may be provided on a compassionate basis through the Jacobus Pharmaceutical Company (telephone, 609-921-7447). It is thought to have a more favorable toxicity profile, and cross-sensitivity with dapsone is uncommon, making it a useful choice for patients who cannot tolerate dapsone [13]. Adults are initiated at a dose of 500 mg twice daily which can be increased until a clinical response is noted up to a maximum dose of 2 g/day [13]. Sulfasalazine, which is metabolized to sulfapyridine, is available and can also be used. The usual starting dose in children with rheumatoid arthritis is 10 mg/kg/day divided into twice daily dosing, with a maintenance dose of 30–50 mg/kg/day (maximum dose 2 g/day) [2].

Adverse effects are similar to those of dapsone, although generally less severe, and include GI upset, thyroid dysfunction, leukopenia, thrombocytopenia, agranulocytosis, and rare renal and hepatic toxicity and psychiatric disturbances. Adequate hydration should be encouraged to minimize the risk of nephrotoxicity due to crystallization in the urine [13]. Like dapsone, sulfapyridine may cause significant hemolysis in patients with G6PD deficiency. A rare but potentially fatal adverse effect of sulfonamide therapy is obliterative bronchiolitis. Parents should be advised to watch for shortness of breath and seek further evaluation by a physician if this symptom is noted.

5.1.4 Other Immunosuppressants

When systemic therapy with corticosteroids or dapsone does not produce an adequate clinical response, adjuvant immunosuppression is often indicated. There is, however, no consensus on which immunosuppressive agents should be used and how; all agents have serious risk profiles [19]. The following are the most frequently used immunosuppressants in the management of ABDC.

5.1.4.1 Azathioprine

Azathioprine is a purine antimetabolite that although is generally well tolerated, is not often used in pediatric patients given concerns for carcinogenicity. It is given at a dose range of 1–3 mg/kg/day (maximum dose 5 mg/kg/day) [2]. Myelosuppression may occur, and patients with thiopurine methyltransferase (TPMT) deficiency (1 in 300) are at risk for a severe form of this. Patients may be tested for TPMT enzyme deficiency before treatment initiation, and dosage should be adjusted according to enzyme activity. Other adverse effects include cutaneous hypersensitivity, alopecia, GI intolerance,

Table 5.3 Mycophenolate mofetil (MMF) dosage guidelines

Body surface area	Dose
<1.25 m^2	600 mg/m^2/dose BID to max 2 g/day
1.25–1.5 m^2	750 mg BID
>1.5 m^2	1,000 mg BID

pancreatitis, and hepatotoxicity. Azathioprine is also teratogenic (pregnancy category D). As such, female patients of childbearing potential should undergo a pregnancy test and be advised in the use of two forms of effective contraception if sexually active. Other baseline evaluations should include a CBC with differential, basic metabolic panel (BMP), LFTs, urinalysis, and TB screening test. CBC with differential and LFTs should be repeated biweekly for the first 2 months of therapy and every 2–3 months thereafter (Table 5.2) [20].

5.1.4.2 Mycophenolate mofetil (MMF)

Mycophenolate mofetil (MMF) inhibits *de novo* purine synthesis and therefore suppresses lymphocyte proliferation, resulting in decreased antibody production. It has been shown to be well tolerated and effective in several autoimmune blistering diseases at a dose of 1.25–2 g/day [21, 22]. In younger children, dosage is adjusted for BSA (Table 5.3). Hematologic disturbances, including anemia, leukopenia, and thrombocytopenia, may occur in a dose-related manner. There is also an increased susceptibility to infection; live and live-attenuated vaccines should be avoided during the course of treatment [2]. As MMF is a potential teratogen (pregnancy category D), a pregnancy test prior to treatment initiation in females of childbearing age and two forms of effective contraception in those who are sexually active are necessary. Monitoring should include a baseline CBC with differential, BMP and LFTs, followed by serial CBC (biweekly × 2–3 months, then monthly) and LFTs (at 1 month and quarterly thereafter) for the first year (Table 5.2). Therapy should be discontinued or the dose reduced in the setting of WBC <3,500–4,000 cells/mm^3 [22]. Prescribers should note the black box warning on the package insert which states that only physicians experienced in immunosuppressive therapy and management of renal, cardiac, or hepatic transplant patients should prescribe CellCept (brand name for MMF). Additionally, the FDA has recently mandated the Mycophenolate Risk Evaluation and Mitigation Strategy (REMS) for prescribers, pharmacists, and patients to ensure the benefits outweigh the risks of first trimester pregnancy loss and congenital malformations associated with mycophenolate use during pregnancy [23].

5.1.4.3 Methotrexate

Methotrexate is a folic acid analogue that inhibits DNA and RNA synthesis, resulting in decreased lymphocyte function and immunosuppression. Methotrexate, off-label for the treatment of ABDC, has been used as second-line monotherapy or in combination with topical or systemic steroids. An initial dose of 0.25 mg/kg weekly may be administered and then slowly increased with appropriate monitoring to a maximum of 0.7 mg/kg given once weekly [4]. GI upset, myelosuppression, interstitial pneumonitis, hepatotoxicity, nephrotoxicity (although not typically at dermatologic doses [24]), and neurotoxicity may complicate the use of methotrexate [24]. Methotrexate is an abortifactant and a teratogen and is therefore, contraindicated in pregnancy (pregnancy category X). Pregnancy testing and counseling are needed prior to treatment initiation in females of childbearing age, along with the use of two forms of effective contraception if sexually active. Unique dermatologic adverse effects include "radiation recall" and epidermal necrosis; other dermatologic effects include photosensitivity, Stevens-Johnson syndrome (SJS), exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis (TEN), erythema, stomatitis, and alopecia [24]. While it is known that long-term, high-dose methotrexate therapy may reduce bone density, the effect of short-term, lower-dose therapy is less clear. Bone pain separate from the child's joints should prompt evaluation for methotrexate-induced osteopathy, which may warrant an MRI. Concomitant use of corticosteroids increases the risk of this adverse effect [4, 25]. To maintain overall bone density, supplementation with vitamin D (400 IU daily) and calcium (500 mg daily for ages 1–3 years,

800 mg daily for ages 4–8 years, 1,300 mg daily for ages 9–18 years) is reasonable [4].

Baseline evaluation includes CBC, BMP, and LFTs and for menstruating females, a pregnancy test. CBC and LFTs should be repeated within 1 week of the initial dose and CBC repeated 5–6 days after every dose escalation. Interval checks of CBC and LFTs should be ongoing with checks 5–6 days after dose increases, then with decrease in frequency to every 2 weeks then monthly and as symptoms dictate. Renal function should be reassessed at least yearly (Table 5.2) [24]. Although studies have failed to demonstrate irreversible hepatotoxicity with non-oncologic doses of methotrexate in children [26, 27], clinicians may consider the risks and benefits of a liver biopsy as for the adult population, where concern is heightened in cases of repeatedly elevated liver enzymes and/or in those with risk factors for hepatic disease (such as obesity, diabetes mellitus, and excessive alcohol consumption) [24]. Supplementation with folic acid (50 μg daily for infants, 1 mg daily for children older than 1 year of age) is recommended to minimize the risk of GI and hematologic adverse effects [4].

5.1.4.4 Cyclophosphamide

Cyclophosphamide is an alkylating agent that suppresses both cellular and humoral immunity. It can be administered as daily oral doses (1–3 mg/kg/day), daily IV boluses (5–9 mg/kg/day), or monthly intravenous infusions (0.5–1 g/m^2 IV) [22]. One study showed daily administration of 2–2.5 mg/kg/day of cyclophosphamide in combination with 1 mg/kg/day of prednisone to be effective in patients as young as 6 years of age with refractory pemphigus [28]. Aggressive hydration is important to minimize the risk of urotoxicity (hemorrhagic cystitis), and oral administration of mesna (sodium 2-mercaptoethanesulfonate) may be considered. Other potential adverse effects include myelosuppression, alopecia, nephrotoxicity, cardiotoxicity, pulmonary fibrosis, leukoencephalopathy, and hepatotoxicity. Of particular concern in children, cyclophosphamide has the potential to cause malignancy and infertility. It also has teratogenic potential (pregnancy category D), so females of childbearing age must be evaluated for pregnancy prior to treatment initiation, and two forms of effective contraception are needed for those who are sexually active. Baseline laboratory evaluation should include a CBC with differential, BMP, LFTs, and urinalysis (Table 5.2). A baseline WBC >5,000/mm^3 and granulocyte count >2,000/mm^3 are required for treatment initiation [22]. CBC and urinalysis should be repeated weekly for the first 2 months and then biweekly. Therapy should be discontinued or the dosage reduced in the setting of WBC <4,000–4,500 cells/mm^3 or platelets <100,000 cells/mm^3 or hematuria. LFTs should be repeated monthly for the first 3–6 months and periodically thereafter [22].

5.1.4.5 Cyclosporine

Cyclosporine suppresses cellular and, to a lesser extent, humoral immunity. It may have some utility as a second-line steroid-sparing adjuvant agent (2.5–5 mg/kg/day; maximum dose 15 mg/kg/day) in pemphigus, BP, EBA, and CBDC. Children may require higher doses to control their disease than adults [2]. Adverse effects that have been reported include a reversible dose-related renal dysfunction as well as permanent renal toxicity, tremors, headache, GI upset, paresthesias, hyperesthesias, acne, hypertrichosis, hypertension, and gingival hyperplasia [2]. Laboratory abnormalities include leukopenia, hyperkalemia, hyperuricemia, hypomagnesemia, and hyperlipidemia [29]. There is an increased risk of non-melanoma skin cancer with long-term treatment, especially when used with other immunosuppressants [2, 29]. Baseline evaluation should include CBC, liver and renal function tests, and fasting lipid profile (Table 5.2). Patients should be monitored every 2 weeks for the first 2 months of therapy and monthly thereafter with repeat CBC, liver and renal function tests, and fasting lipids [29]. In females of childbearing age, a baseline pregnancy test is indicated as cyclosporine is a pregnancy category C drug. Sun precautions should also be advised for all patients.

5.1.4.6 Colchicine

Colchicine, which exerts its anti-inflammatory effects by inhibiting neutrophil chemotaxis and adhesion, has been used to treat the neutrophilic bullous dermatoses (DH, CBDC, IgA pemphigus,

EBA, bullous SLE) [30]. It may be used alone or in combination with systemic steroids at an empiric dose of 0.5 mg orally twice daily (patients age 3–9 years) [31, 32]. Colchicine should not be used in patients with blood dyscrasias or serious gastrointestinal, renal, hepatic, or cardiac disorders. Diarrhea is a common side effect. Females of childbearing potential should be evaluated for pregnancy prior to treatment as this drug is pregnancy category C. Monitoring should include CBC, LFTs, BMP, and urinalysis every 3 months (Table 5.2) [30, 33].

5.1.4.7 Nicotinamide

Nicotinamide is a vitamin B analogue with anti-inflammatory properties. There is only one report of effective monotherapy with nicotinamide in treating an adult patient with a localized bullous eruption [34]. In combination with dapsone, it was reported to be effective in a child with CBDC [35]. Combination therapy with nicotinamide and tetracycline has also been reported as effective in adults with linear IgA disease, BP, and MMP [36–38]. One randomized controlled study compared nicotinamide (1.5 g/day) plus tetracycline (2 g/day) to prednisone (40–80 g/day) in 20 adults with BP and showed that the combination regimen had comparable efficacy [37]. However, tetracycline antibiotics are contraindicated in young children less than 8 years of age. There are no dosing guidelines for treating pediatric patients with nicotinamide, but one study evaluating nicotinamide in children as young as 5 years old with newly diagnosed type I diabetes utilized doses of 1–2 mg/kg/day [39]. Although it is derived from nicotinic acid, nicotinamide does not have the same vasodilatory, GI, or hypolipemic effects as nicotinic acid. Nicotinamide is, however, hepatotoxic and should be used with caution [13].

5.1.5 Antibiotics

Systemic antibiotics, either alone or in combination with other therapies, are often utilized as a treatment option for children. The benefit of treating ABDC with antibiotics is that, unlike many of the other treatment options described, most generally do not require blood monitoring which is particularly advantageous in the treatment of children. Erythromycin has been reported to be used successfully in CBDC, BP, bullous SLE and mixed immunobullous disease of childhood [40–42]. Its benefit has been attributed to the anti-inflammatory effects [43], although it also increases the serum level of corticosteroids and can therefore have a steroid-sparing effect when used in combination [1]. The most common adverse effect of therapy is GI upset, while serious complications are extremely rare. Successful treatment with dicloxacillin and oxacillin, both at doses of 50 mg/kg daily, has also been described. Maximum dose for dicloxacillin is 2 g/day and oxacillin maximum is 12 g/day. Potential side effects include GI intolerance, urticaria and other allergic reactions, and rare transient hepatic dysfunction [17].

TMP-SMX has also been reported to be used successfully in CBDC [44]. Caution must be used when prescribing TMP-SMX given the potential for severe allergic reactions including DRESS syndrome, SJS, and TEN. Patients must be warned to seek prompt evaluation for rash or flu-like symptoms while on TMP-SMX. Patients with autoimmune disease may be at higher risk of these allergic reactions. TMP-SMX is a folate antagonist and is therefore contraindicated in patients with megaloblastic anemia and in patients taking methotrexate [45, 46]. Hematologic side effects including aplastic anemia, neutropenia, and agranulocytosis have all been reported, and CBC with differential should be monitored in patients receiving long-term therapy [45]. Hemolytic anemia is a side effect in patients with G6PD deficiency. In females of childbearing age, a baseline pregnancy test is also indicated as TMP-SMX is a pregnancy category C drug.

5.1.6 Intravenous Immune Globulin

Intravenous immune globulin (IVIg) is a purified source of human immune globulins from

pooled plasma that is being increasingly used in the treatment of pediatric autoimmune and inflammatory conditions. Its use in ABDC should only be considered for patients who are resistant and nonresponsive or who develop serious adverse effects to first-line therapies. Its use has been shown to produce a decline in circulating pathogenic antibodies, with resultant clearing of skin disease and a steroid-sparing effect [47, 48]. In older children, high-dose IVIg has been used with reported success in cases of EBA [49].

IVIg is administered as an intravenous infusion of 400–1,000 mg/kg at a rate of 0.01 ml/kg/min, doubled every 15–30 min to a maximum rate of 0.08 ml/kg/min. If adverse events occur, the infusion should be stopped until they subside and then restarted at the prior tolerated rate [2]. Sucrose-containing preparations should not be infused at a rate greater than 3 mg/kg/min [2]. Potential adverse reactions include infusion-related systemic reactions (most commonly headache, fever, nausea, vomiting, flushing, chills, and lethargy) that may be prevented by premedication with systemic steroids, antihistamines, and/or antipyretics. Adverse reactions occur in less than 5 % of patients overall [50], although a recent study of children receiving IVIg treatment for juvenile dermatomyositis reported an incidence of adverse effects in 9 % of infusions [51], suggesting that children with autoimmune disease may be more susceptible to these reactions. Products with high IgA content were more likely to cause infusion-related adverse reactions in this cohort [51]. Severe systemic reactions such as SJS, hemodynamic instability, respiratory distress, and anaphylaxis may also occur, although much less commonly. An IgA level may be checked prior to treatment in nonurgent situations as patients with IgA deficiency are known to be at higher risk of anaphylaxis during IVIg infusions. Other risks include aseptic meningitis syndrome, acute renal failure, and venous thrombosis [2]. Overall, pediatric patients appear to tolerate IVIg infusions better than their adult counterparts. Immunizations should be delayed for 3 months after administration of IVIg [11].

5.1.7 Rituximab

There have recently been an increasing number of reports of successful treatment of severe and refractory ABDC with rituximab (MabThera™, Roche, Basel, Switzerland and Rituxan™, Genentech, South San Francisco, CA). A chimeric monoclonal antibody that targets the cell surface antigen CD20 on B cells [52, 53], rituximab was initially developed for use in B cell malignancies. After its safety and efficacy for this indication were demonstrated, rituximab became a therapeutic candidate for autoimmune conditions, exploiting its B cell-depleting properties.

Rituximab is associated with several infusion-related adverse effects including headache, fever, chills, urticaria, pruritus, and hypotension, which may be controlled by premedication. Potential dermatologic effects include SJS, TEN, and vesiculobullous reactions [54]. There is also an increased risk of malignancy, and fatal hypersensitivity reactions and arrhythmias have been reported in adults undergoing treatment for other indications [54–56]. As a consequence of immunosuppression, serious and potentially fatal infections have been reported in patients treated with rituximab. These seem to occur at a higher rate in patients undergoing treatment for autoimmune bullous diseases than for other indications [57]. It has been hypothesized that this may result from the extensive denuded epithelium and the presence of protein and glucose in blister fluids that provide a medium for growth of organisms in patients with blistering diseases [58]. Patients with BP and those previously treated with high-dose immunosuppressants may be at particularly high risk for complications [57]. Among three children included in a recent review, two experienced long-standing hypogammaglobulinemia, and one also suffered devastating infectious complications [57].

Given the significant risk of complications in the pediatric population, rituximab should be considered only for a select cohort of patients with recalcitrant blistering diseases and should be administered under careful monitoring. It is recommended to consider treatment only for patients who have not responded to 3 months of treatment with at least two regimens that include

a combination of systemic corticosteroids and another immunosuppressive agent [57]. Of the ABDC, pemphigus and EBA seem to respond best to rituximab [57]. Prior to drug initiation, active infection, particularly tuberculosis and viral hepatitis, should be ruled out. In addition to laboratory evaluation with CBC, LFTs, BMP, and urinalysis, children should undergo a baseline cardiac evaluation, as heart disease may increase their susceptibility to infusion-related hypotension. A pregnancy test should be administered to females of childbearing potential and an effective means of contraception implemented during and for 12 months after treatment [54].

Given the limited experience with rituximab use in ABDC [53, 59, 60], the optimum frequency and duration of administration remain to be elucidated. Unless the child's weight allows the adult rheumatoid arthritis dosing, most reported cases used the scalable dosing of four weekly infusions as used for lymphoma. One protocol which has been described based on the experience with treating childhood SLE [61] is as follows:

(a) Rituximab administered weekly for two to four doses.
(b) An initial dose of 188 mg/m^2 infused over 4 h.
(c) Subsequent doses of 375 mg/m^2 infused over 6–8 h.
(d) Premedication 30 min before each infusion with allopurinol, paracetamol, antihistamines, and hydrocortisone.
(e) Vital signs should be checked hourly during the infusion.

Clinical response should be assessed frequently and the decision to continue infusions readdressed. One infant treated with rituximab for severe BP had a remission after two infusions [59], while a child with pemphigus required many more treatments [60]. In a series of 17 adult patients treated for their autoimmune blistering diseases, relapse occurred in approximately half of patients, and complete or partial remission was achieved with a second course of treatment [62]. Single-cycle and low-dose rituximab have also been reported to be helpful in adults with PV [63].

If treatment is initiated, patients should continue their pretreatment immunosuppressant regimen until a clinical response is noted, at which point the prior medications can be slowly tapered. Combination therapy with IVIg may prevent hypogammaglobulinemia, although reports of synergistic benefit are conflicting [57, 64]. Upon discontinuation of rituximab, patients should continue to be closely monitored for signs and symptoms of infection. For 2 years after treatment cessation, B cell levels, total immunoglobulins and specific antibodies against HSV, and autoantibodies may require periodic monitoring [57]. The use of rituximab in children has been associated with a decline in immunization-derived antibodies [60, 65].

5.1.8 Plasmapheresis and Immunoadsorption

Plasmapheresis is a treatment modality in which the patient's blood is drawn, filtered, and the cellular elements returned. It has been used primarily in adult patients with autoimmune bullous diseases who are resistant to other systemic therapies, although it has been safely used in children with other diseases, including SJS/TEN [66]. The results of controlled trials assessing the benefit of plasmapheresis in autoimmune bullous diseases have been conflicting [67, 68]. The theory of use is that by removing the pathogenic autoantibodies from the patient's blood, plasmapheresis can result in disease improvement. There is some evidence that plasmapheresis followed by immunosuppression therapy may be beneficial for adult patients with severe PV unresponsive to systemic corticosteroids [69]. A steroid-sparing effect of plasmapheresis has been reported in adult patients with BP [70], although subsequent studies failed to confirm any benefit of plasmapheresis and systemic steroids over systemic corticosteroids alone [71]. A rebound rise in antibody titers often follows plasmapheresis, which may be allayed by subsequent immunosuppressive drug therapy.

Immunoapheresis is a procedure similar to plasmapheresis in which immunoglobulins are selectively removed through exposure to an immunoglobulin binding matrix, and plasma is returned to the patient depleted of immunoglobu-

lins. In addition to allowing for processing of a greater plasma volume per session, it is associated with lower rates of adverse events than plasmapheresis. It has been used with reported success in adults with pemphigus, BP, CBDC, and EBA [67, 72].

Central access is required for both procedures, and therefore, the risk of infection and other central line complications must be considered. Treatment in an inpatient setting has been recommended [73]. Anticoagulation is required to prevent clot formation in these extracorporeal procedures. In the pediatric setting, higher levels of anticoagulation are needed due to the use of smaller tubing and lower blood flow velocities. While systemic heparin is used at some centers, regional citrate anticoagulation is considered the standard procedure in pediatric apheresis [74]. Citrate, which prevents coagulation through binding calcium, has the potential to cause several side effects, including paresthesia, hypocalcemia, hypotension, and bradycardia. Anemia is particularly common in patients undergoing simultaneous immunosuppression [73]. Contraindications include body weight less than 15 kg, severe cardiovascular disease, treatment with an angiotensin converting enzyme (ACE) inhibitor, known hypersensitivity to a material used in the exchange column, severe systemic infection, hypofibrinogenemia, and inadequate anticoagulation [73].

5.1.9 Extracorporeal photopheresis

Extracorporeal photophoresis (ECP) is a form of immunotherapy initially approved for the treatment of cutaneous T-cell lymphomas. After ingestion of methoxypsoralen, the patient's blood is collected and peripheral lymphocytes exposed to ultraviolet A light, and then returned to the patient. The mechanism of action of ECP remains unknown. ECP has been used to induce remission in drug-resistant autoimmune bullous diseases [75, 76], although the pediatric literature is limited [77]. The combined use of plasmapheresis and ECP in a child with drug-resistant BP has been reported [77]. Adverse effects include nausea and photosensitivity, hypotension, congestive heart failure, flushing, and tachycardia. Again, central access is required.

5.2 Treatment of Specific Diseases

5.2.1 Chronic Bullous Disease of Childhood

Dapsone is the drug of choice for CBDC. Treatment should be initiated at less than 0.5 mg/kg/day and increased slowly until blistering and symptoms are controlled (maximum dose 100 mg/day) [2]. It is important to rule out G6PD deficiency prior to use and to monitor as described above. Sulfapyridine is another first-line agent [17], and other sulfonamides may be of benefit. Dapsone and sulfonamides can be combined for improved efficacy without reported additive side effects [13]. Systemic steroids may be added at the onset of disease and during flares to control symptoms, although long-term use is not advisable given their side effect profile. Topical steroids to recent intact lesions may be used in combination with systemic therapies as well [78].

Children in whom sulfonamides are contraindicated may be treated with alternative agents. Systemic antibiotics represent another treatment option that can be useful while awaiting the results of diagnostic tests or for patients who cannot tolerate first-line interventions. Successful treatment with erythromycin, presumably through its anti-inflammatory actions, has been described [41]. Erythromycin as monotherapy is unlikely to result in sustained improvement of CBDC, but its administration upon initial patient evaluation may lead to early improvement while awaiting further workup [79]. Although not evidence based, successful treatment with dicloxacillin, oxacillin, and trimethoprim-sulfamethoxazole have also been reported [17, 44]. In patients with inadequate response to dapsone, sulfonamides, or antibiotics, systemic corticosteroids, colchicine (5 mg BID if at least 3 years old), and MMF (see Table 5.3 for dosing) are alternative therapies [13, 21, 31, 32].

The prognosis of CBDC is unaffected by the severity of blistering and generally positive. Almost all cases spontaneously remit before puberty and usually within the first 5 years of symptom onset [80]. Cutaneous lesions are more responsive to systemic intervention than their mucosal counterparts, which may be more likely to respond to topical steroids. Given the known natural history of CBDC and its ultimate remission, regular attempts should be made to wean patients off of therapy in order to avoid the potential adverse effects.

5.2.2 Dermatitis Herpetiformis

DH is a pruritic, papulovesicular, and bullous eruption associated with gluten sensitivity and celiac disease. It is one of the most common ABDC, although it predominantly presents after the second decade. It is most common in individuals of Northern European descent and affects males more than females. It tends to affect the extensor surfaces (elbows, knees, sacrum, buttocks, and shoulders) and occasionally the face, eyelids, hairline, posterior nuchal area, and scalp. Symmetrical clusters of small, clear tense vesicles that rupture easily are found amidst excoriated papules and postinflammatory hyper- or hypopigmentation [18]. In children, DH may be confused with arthropod bites, scabies, urticaria, atopic dermatitis, and pityriasis lichenoides et varioliformis acuta. A lesional biopsy may be required to confirm the diagnosis [18]. A gluten-free diet alone is sufficient to control the associated gastroenteropathy, but without additional intervention the cutaneous disease will take at least 1–3 months after the most recent gluten exposure to resolve. For this reason, sulfones or sulfonamides, such as dapsone and sulfapyridine, are often useful to suppress the skin disease. Unfortunately, such therapy has no effect on the associated GI disease or risk of DH-associated conditions, including autoimmune diseases such as insulin-dependent diabetes, connective tissue disorders, thyroid diseases, sarcoidosis, vitiligo, alopecia areata, pernicious anemia, splenic atrophy, and malignancy [81]. An initial dose of 2 mg/kg/day (maximum dose 100 mg/day) of dapsone is recommended [18]. This dose may then be tapered to an optimal dose of 12.5–50 mg/day once the vesicles are suppressed [18]. Typically a dramatic improvement is seen within 24–48 h of initiating treatment. When skin lesions have resolved, this dose can be further tapered and discontinued after several months on a strict gluten-free diet, although it may need to be restarted for subsequent flares [82]. While systemic corticosteroids are not generally effective in DH [82], potent topical steroids may be added to alleviate pruritus [83]. Antihistamines may also play a limited role in controlling DH-associated pruritus [82]. Titers of circulating IgA to tissue transglutaminase reflect the degree of jejunal disease and can be used to monitor response to therapy and disease recurrence [84]. The prognosis of this disease is unclear, in part due to the difficulty of lifelong adherence to the gluten-free diet. Accidental gluten exposures are common triggers of disease flares.

5.2.3 Pemphigus

Pemphigus is a group of severe, potentially life-threatening disorders characterized by flaccid bullae arising on otherwise normal-appearing skin and mucosa. Antibodies directed against components of the desmosome cause this phenotype. Pemphigus can be further classified as pemphigus vulgaris (PV), pemphigus foliaceus (PF), drug-induced pemphigus, IgA pemphigus, and paraneoplastic pemphigus.

PV is extremely rare in children but generally has a better prognosis than its adult counterpart. Systemic therapy, however, is required to decrease disease-related mortality. The oral mucosa is involved in 95 % of patients, often as the first site of disease (Fig. 5.1). PV may also affect esophageal and ileal mucosa, resulting in a protein-losing enteropathy [85, 86]. Cutaneous lesions preferentially affect the pressure points on the feet, back and seborrheic areas. Systemic

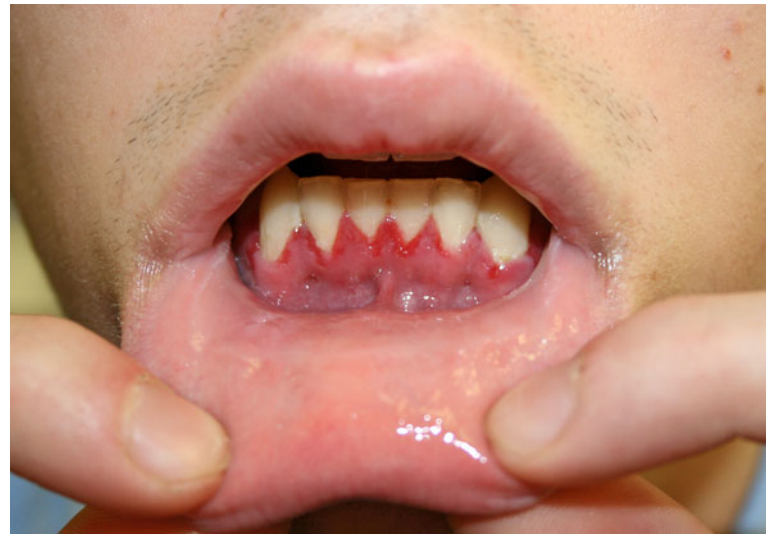

Fig. 5.1 Gingival erosions in a patient with juvenile pemphigus vulgaris

steroids are the mainstay of therapy for PV. Initial treatment with 1–2 mg/kg/day oral prednisone or in IV pulses for up to 3 months should be instituted [5, 18]. If this therapy produces an adequate clinical response, then alternate-day therapy followed by gradual tapering and discontinuation can be attempted. If the disease persists beyond 3 months, then adjuvant therapies can be added, historically beginning with dapsone [87]. If this combination does not provide adequate improvement, several other therapies have been reported with success. Gurcan and Ahmend recommend methotrexate as the second-line therapy at 5–10 mg/week [88]. Other options include MMF (see Table 5.3 for dosing) [89], cyclosporine (5 mg/kg/day) [90], azathioprine (2–4 mg/kg/day) [90], hydroxychloroquine [86], and high-dose IVIg. IVIg (2 g/kg/cycle) has been used successfully following failed systemic immunosuppressant therapy in some and as initial therapy in others [91, 92]. Investigations of the use of IVIg in a mouse model of PV have also demonstrated its efficacy [93].

With the advent of rituximab and the increasing evidence of successful treatment response, many providers are choosing it as an adjuvant therapy for treatment-resistant cases before moving through a paradigm of multiple other toxic medical therapies [64, 94]. Successful treatment with this monoclonal antibody has been reported in several children with PV, although not without a high rate of potentially devastating infectious complications [53, 60]. Nonetheless, systemic treatment may induce a sustained remission, with repeat treatments only as needed for recurrences.

PF is the milder, more superficial form of pemphigus and is more common in children. The small superficial bullae rupture easily to leave shallow erosions, and oral lesions are rare. Overall, most patients are generally not severely ill, but rarely the disease may progress to resemble a generalized exfoliative dermatitis. Suprapotent topical steroids may be sufficient in some patients, but many require dapsone therapy alone or with systemic corticosteroids for disease clearance. Once resolved, PF is less likely to recur than PV.

Drug-induced pemphigus generally improves with removal of the offending medication, although systemic treatment may be indicated to assist with resolution. In children, pemphigus has been reported in association with montelukast administration [95], a vaccine against tetanus and diphtheria containing sodium ethylmercury thiosalicylate as a preservative [96], and amoxicillin [97, 98]. Other drugs implicated in adults include penicillamine, captopril and other thiols, antibiotics (most commonly penicillin and its derivatives), pyrazolone derivatives, and immunomodulators

[99]. These compounds are felt to induce pemphigus in part because they contain either a thiol group or a disulfide bond that readily releases a thiol group, which modifies the desmogleins, increasing their antigenicity [99]. IgA-induced pemphigus improves within 24–48 h of therapy with dapsone or sulfapyridine, while systemic steroids and other immunosuppressants are not as effective. Successful treatment with oral retinoids for an adult with IgA pemphigus has also been described [100].

Paraneoplastic pemphigus in children is often associated with Castleman's disease and has a poor prognosis. While mucocutaneous lesions may improve in the months following surgical excision of the associated lymphoproliferation, affected children frequently develop bronchiolitis obliterans despite excision of the tumor [18, 101, 102]. In a recent review, 17 of 24 children who developed this complication, presenting initially with shortness of breath and cough, suffered fatal outcomes [103]. The administration of IVIg before and during tumor resection is recommended to prevent the development of bronchiolitis obliterans [101]. Patients with associated malignancies, other than Castleman's disease, have a poor prognosis and most succumb to their disease. In addition to treating the malignancy, immunosuppressive therapy should be initiated for management of the pemphigus, although the ultimate prognosis may not be affected.

5.2.4 Epidermolysis Bullosa Acquisita

Epidermolysis bullosa acquisita (EBA) is a subepidermal blistering disorder that presents in three forms. The classic form resembles dominant dystrophic EB with acral blistering, scarring, and milia, while another variety is phenotypically similar to mucous membrane pemphigoid (MMP). The form that most commonly occurs in children is characterized by an inflammatory generalized eruption that is clinically indistinguishable from BP unless indirect immunofluorescence is performed to differentiate the two diseases (Fig. 5.2). Mucosal involvement may be present and severe cases can lead to malnutrition, blindness, and genitourinary strictures.

The first line of treatment is dapsone (2 mg/kg/day; maximum 100 mg/day) in combination with systemic steroids (1 mg/kg/day of prednisone). On this regimen, skin lesions typically respond within weeks. At that point, prednisone should be tapered as much as possible. Remission often occurs within 2 years [18]. Other treatments with reported success include MMF (with steroid-sparing effects in combination with prednisolone and dapsone) [104], rituximab [105, 106], colchicine, infliximab, photopheresis, IVIg, nicotinamide, and erythromycin [84, 107]. A recent study showed that T cells are required for phenotype expression in an EBA murine model,

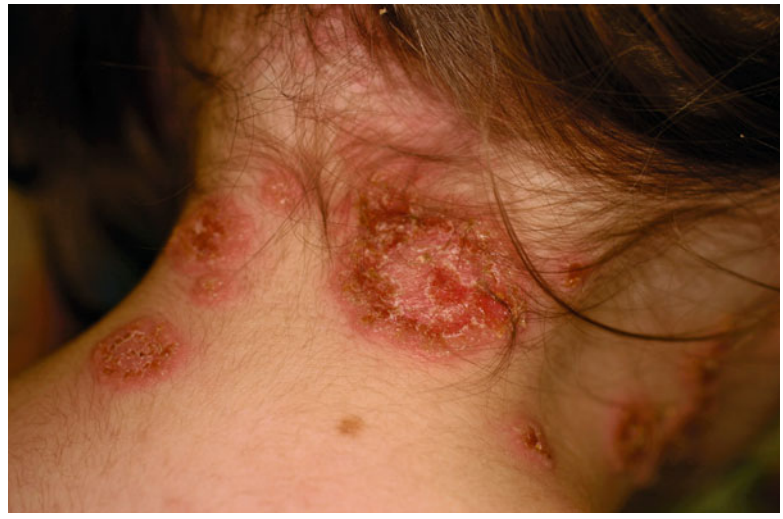

Fig. 5.2 Three-year-old with childhood epidermolysis bullosa acquisita

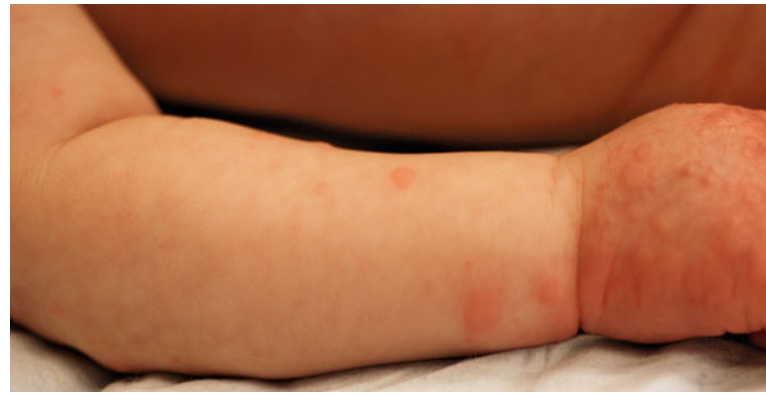

Fig. 5.3 Urticarial papules and vesicles on the extremity of an infant with bullous pemphigoid

providing the basis for the development of T-cell-directed immunomodulatory strategies for treatment of this disease [108]. Children with EBA generally respond more rapidly to systemic treatment than adults [109] and most children enter remission within 2 years [84, 110].

5.2.5 Bullous Pemphigoid

Bullous pemphigoid is a blistering disorder characterized by large, tense, subepidermal bullae on erythematous or normal-appearing skin. It rarely occurs in children (Fig. 5.3). The course is usually indolent with rare relapses [111, 112]. Blisters resolve without scarring, and only 25 % of affected children have oral mucosal involvement. If affected, infants are more likely to have generalized involvement than older children and are more likely to require systemic therapy [111].

Systemic corticosteroids (1–2 mg/kg/day) are the first-line intervention for generalized or severe cases [18]. If the clinical response to steroids is inadequate, other immunosuppressive agents may be added to the regimen or used in place of steroids. These include sulfapyridine (2 mg/kg/day) and dapsone (3–6 mg/kg/day; maximum dose 100 mg/day). Erythromycin (50 mg/kg/day) with or without nicotinamide (40 mg/kg/day) has been reported to be beneficial, likely through the anti-inflammatory effects of the macrolide [37]. The use of azathioprine with steroids is no longer recommended, as there is evidence that it may increase mortality [71, 113]. Other systemic therapies with reported success include the combination of IVIg and dapsone, MMF, and rituximab [59]. Finally, success has been reported with a combination of plasmapheresis and extracorporeal photochemotherapy in a severe refractory pediatric case [77].

If recognized and treated, the prognosis of childhood BP is favorable, with most children entering remission within several weeks to months and almost all within 1 year.

5.2.6 Mucous Membrane Pemphigoid

MMP is a variant of BP in which blisters primarily affect mucosal surfaces. While it is extremely rare in children [114], it has significant potential for permanent and devastating complications and therefore requires prompt recognition and intervention. The oral cavity is most commonly involved and may be the sole manifestation of disease; the prognosis of oral disease is positive as these lesions often respond to topical therapy and heal without synechia [114]. In contrast, patients with ocular involvement are at high risk for permanent vision loss and should be treated with systemic immunosuppressants [115]. While less common, esophageal lesions can lead to malnutrition and strictures and laryngeal lesions can be life-threatening by compromising the airway [18, 116]. Genital involvement also occurs and subsequent fibrosis may compromise sexual function [114]. Treatment options include systemic steroids, dapsone, sulfapyridine, and

azathioprine, alone or in combination [84, 114, 115]. The addition of topical steroid creams and oral rinses may be beneficial. One recent report of a child with significant ocular involvement describes a maintenance regimen of dapsone and ocular cyclosporine drops following an initial course of steroids [114]. Despite the potential for severe and lasting complications, if treated, complete resolution of MMP is possible and few cases persist into adulthood [18].

5.2.7 Bullous Systemic Lupus Erythematosus

Rarely, children with SLE develop this chronic widespread, pruritic non-scarring blistering eruption with tense bullae in sun-exposed areas. The first-line intervention is dapsone, to which bullae usually respond quickly [80, 117]. The presence of neutrophils in bullae indicates a likely favorable response to dapsone therapy. It should be noted that patients with SLE may have significant anemia due to their underlying disease which could put them at greater risk for morbidity from dapsone-induced hemolysis [13]; extra precautions should be taken to monitor these patients. As with many of the other ABDC discussed previously, successful treatment with systemic steroids alone or in combination with other immunosuppressive agents has been reported. These include methotrexate, MMF, azathioprine, cyclophosphamide, and cyclosporine, whose uses have been reported with variable results. The prognosis of this bullous disease in children is generally positive, although the ultimate outcome depends on the nature of systemic involvement.

5.2.8 Other ABDC

There are other rare ABDC that do not typically require systemic treatment. Pemphigoid gestationis is a bullous disease that presents during the second or third trimester of pregnancy or immediately postpartum in 1 of 50,000 pregnancies. In 10 % of cases, newborns of affected mothers show signs of cutaneous involvement due to transplacental transfer of antibodies. In most cases, affected infants' lesions remit within several weeks as IgG titers fall and no therapy is required; rarely, moderate potency topical steroids may be necessary. Neonatal bullous disease due to placental transfer of maternal IgG autoantibodies has also been reported in infants born to mothers with PV, PF, and EBA [118–121].

Conclusion

Autoimmune bullous diseases are rare in children and the treatment of ABDC is particularly challenging for several reasons. The age of these patients makes them especially vulnerable to not only the long-term sequelae of their disease but also the adverse effects of the available treatment modalities. The impact of both disease and treatment on development must be considered.

Although topical wound care is also necessary, systemic therapy is the mainstay of treatment for ABDC. The first-line therapy depends on the subtype of ABDC, and thus, a thorough workup of the patient is essential in order to narrow therapy to what is generally known to be the most effective treatment options. It is important to weigh the risks and benefits of the various treatment modalities, especially in pediatric patients. Initial labs should be obtained prior to treatment initiation to assess for any contraindications to drug therapy, and patients should subsequently be monitored closely for adverse effects. As all treatment approaches are immunomodulatory, patients may be more susceptible to infection. Systemic therapy should be tapered as tolerated when clinical response is noted.

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Connective Tissue Disease

6

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Key Points

- Management of many of the connective tissue disorders (CTD) requires a multidisciplinary approach, given a number of organs may be affected.
- The particular disease, including subtype, and its prognosis often dictate if systemic treatment is warranted; other important factors favoring systemic therapy include widespread skin disease, potentially scarring/disfiguring lesions, likelihood of affecting or already affecting function, and internal organ involvement.
- Pediatric differences with CTD:
  - Kidney disease is more common and with more complications in children with systemic lupus erythematosus.
  - Linear morphea is the most common subtype in children and typically requires systemic therapy.
  - Pediatric systemic sclerosis usually has better prognosis than adult disease, with fewer renal crises; occurrence as an overlap syndrome is also more common in this age group.
  - Interstitial lung disease is rare in juvenile dermatomyositis, but calcinosis cutis may be noted.

Abbreviations

ACLE	Acute cutaneous lupus erythematosus
CCLE	Chronic cutaneous lupus erythematosus
CLE	Cutaneous lupus erythematosus
CTD	Connective tissue disease
dcSSc	Diffuse cutaneous systemic sclerosis
DLE	Discoid lupus erythematosus
JDM	Juvenile dermatomyositis
jSSc	Juvenile systemic sclerosis
lcSSc	Limited cutaneous systemic sclerosis
NLE	Neonatal lupus erythematosus
pSLE	Pediatric systemic lupus erythematosus
RP	Raynaud's phenomenon
SCLE	Subacute lupus erythematosus
SLE	Systemic lupus erythematosus

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Children with connective tissue disease may frequently require treatment other than topical therapy for their disorder. This chapter will cover those connective tissue diseases with cutaneous features and that may require consideration for systemic treatment—in particular, cutaneous and systemic lupus erythematosus, morphea, systemic sclerosis, and juvenile dermatomyositis. Clinical presentations will be briefly reviewed, with a focus on recognizing disease subtypes or clinical scenarios that deserve stronger consideration for systemic therapy. In addition, the dermatologist's role in providing adjunctive therapy to control cutaneous manifestations is discussed.

6.1 Cutaneous Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) is a rare disease with an estimated incidence of 3.08 per 100,000 adults [1]. The incidence in children is not known, though it is thought to be less common than adult disease. The female sex predilection present in postpubertal children and adults is not as strong in prepubertal children. CLE in children may have a stronger association with systemic lupus erythematosus (SLE) than in adults [2]. The treatment of systemic lupus erythematosus (SLE) is discussed separately below.

Gilliam and Sontheimer's classification scheme divides cutaneous lupus erythematosus into lupus-specific and lupus-nonspecific skin lesions. Lupus-specific lesions can be further subdivided into acute, subacute, and chronic lesions and are listed in Table 6.1. Lupus-nonspecific skin lesions are numerous and reviewed in the systemic lupus erythematosus section and in reference [3].

Table 6.1 Lupus-specific skin lesions

Acute cutaneous lupus erythematosus
Localized (malar rash)
Generalized
Toxic epidermal necrolysis-like
Subacute cutaneous lupus erythematosus
Annular
Papulosquamous
Mixed
Chronic cutaneous lupus erythematosus
Discoid lupus
Lupus panniculitis/profundus
Tumid lupus
Mucosal lupus
Chilblain lupus
Discoid lupus-lichen planus overlap

6.1.1 Clinical Presentations

6.1.1.1 Acute Cutaneous Lupus Erythematosus (ACLE)

ACLE is nearly always seen in the setting of systemic disease. The classic malar rash is the prototypical example of ACLE (Fig. 6.1). Erythematous macules or papules coalesce into confluent patches or plaques. The eruption is symmetric on the nose and cheeks, typically crossing the nasal bridge but sparing the nasolabial folds. It can extend to the forehead, ears, chin, or neck. Generalized ACLE presents with similar macules and papules in a widespread distribution, favoring sun-exposed areas such as the upper chest and extensor forearms. When present on the dorsal hand, the lesions affect interphalangeal spaces and spare the joints, in contrast to dermatomyositis. The maculopapular types of ACLE typically heal without scarring.

Vesicles and bullae may be seen in multiple forms of ACLE. Florid inflammation and basilar vacuolization may result in blisters within the maculopapular areas of ACLE. Bullous lupus erythematosus is an uncommon but distinct variant caused by autoantibodies directed against collagen VII. Vesicles and bullae are present on sun-exposed sites, although the axillae and mucosal sites may also be affected. Rarely, a severe toxic epidermal necrolysis-like eruption may occur in the setting of SLE, although it is unclear whether this is a lupus-specific reaction [4]. The vesiculobullous variant may be the first presentation of lupus, causing a diagnostic dilemma.

6.1.1.2 Subacute Cutaneous Lupus Erythematosus (SCLE)

SCLE presents as a symmetric, photodistributed, erythematous, scaly eruption. Individual lesions may appear psoriasiform as in the papulosquamous variant or have central clearing as in the

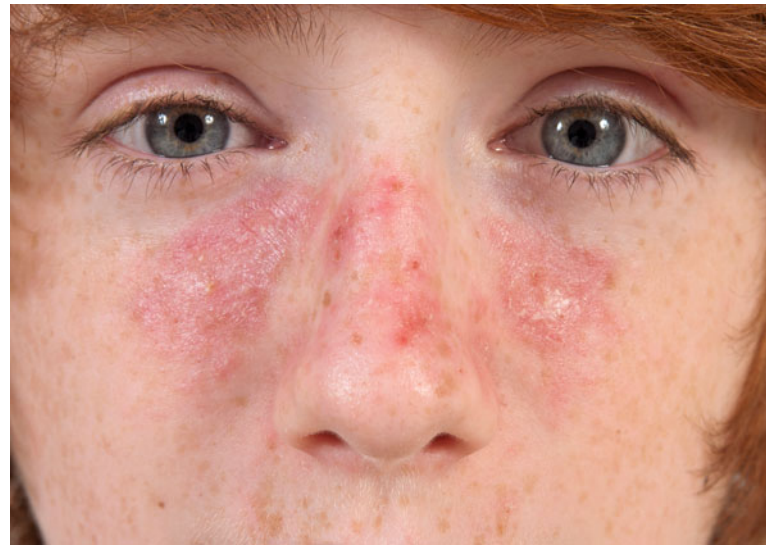

Fig. 6.1 Malar rash of acute cutaneous lupus (ACLE)

annular variant. Mixed morphologies are common, and rare variants demonstrating other morphologies have been reported. SCLE is the most photosensitive subtype of CLE and tends to affect the neck, upper chest and back, and extensor arms and hands. Vesiculobullous lesions can sometimes arise, especially along the periphery of the annular plaques. SCLE may resolve with telangiectasia but typically does not scar.

6.1.1.3 Chronic Cutaneous Lupus Erythematosus (CCLE)

Discoid lupus erythematosus (DLE) is the prototypical example of CCLE and the most common form of CLE overall. Classic DLE is characterized by well-demarcated, erythematous plaques with adherent scale (Fig. 6.2). It most frequently involves the head and neck with a predilection for the scalp and ears, though generalized disease may be present. DLE lesions heal with atrophy, scarring, dyspigmentation, and cicatricial alopecia. There are over 20 other subtypes of DLE with different morphologies, including a proposed DLE-lichen planus overlap syndrome (reviewed in [5]). An association with SLE is seen in 20–25 % of children with DLE, higher than that seen in adults [6–8].

Lupus profundus, also called lupus panniculitis, is another form of CCLE. Tender nodules and plaques preferentially affect areas of fat deposition such as the trunk, buttocks, and proximal extremities.

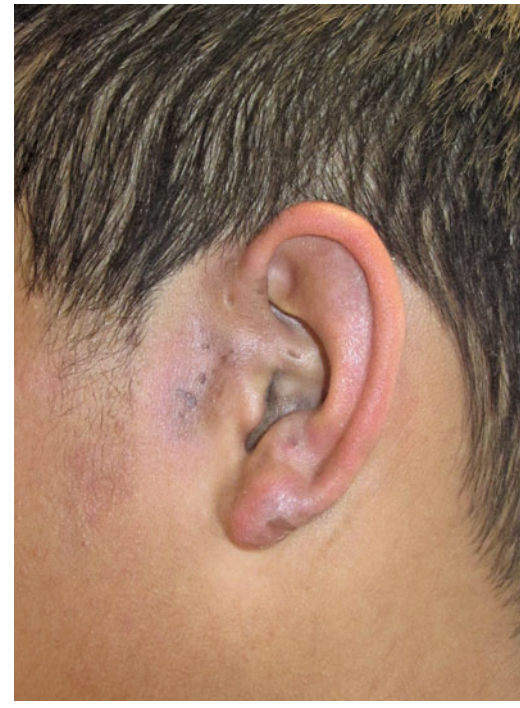

Fig. 6.2 Discoid lupus lesions (DLE) of the ear

Some lesions have no overlying skin change, while features of DLE may be present in others.

Tumid lupus is characterized by erythematous or violaceous plaques with scale or other surface change. The lesions are typically photodistributed on the face, neck, upper chest and back, and extensor arms. Tumid lupus resolves without scarring.

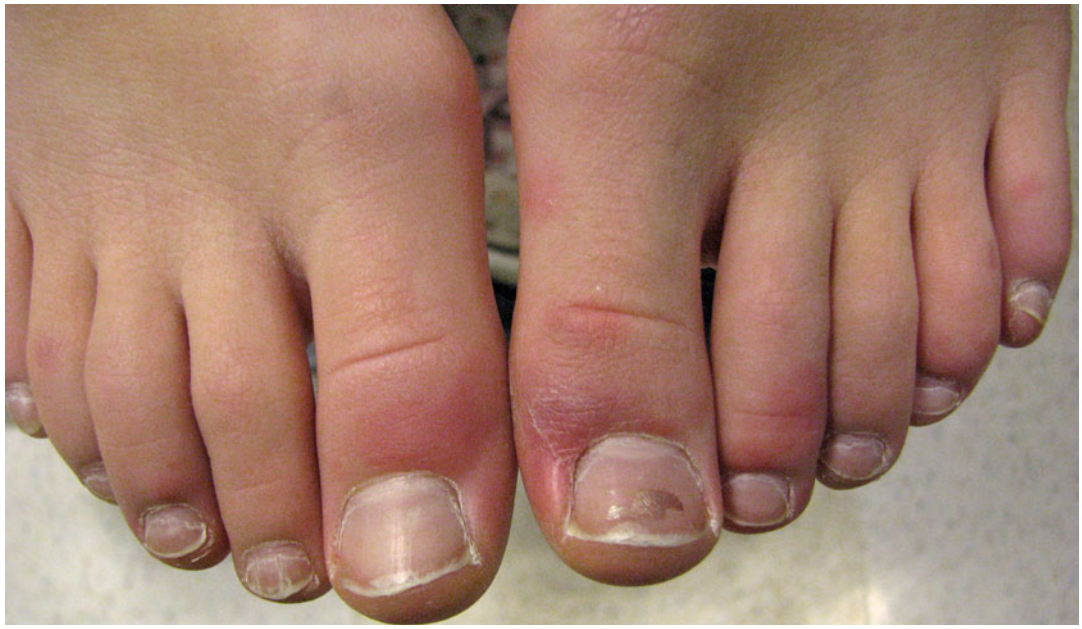

Fig. 6.3 Chilblain lesions of the toes

Lesions may be seen on mucosal sites as a lupus-specific finding and without systemic involvement. It is most common on the oral mucosa but can affect any mucosal site. Both DLE and SCLE may affect the mucosa, typically the lips or buccal mucosa, though the morphology may be altered by the location. Lesions may be asymptomatic or painful. Mucosal involvement is also a common feature of SLE and is discussed separately below. The morphologic spectrum is wide, including palatal erythema, erythematous macules and patches, oral and nasal erosions and ulcers, and intact vesicles [9].

Chilblain lupus is a rare form of CCLE. Violaceous, painful papules and plaques arise on acral sites after cold exposure (Fig. 6.3). Ulceration, hyperkeratosis, or scarring may develop with time. The fingers, toes, nose, and ears are predominately affected. Chilblain lesions may also be seen as an isolated finding (called pernio or chilblains), as part of Aicardi-Goutieres syndrome, or associated with SLE.

6.1.2 Candidates for Systemic Therapy

The main goals of CLE treatment are to prevent new lesions, reduce disease activity, and minimize scarring. Referral to a pediatric rheumatologist for evaluation of systemic disease may be considered for any child with CLE, though all children who have systemic manifestations or meet SLE diagnostic criteria should definitely be referred to a pediatric rheumatologist for management. Systemic therapy should be considered for any child with widespread disease or potentially disfiguring lesions, especially on the head and neck. There is some data in adult patients to suggest that treatment with hydroxychloroquine or prednisone can delay onset of SLE in high-risk patients, suggesting that hydroxychloroquine could be considered for children with CLE but who do not yet meet SLE criteria [10]. In general, the subtypes that deserve stronger consideration for systemic treatment include ACLE, DLE, lupus profundus, and chilblain lupus.

6.1.3 Treatment

6.1.3.1 Prevention

Avoidance of ultraviolet (UV) light is essential for patients with photosensitive CLE. UV light can induce skin lesions and may even be responsible for flares of SLE [11, 12]. Both UVA2 and UVB wavelengths can trigger disease, and these

wavelengths may be found in indoor lamps in addition to natural sunlight and tanning beds [13, 14]. Sunscreen has been demonstrated in a randomized controlled trial to prevent CLE lesions, while another study suggested that it may improve clinical outcome in SLE [15]. Patients with CLE should be counseled to refrain from tanning, avoid sun whenever possible, use broad-spectrum sunscreen, and wear photo-protective clothing. Because vitamin D is primarily synthesized in the skin after UVB exposure, daily supplementation with at least 400 units of cholecalciferol should be considered in CLE patients, especially in those on long-term corticosteroids [16].

6.1.3.2 Topical Therapy

Treatment with topical agents can be considered first-line therapy for patients with mild CLE not requiring systemic intervention. These topical medications may sometimes be used as adjuncts to treat recalcitrant skin disease in patients requiring systemic therapy.

Topical corticosteroids are the mainstay of treatment for CLE, although evidence for their use from randomized controlled trials is limited [17, 18]. The choice of the topical corticosteroid depends on the level of disease activity in individual lesions, the body site, and patient factors. DLE tends to be more recalcitrant to topical therapy and high-potency topical corticosteroids or occlusion may be necessary, though such measures may have a higher risk of causing atrophy, which is of special concern given the inherent atrophogenic potential of DLE. In some DLE lesions, intralesional corticosteroids may have improved efficacy, though tolerability may limit its use. Triamcinolone 2.5–5 mg/ml for the face and 10 mg/ml for other sites may be injected intradermally every 6–8 weeks.

Topical calcineurin inhibitors have demonstrated efficacy in CLE and are a useful alternative to topical corticosteroids. Randomized trials comparing tacrolimus 0.1 % ointment and pimecrolimus 1 % cream have shown efficacy comparable to that of topical corticosteroids, but without the risk of atrophy [18, 19]. Tacrolimus 0.03 % ointment compounded in clobetasol propionate 0.05 % ointment was shown in a small retrospective study to be superior to tacrolimus 0.1 % ointment or clobetasol propionate 0.05 % ointment alone [20].

Other topical agents have also been used. R-salbutamol is a β2-receptor agonist with anti-inflammatory properties. A randomized controlled trial showed that R-salbutamol 0.5 % cream was superior to placebo [21]. Isolated case reports have suggested that imiquimod 5 % cream may be effective in treating DLE [22, 23]. As imiquimod is a Toll-like receptor activator, it could theoretically stimulate inflammation, and there have been reports of lupus-like reactions with its use for other indications [24–26]. Topical retinoids also have reported efficacy in DLE in two case reports [27, 28].

6.1.3.3 Systemic Therapy

Antimalarials, including hydroxychloroquine, chloroquine, and quinacrine, are the treatments of choice for CLE that requires more than topical therapy. The mechanisms of action for these drugs are related to suppression of antigen presentation, inhibition of cytokine and prostaglandin synthesis, inhibition of Toll-like receptor signaling, and photo-protection [29]. Although there are only two randomized studies using hydroxychloroquine and chloroquine to treat CLE, there is an abundance of retrospective data to support their use [30, 31].

Hydroxychloroquine is the first-line antimalarial with response rates of approximately 50 % [30, 32]. See Table 6.2 for dosing, monitoring, and adverse effects. In adult patients who do not respond to hydroxychloroquine alone, combination therapy with quinacrine has been suggested; however, quinacrine is no longer commercially available in the United States, and the use of this combination regimen has not been reported in children [32, 33]. Chloroquine is the second-line antimalarial used to treat CLE. There is a delay of 6–8 weeks before antimalarials reach full efficacy, and systemic corticosteroids may be considered for bridge therapy in severe or acute cases. Oral prednisone or prednisolone may be administered for the first 2–4 weeks of antimalarial therapy, followed by a taper.

Second-line agents for treatment of recalcitrant CLE include methotrexate (MTX), acitretin, isotretinoin, mycophenolate mofetil, azathioprine, dapsone, thalidomide, lenalidomide, intravenous immunoglobulin, rituximab, cyclophosphamide, and cyclosporine. The authors of a 2011 review

Table 6.2 Common medications used for pediatric connective tissue diseases

Medication	Indications	Pediatric dose	Formulations (variable by country)	Screening and monitoring	Side effects and toxicities
Prednisone/ prednisolone	CLE SLE Morphea jSSc JDM (used for rapid control of disease and bridge therapy)	Up to 2 mg/kg/day (maximum dose 60–80/ day)	Prednisolone 15 mg/5 ml oral solution in United States Prednisolone 5 mg/5 ml oral solution in Canada Prednisone 1, 2.5, 5, 10, 20, 50 mg tablets	Consider periodic blood pressure, height, weight, and ophthalmologic assessments if on prolonged therapy	Gastrointestinal upset Insomnia Weight gain Behavioral changes Hyperglycemia Hypertension Avascular necrosis Adrenal suppression Growth suppression Osteopenia Infection risk Cataracts Glaucoma Hirsutism Easy bruising Striae
Methylprednisolone	CLE SLE Morphea jSSc JDM (used for rapid control of disease and bridge therapy)	30 mg/kg/day for three consecutive days a month for 3 months (maximum dose 1,000 mg/day)	Intravenous solution	Consider potassium level pre-administration	Generally better tolerated than oral corticosteroids Anaphylactic reactions Arrhythmias Hypokalemia
Hydroxychloroquine	CLE SLE JDM	6.5 mg/kg/day divided daily-twice daily (based on ideal body weight)	25 mg/ml compounded oral suspension 200 mg tablet (scored)	Consider baseline glucose-6-phosphate dehydrogenase enzyme level in individuals with family history or at high risk of deficiency Consider CBC, LFT, and BUN/Cr every 3–4 months Baseline ophthalmologic examination within the first year of use with repeat screening every 5 years for low-risk patients, more frequently for high-risk patients[a]	Gastrointestinal upset Hyperpigmentation Myopathy Reversible corneal deposits Irreversible retinopathy
Chloroquine	CLE SLE JDM	3 mg/kg/day divided twice daily	15 mg chloroquine phosphate/ml compounded oral suspension		

Methotrexate[b]	SLE jSSc	10–15 mg/m^2 subcutaneous once weekly (maximum dose 25 mg/week) or 15–20 mg/m^2 oral once weekly (maximum dose 15–25 mg/week)	25 mg/ml injectable solution (may be given orally) 2.5 mg tablets	Vaccinate against varicella before initiation if not immune CBC, LFT, and BUN/Cr[c] prior to initiation CBC and LFT monthly for 3 months, then every 2–3 months	Teratogenicity Gastrointestinal upset Ulcerative stomatitis Myelosuppression Hepatotoxicity Pulmonary fibrosis
	Morphea	1 mg/kg oral or subcutaneous once weekly (maximum dose 25 mg/week)			
	JDM	15 mg/m^2 or 1 mg/kg subcutaneous once weekly (maximum dose 40 mg/week)			
Azathioprine	SLE	2–3 mg/kg once daily (maximum dose 150 mg/day)	50 mg/mL oral suspension compounded from tablets 50 mg tablets	CBC, LFT, and BUN/Cr prior to initiation Consider thiopurine methyltransferase enzyme activity prior to initiation CBC and LFT monthly for 3 months, then every 2–3 months	Gastrointestinal upset Myelosuppression Hepatotoxicity Pancreatitis
Mycophenolate mofetil[d]	SLE	600 mg/m^2/day divided twice daily (maximum dose 3 g/day)	200 mg/ml oral suspension 250 mg and 500 mg capsules	CBC, electrolytes, LFT, and BUN/Cr[c] prior to initiation CBC every 2–4 weeks for 2 months, then every 2–3 months	Gastrointestinal upset Myelosuppression
	Morphea	<1.25 m^2: 600 mg/m^2 twice daily 40–50 kg or 1.25–1.5 m^2: 750 mg twice daily >50 kg or >1.5 m^2: 1,000 mg twice daily			

CBC complete blood count, *LFT* liver function tests, *BUN/Cr* blood urea nitrogen/creatinine

[a]Risk factors: therapy >5 years, >6.5 mg/kg/day of hydroxychloroquine or >3.0 mg/kg/day of chloroquine, cumulative dose >1,000 g of hydroxychloroquine or >460 g of chloroquine, liver disease, kidney disease, retinal disease, or maculopathy

[b]Subcutaneous dosing of methotrexate is preferred due to reduced oral bioavailability at oral doses >15 mg/week

[c]Dose adjustment if renal failure is present

[d]Pharmacokinetic studies clinically available for individual monitoring of serum drug levels

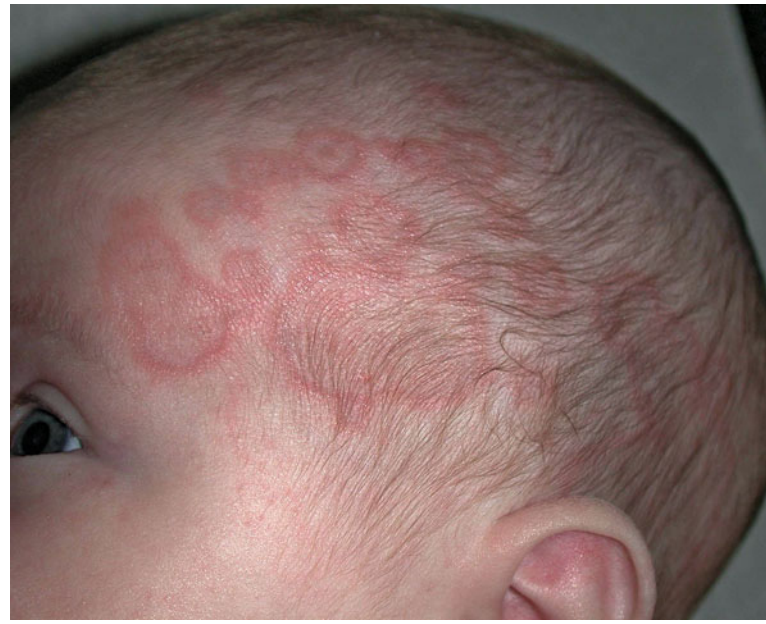

Fig. 6.4 Neonatal lupus (NLE) lesions on the face and scalp

paper summarizing the evidence for each intervention recommended the addition of methotrexate to the antimalarials for nonresponders [34]. Of note, dapsone is the treatment of choice for bullous LE, with rapid response within 24–48 h to low doses of 25–50 mg daily [35].

6.1.3.4 Physical Treatments

Despite the fact that UV light is a trigger of CLE, UV phototherapy has been used successfully for treatment. A case report suggests that ultraviolet A-1 (UVA-1) is effective for SCLE, while there is stronger evidence from prospective studies for UVA-1 efficacy in improving the cutaneous and systemic manifestations of SLE [36–39]. Photodynamic therapy with either methylaminolevulinic acid or 5-aminolevulinic acid has been proposed as a treatment option for CLE, though the evidence is mixed [40–42]. Extracorporeal photopheresis also has reported efficacy in treatment-refractory cases [43–45].

6.2 Neonatal Lupus Erythematosus

Neonatal lupus erythematosus (NLE) is a passively acquired disease caused by transfer of maternal autoantibodies, most commonly anti-Ro (anti-SSA). The disease occurs in 1 of every 20,000 live births [46]. The female to male ratio is equal or somewhat increased at 2:1 [47, 48]. The cutaneous manifestations of NLE closely resemble SCLE with annular, erythematous, scaly plaques (Fig. 6.4). The most common location is the head and neck, and periorbital accentuation is characteristic, although lesions may be seen in other locations or be generalized. Lesions may be present at birth or appear within the first 2 months of life. As maternal autoantibodies are cleared from the infant's circulation, the disease spontaneously improves over the course of weeks to months. NLE may resolve with telangiectasias, dyspigmentation, and rarely atrophy.

Extracutaneous disease can be seen in NLE. The most common cardiac finding is complete heart block, though other arrhythmias and other cardiac complications have been reported [49]. Hepatobiliary disease is usually present as asymptomatic and transient elevation of the transaminases, conjugated hyperbilirubinemia, or rarely liver failure [50, 51]. Hematologic abnormalities such as anemia, thrombocytopenia, and neutropenia are also present in a substantial minority [50].

Most of the cutaneous and extracutaneous manifestations of NLE improve as the levels of circulating maternal autoantibodies decrease. In general, watchful monitoring is sufficient and treatment is not necessary. The exceptions are

complete heart block and other arrhythmias, which often require pacemaker placement and management by a pediatric cardiologist.

6.3 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disorder with an estimated incidence ranging from 0.36 to 2.5 per 100,000 in the pediatric population age 0–19 years, with more females affected [52]. Higher incidence rates are reported among African-American, Hispanic, Asian, and Native American groups [53].

The American College of Rheumatology (ACR) classification system for SLE is based on multiple organ involvement. Four out of 11 ACR criteria are required to fulfill classification for SLE as listed in Table 6.3 [54, 55]. It should be stressed, however, that these criteria are useful but not necessary for diagnosis of SLE. Although not fully evaluated in pediatric SLE (pSLE), the criteria have a greater than 95 % sensitivity and specificity in diagnosis of pSLE [56]. The mean age at time of diagnosis of pSLE is adolescence, at approximately 11–13 years of age; diagnosis at age less than 5 years is rare. Time to diagnosis from onset of symptoms varies and ranges from 1 month to 5 years. pSLE is associated with greater severe disease manifestations and increased morbidity and mortality in comparison to adult-onset SLE and other pediatric rheumatologic conditions such as juvenile arthritis [57, 58].

Table 6.3 Systemic lupus erythematosus classification criteria

Criteria (4 out of 11 required)	Definition
Malar rash	Flat or raised, fixed erythema over malar eminences, sparing nasolabial folds
Discoid rash	Elevated erythematous patches with adherent keratotic scaling and follicular plugging; atrophic scarring with older lesions
Photosensitivity	Sunlight-evoked skin rash by history or physician exam
Oral ulcers	Oral or nasopharyngeal ulcers, typically painless
Arthritis	Nonerosive arthritis involving two or greater peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	Pleuritis convincing history of pleuritic pain or rub on auscultation or evidence of pleural effusion or Pericarditis documented by electrocardiogram, echocardiogram, or rub
Renal disorder	Persistent proteinuria greater than 0.5 g/day or cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
Neurological disorder	Seizures or psychosis, both should be in absence of offending drugs or metabolic derangements
Hematological disorder	Hemolytic anemia with reticulocytosis or leukopenia <4,000/μL on two or more occasions or lymphopenia <1,500/μL on two or more occasions or thrombocytopenia <100,000/μL
Immunological disorder	Antibody to native DNA, or antibody to Sm protein, or antiphospholipid antibodies—either anticardiolipin antibodies, presence of the lupus anticoagulant or false-positive serological test for syphilis
Antinuclear antibody	Abnormal antinuclear antibody by immunofluorescence or an equivalent assay

6.3.1 Clinical Presentations

SLE often presents with nonspecific systemic constitutional symptoms including fever, fatigue, weight loss, generalized lymphadenopathy, and hepatosplenomegaly in addition to organ-specific inflammation. All organ systems may be involved, and the most commonly affected organs in pSLE include mucocutaneous, musculoskeletal, and kidney involvement [59]. Other commonly recognized organ involvement includes neuropsychiatric symptoms, the gastrointestinal system, and cardiopulmonary systems [60, 61] (see Table 6.4).

6.3.1.1 Mucocutaneous

Oral and nasal mucosal involvement ranges from hyperemia, petechiae, painless oral ulcers of the hard palate, superficial ulcers of the

Table 6.4 Frequencies of clinical symptoms and signs in pSLE

Symptom/sign	Frequency (%)
Constitutional and generalized symptoms	
Fever	37–100
Lymphadenopathy	13–45
Hepatosplenomegaly	19–43
Weight Loss	21–32
Musculoskeletal	
Arthritis	60–90
Myositis	<5
Nephritis	48–100
Skin	60–90
Malar rash	30–80
Discoid rash	<5
Photosensitivity	17–58
Mucosal ulceration	30–40
Alopecia	15–35
Other rashes	42–55
Neuropsychiatric disease	15–95[a]
Psychosis	8–18
Seizures	5–47
Headaches	10–95
Cognitive dysfunction	12–55
Acute confusional state	8–35
Peripheral nerve involvement	<5
Cardiovascular disease	25–60
Pericarditis	20–30
Myocarditis	<5
Pulmonary disease	18–81
Pleuritis	20–30
Pulmonary hemorrhage	<5
Pneumonitis	<5
Gastrointestinal disease	24–40
Peritonitis (sterile)	12–18
Abnormal liver function	25–45
Pancreatitis	<5

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[a]Headache reported in 95 % of patients

nasal septum, and rarely, nasal septum perforation.

The hallmark of SLE is the malar rash, and other lupus-specific skin lesions are discussed above in the CLE section. Additional, nonspecific cutaneous findings in pSLE and other vasculitides include Raynaud's phenomenon (15–20 %), abnormal nailfold capillary loops, and vasculitic rashes demonstrating as painful skin ulceration, nodules, and punctate erythema. Palpable purpura can be seen and is often confused as Henoch-Schonlein purpura. Alopecia of the scalp is common though scarring is rare.

6.3.1.2 Musculoskeletal

Musculoskeletal involvement is common throughout the course of the disease. The most common manifestations include arthralgia, arthritis, and tenosynovitis. The arthritis is usually polyarticular, symmetric, and painful, but nonerosive and nondeforming. Large and small joints are equally involved. Morning stiffness is typical. Myalgia is seen in up to 30 % and myositis less often. Less common findings include avascular necrosis and osteopenia or osteoporosis (sometimes with bone fragility fractures), especially with glucocorticoid treatment.

6.3.1.3 Renal

Kidney disease is more commonly seen in pSLE and is associated with significant morbidity and mortality in this age group [57, 61]. Approximately 50–75 % of children will have renal involvement, and of those who develop renal disease, 90 % will occur in the first 2 years from diagnosis [60]. All pSLE patients should have routine monitoring of renal function with blood pressure, urine analysis for sediment (protein, heme, casts), and serology for creatinine. Manifestations of renal involvement include mild proteinuria to nephrotic-range proteinuria, microscopic hematuria, urinary casts, hypertension, and peripheral edema. Severe renal insufficiency and acute renal failure can occur. In cases of acute renal failure, pSLE should be suspected if the child demonstrates evidence of thrombotic thrombocytopenic purpura, a microangiopathic hemolytic anemia. In the kidney, the glomerulus is most affected and termed lupus nephritis, with six classes defined based on degree of affected glomeruli, mesangial proliferation, and diseased kidney. Both type III and IV SLE glomerulonephritis are indications to start immunosuppressive treatment to prevent end-stage renal disease. The incidence of end-stage renal disease has declined over the last few decades with the

use of progressive immunosuppressive medications. Outcome has also improved with one study reporting greater than 90 % patient survival over an 11-year period with the use of immunosuppressive therapy [62].

6.3.2 Candidates for Systemic Therapy

The care of a child with pSLE requires a multidisciplinary team: a pediatric rheumatologist, pediatric dermatologist for skin manifestations, pediatric nephrologist if renal disease is involved, primary care physician, adolescent medicine provider, behavioral specialist, social worker, dietician, and physical and occupational therapist. Virtually all children with pSLE will receive systemic pharmacotherapy. Drug therapy is tailored to the organ systems involved and severity of disease. Only prednisone and aspirin are approved by the Federal Drug Authority (FDA) for use in pSLE. All other immunosuppressive drugs are used off-label. Choice of drug is also driven by consideration of risks and benefits to the child due to drug side effects.

6.3.3 Treatment

Antimalarials, hydroxychloroquine and chloroquine, are often first-line agents in the treatment of mild systemic inflammation including constitutional symptoms, rash, arthritis, and hypocomplementemia and for disease maintenance treatment. Notably, antimalarials also effectively reduce lipidemia and aid in the prevention of premature atherosclerosis [63].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay of therapy for musculoskeletal complaints including myalgia, arthralgia, and arthritis and are also used for serositis [64]. The cyclooxygenase 1 (COX-1) inhibitor, naproxen, is the most commonly used NSAID in pSLE for reasons of twice-daily dosing and general tolerability. COX-1 inhibitors catalyze arachidonic acid in the cell membrane to prostaglandins and thromboxane. Prostaglandins are involved in inflammation. For naproxen, 15 mg/kg divided twice daily is the accepted anti-inflammatory dose and is available in both oral and liquid preparations. Major dose-dependent side effects include gastrointestinal toxicity (dyspepsia, ulcer, diarrhea) and acute renal failure. Blood hemoglobin to assess for anemia, serum liver enzymes for NSAID-induced hepatitis, and urine analysis with creatinine should be obtained if clinically indicated. Photosensitivity is associated with pseudoporphyria of sun-exposed skin, especially in fair, blue-eyed children, and is reversible with cessation of drug [65]. Aseptic meningitis is also a concern in pSLE.

Corticosteroids are effective for rapid control of symptoms. Most children (>90 %) receive oral or intravenous steroids at some point during their disease course [66]. Oral dosing varies and is based on disease severity and duration. Intravenous administration of pulse steroid is usually reserved for severe symptom control. Serum potassium level may be checked pre-administration to avoid potential cardiac arrhythmia. No studies in children have been done to determine optimal dosing. Awareness of steroid toxicity in children is essential in determining dose, dosing schedule, and length of use.

Immunosuppressive agents are used primarily for class III and IV glomerulonephritis and neuropsychiatric involvement or as a steroid-sparing agent for clinical manifestations resistant to corticosteroid taper. Methotrexate, a dihydrofolate reductase inhibitor, is used as a first-line, second agent for resistant arthritis and skin manifestations (see Table 6.2). Common adverse effects include ulcerative stomatitis, leukopenia, and raised serum liver transaminases. Folic acid 1 mg/day for prevention of adverse mucocutaneous effects, gastrointestinal intolerance, and liver function abnormalities due to MTX may be beneficial [67, 68]. Azathioprine is also used for persistent arthritis as well as for renal disease, cytopenias, serositis, and vasculitic rash. Azathioprine, a purine antagonist, works to inhibit both cellular and humoral immunity. Prescribed as a steroid-sparing agent, it is considered a maintenance drug after initial immunosuppressive treatment for severe disease. Mycophenolate mofetil is used for induction of remission in lupus nephritis and is considered the primary maintenance medication for severe organ manifestations [69]. Mycophenolate mofetil's mechanism of action is similar to azathioprine, as it

blocks growth of T and B cells as a reversible inhibitor in the purine biosynthesis pathway. In comparison to azathioprine, mycophenolate is associated with a more tolerable side effect profile with less bone marrow suppression and decreased incidence of opportunistic infections [69]. Pharmacokinetic studies may be performed to tailor dosing to individual patients.

Immunosuppressive drug choice depends on kidney lesion histology, patient ethnicity, drug side effect profiles, medication compliance ability (which can also dictate medication delivery route—oral versus subcutaneous versus intravenous), and insurance mandates [70]. For children with glomerulonephritis, a combination of a low-salt diet, fluid restriction, and antihypertensive medications, particularly angiotensin converting enzyme inhibitors, are important for control of hypertension, proteinuria, and peripheral edema. A recent randomized, double-blind, placebo-controlled multicollaborative trial evaluating a lipid-lowering statin showed no conclusive benefit in subclinical atherosclerosis progression in pSLE [71].

Cyclophosphamide, an alkylating agent, is prescribed primarily for induction therapy of significant renal disease, severe neuropsychiatric SLE, and in cases of initial immunosuppressive treatment failure. Intravenous monthly dosing at 500–1,000 mg/m^2 with a maximum of 1,500 g/month is typical, with sequential increases in dose as tolerated until remission is achieved [72, 73]. Oral daily dosing is available but has a considerable greater toxicity, and therefore, not usually employed. Toxicity includes amenorrhea, infertility, infection, and secondary malignancies. Corticosteroids are used in all regimens demonstrating efficacy of cyclophosphamide in SLE.

Promising new drugs are essential in improving pSLE mortality rates, which have not changed drastically in the last 30 years. Drugs affecting B cells include rituximab, a monoclonal antibody against CD20+ B cells that is primarily used for cytopenias and in conjunction with other immunosuppressive medications for recalcitrant disease, and belimumab, an anti-B-lymphocyte stimulator antibody approved for mild SLE symptoms in adults only [74, 75]. Further studies are needed to validate their use in children with lupus.

Contraception methods should be considered in all adolescents with SLE as pregnancy can increase morbidity for the fetus and mother. For those without antiphospholipid antibodies, estrogen-containing barriers can be employed. Otherwise, progesterone-only devices are preferred alternatives to decrease possible thrombotic risks.

6.4 Morphea

Morphea, also known as localized scleroderma, is a fibrosing disorder of the skin. It is a rare disease with an estimated annual incidence of 2.7 per 100,000 [76]. Adults and children are affected equally, with a mean age of onset at 7–10 years in children [77–79]. Most affected children are white, and girls outnumber boys by 2.4–3:1[77–79].

6.4.1 Clinical Presentations

Morphea can be classified into multiple subtypes, including circumscribed, generalized, deep, linear, pansclerotic, and mixed [80]. The mixed subtype designates the presence of two or more of the other subtypes.

Circumscribed, or plaque morphea, is characterized by three or fewer, discrete, indurated plaques. It may be superficial with the inflammation confined to the dermis and present as a sclerotic white plaque with a violaceous rim. Deep circumscribed morphea is caused by inflammation in the subcutaneous tissues, fascia, or muscle; the overlying skin may or may not be involved but is bound down to the underlying tissues. Circumscribed morphea is seen in 26–37 % of childhood cases and is the second most common form of morphea in children [77–79].

The lesions of generalized morphea start in a similar fashion to those of circumscribed morphea. With time, however, they become larger than 3 cm, four or more develop, and they involve more than two anatomic sites (Fig. 6.5). This form of morphea is uncommon, present in 6.6–9 % of children [77–79].

Linear morphea is the most common form in children, comprising 41.8–67 % of cases [77–79].

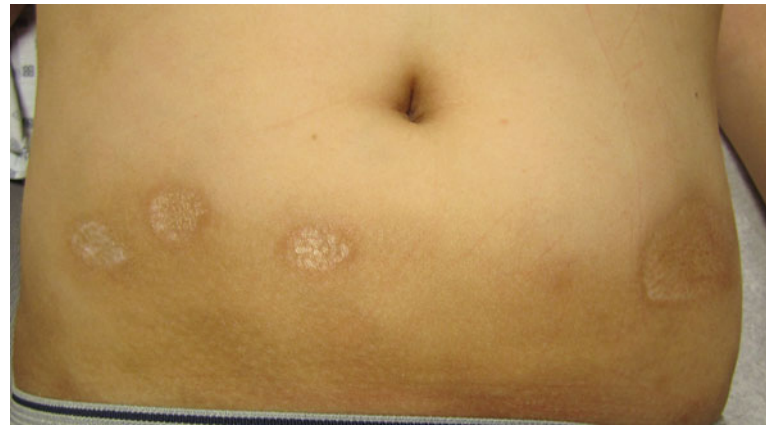

Fig. 6.5 Generalized morphea on the abdomen

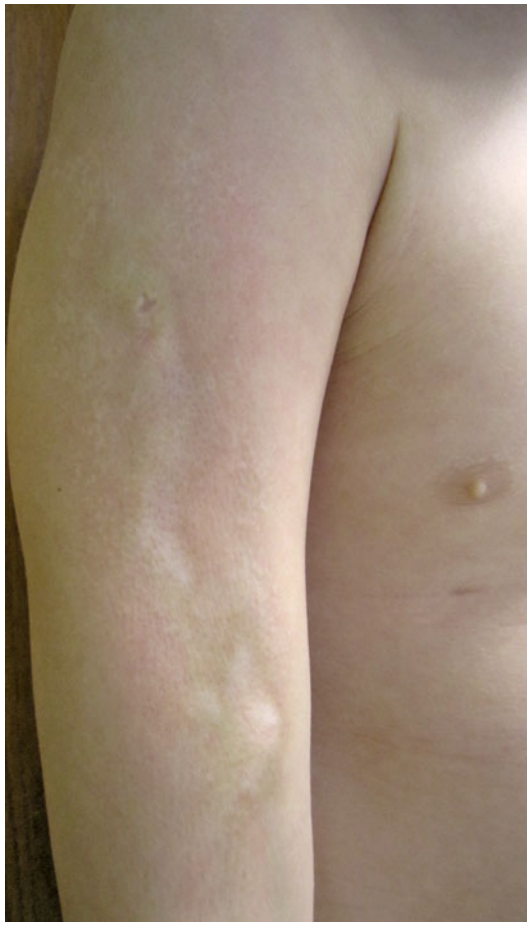

Fig. 6.6 Linear morphea on the arm

It presents as a linear plaque that follows lines of Blaschko (Fig. 6.6) [81, 82]. Linear morphea tends to extend deeply into the dermis, subcutaneous tissue, fascia, muscle, and even bone. When present on the limb, it can cause muscle or bony atrophy, limb length discrepancies, and flexion contractures. Linear morphea on the head and neck is called *en coup de sabre*, and Parry-Romberg syndrome (progressive hemifacial atrophy) may be considered a severe variant of *en coup de sabre*. Both *en coup de sabre* and Parry-Romberg syndrome can be associated with neurologic abnormalities such as abnormal imaging findings, seizures, and headaches, as well as ocular abnormalities such as uveitis.

Pansclerotic morphea is a severe and disabling variant characterized by rapid generalized involvement of the body with sparing of the fingers and toes. The fibrosis involves the subcutis and may extend deeply into bone, causing muscle and bone atrophy and flexion contractures. This form of morphea may be complicated by cutaneous ulcers and squamous cell carcinoma [83]. In contrast to systemic sclerosis, internal organs are not involved.

Extracutaneous manifestations are seen in 22–67 % of children [77, 79, 84]. Joint manifestations such as arthritis and arthralgias are the most common, typically seen in the affected limb of linear morphea but also seen at distant sites. Neurologic involvement, including seizures and headaches, is most common with *en coup de sabre* morphea and Parry-Romberg syndrome, though it may be seen with other subtypes. Gastroesophageal reflux and restrictive pulmonary disease are rarely reported.

Antinuclear antibodies (ANA) are found in approximately half of children, with a lower

incidence of specific autoantibodies such as anti-Scl 70 antibody, anti-dsDNA antibody, anticentromere antibody, and anti-histone antibody, but the clinical significance of such autoantibodies is unclear [79]. Sixteen percent of children are positive for rheumatoid factor, and there is a significant correlation between the presence of rheumatoid factor and arthritis [79].

6.4.2 Candidates for Systemic Therapy

Morphea is a slowly progressive and insidious disease. Inflammation and active disease evolves into irreversible damage and scarring. Many patients, except for those with the pansclerotic subtype, have spontaneous resolution of their disease and enter remission, though the disease sequelae usually remain. Treatment can halt further progression of the disease but is not very effective in reversing disease damage. There is a mean delay of 11–19 months before the correct diagnosis is made, so prompt recognition of the disease and initiation of appropriate treatment is imperative to prevent further morbidity [77, 79, 85].

Given the natural history of morphea, there is a treatment window during the active phase when immunomodulatory therapy is effective. Signs of active disease may be difficult to appreciate but include new or enlarging lesions, erythematous or violaceous lesion borders, and increased local temperature. Children with active disease should be started on treatment effective for their form of morphea. At the same time, systemic immunomodulatory treatment should not be used for children with quiescent disease and only scarred lesions. It may be difficult to appreciate the subtle changes of progressive disease, so sequential visits assisted by photography may be beneficial in determining disease activity prior to starting treatment for questionable cases and for assessing response during treatment courses. Treatment should be continued until signs of disease activity have ceased for 6–12 months, though patients should be closely monitored after discontinuation of therapy for signs of relapse, as 28–44 % of children relapse within 2 years of treatment cessation [86, 87]. Disease recurrence after a period of several years is uncommon but possible.

One study looking at the prescribing patterns of different specialties found that rheumatologists were much more likely than dermatologists to prescribe systemic medications for a given subtype, especially in children, suggesting that dermatologists undertreat some cases of morphea [88]. Children who have superficial circumscribed morphea can be treated with topical therapy, with consideration for phototherapy as a second-line agent. Phototherapy or systemic immunomodulators should be considered for superficial generalized morphea. Strong consideration should be given to systemic treatment to prevent further disease morbidity for any child with pansclerotic morphea, deep morphea, morphea on the face, linear morphea crossing a joint, or extracutaneous manifestations. Unfortunately, pansclerotic morphea tends to progress relentlessly despite treatment.

6.4.3 Treatment

6.4.3.1 Topical Therapy

Topical therapy may be considered for superficial variants of circumscribed morphea. Although topical corticosteroids are traditionally used, there is little evidence from prospective trials to support their efficacy. In general, medium-potency (e.g., triamcinolone acetonide, betamethasone valerate) to high-potency (e.g., clobetasol propionate) corticosteroids are used. The atrophogenic potential of topical corticosteroids should be kept in mind, especially since the morphea disease process may also result in atrophy. Tacrolimus 0.1 % ointment twice daily under occlusion has demonstrated efficacy and does not cause atrophy [89, 90]. Topical calcipotriene ointment twice daily under occlusion has also shown benefit in one trial [91]. A pilot study examining the use of imiquimod 5 % cream showed promising benefit, although its benefits are more significant for the sclerotic or fibrotic lesions rather than active lesions [92]. Topical

therapy should not be used for deep or progressive disease.

6.4.3.2 Phototherapy

Phototherapy is another option for superficial disease, either circumscribed or generalized. As ultraviolet light does not penetrate beyond the dermis, phototherapy should not be used for deep disease or those cases with extracutaneous manifestations. Level I evidence for efficacy exists for UVA-1, narrow band ultraviolet B (NBUVB), and broadband ultraviolet A (BBUVA), with the most evidence for UVA-1. Medium-dose UVA-1 was shown to be efficacious for morphea in a controlled trial when administered at a dose of 48 J/cm^2 four times a week for 5 weeks [93]. Several uncontrolled studies also support the use of medium-dose UVA-1 for the treatment of morphea [94–98]. A randomized controlled trial compared medium-dose UVA-1 with low-dose UVA-1 and NBUVB [99]. Improvement was seen with all three modalities, though patients treated with medium-dose UVA-1 had significantly improved skin scores compared to NBUVB. There was no significant difference in scores when comparing low-dose UVA-1 and NBUVB. Interestingly, this trial showed no difference in efficacy between medium- and low-dose UVA-1, while two others have suggested that morphea response to UVA-1 is dose dependent [100, 101]. Whether UVA-1 is less effective in patients of darker skin types is controversial, and results of studies are conflicting [102, 103]. Broadband UVA has been investigated in three controlled trials and shown to be effective for morphea [104–106]. Psoralen plus UVA has been used in uncontrolled trials, though this form of photochemotherapy should generally be avoided in children because of the risk of cutaneous malignancy [107, 108].

6.4.3.3 Systemic Immunomodulators

In a survey of North American pediatric rheumatologists, the most common systemic treatment regimen for morphea is pulsed methylprednisolone plus methotrexate [109]. The Childhood Arthritis and Rheumatology Research Alliance has developed three consensus treatment plans for children with morphea [110]. There is the most evidence for methotrexate combined with systemic corticosteroids in the treatment of morphea, and this regimen should be considered first line for any child who requires systemic immunomodulators. For children with contraindications to methotrexate or progressive disease despite methotrexate treatment, mycophenolate mofetil can be considered as an alternative agent [111].

Methylprednisolone is administered intravenously once a day for three consecutive days a month for the first 3 months. This regimen has been used successfully in pediatric patients [112]. Alternatives to the intravenous methylprednisolone include oral prednisolone or prednisone for the first 1–3 months [113, 114]. Pulsed methylprednisolone is generally better tolerated with fewer side effects than daily oral corticosteroid dosing [115]. With a 1–3 month course of oral corticosteroid treatment, adrenal suppression occurs and a gradual wean should be performed.

Other systemic agents with limited and mixed evidence but reported efficacy in morphea include D-penicillamine, cyclosporine, and hydroxychloroquine [116–120]. Multiple therapies such as cyclophosphamide, azathioprine, methotrexate, bosentan, intravenous immunoglobulin, antithymocyte globulin, cyclosporine, and phototherapy have been tried in pansclerotic morphea, though with limited efficacy [121–127]. Physical therapy should be considered as an adjunctive therapy for those children with joint involvement.

6.5 Eosinophilic Fasciitis

Eosinophilic fasciitis is a fibrosing disorder that is considered by some to be a variant of morphea, while others argue that it is a distinct disease [76, 128]. Children with eosinophilic fasciitis have indurated, edematous, erythematous, *peau d'orange* plaques that may eventually progress to fibrosis and a bound down appearance to the skin. The onset is sudden, with strenuous physical activity thought to be a trigger. The disease usually involves the bilateral extremities in a symmetric

manner. Flexion contractures, arthritis, and carpal tunnel syndrome are common. Characteristic laboratory abnormalities include peripheral eosinophilia, hypergammaglobulinemia, positive ANA, and elevated erythrocyte sedimentation rate (ESR). All children with eosinophilic fasciitis should be started on systemic therapy.

6.5.1 Treatment

No prospective trials for the treatment of eosinophilic fasciitis exist, so current knowledge about treatment comes from case reports and case series. Systemic corticosteroids are the mainstay of treatment. In nearly all patients, there is rapid response to oral prednisolone or prednisone 1–2 mg/kg/day, although pulse methylprednisolone has also been used [129, 130]. Spontaneous remission of the disease is common, and the corticosteroids can typically be weaned within 1 year of initiation [131]. Second-line agents for recalcitrant disease may include methotrexate, infliximab, hydroxychloroquine, mycophenolate mofetil, rituximab, antihistamines, and D-penicillamine.

6.6 Systemic Sclerosis

Juvenile systemic sclerosis (jSSc) is an extremely rare disease with an estimated incidence of 0.05 per 100,000 children [132]. The mean age of onset is at 8 years old [133, 134]. Girls outnumber boys, though the sex distribution is not as striking as in adult-onset disease. Children with jSSc have a much better prognosis than their adult counterparts and are also more likely to have overlap syndromes than adult cases.

Provisional classification criteria for jSSc were developed in 2007 [135]. The major and minor criteria are listed in Table 6.5. The diagnosis of jSSc requires the presence of one major and two minor criteria and with disease onset before 16 years. Notably, sclerosis of the skin proximal to the metacarpophalangeal or metatarsophalangeal joints is the sole major criterion and is required for diagnosis.

Table 6.5 Juvenile systemic sclerosis provisional classification criteria

Major criterion
Proximal skin sclerosis/induration of the skin
Minor criteria (organ-specific involvement)
Cutaneous
Sclerodactyly
Peripheral vascular
Raynaud's phenomenon
Nailfold capillary abnormalities
Digital tip ulcers
Gastrointestinal
Dysphagia
Gastroesophageal reflux
Cardiac
Arrhythmias
Heart failure
Renal
Renal crisis
New-onset arterial hypertension
Respiratory
Pulmonary fibrosis on radiography or high-resolution computed tomography
Decreased diffusing capacity for carbon monoxide (DLCO)
Pulmonary arterial hypertension
Neurologic
Neuropathy
Carpal tunnel syndrome
Musculoskeletal
Tendon friction rubs
Arthritis
Myositis
Serologic
Antinuclear antibodies
SSc-selective autoantibodies (anticentromere, anti-topoisomerase I [Scl-70], antifibrillarin, anti-PM-Scl, antifibrillin, or anti-RNA polymerase I or III)

One major and two minor criteria must be fulfilled

6.6.1 Clinical Presentations

There are three main clinical subtypes of jSSc. Diffuse cutaneous systemic sclerosis (dcSSc) is characterized by rapidly progressive and generalized skin thickening (proximal to elbows and knees) with early involvement of the pulmonary, renal, and cardiovascular organ systems. Limited cutaneous systemic sclerosis (lcSSc; formerly

known as CREST syndrome, [calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia]) has nonprogressive sclerosis limited to the distal extremities and late visceral involvement. Overlap jSSc is the coexistence of dcSSc or lcSSc with features of other connective tissue syndromes.

6.6.1.1 Cutaneous Manifestations

Raynaud's phenomenon (RP) is the most common manifestation of jSSC, present in approximately 70 % at the time of disease onset and nearly 100 % at some point during the course of disease [133, 134, 136]. A sequential color change from white to blue to red represents vasoconstriction with pallor, cyanosis, and ultimately reperfusion. RP occurs primarily in the fingers but can also affect other acral areas such as the toes, ear, or nose. The color change can be accompanied by symptoms such as numbness or tingling. The vasculopathy that predisposes to RP also causes nailfold capillary changes, digital pitting and ulcers, and eventually auto-amputation. Examination of the nailfolds by capillaroscopy will reveal dilated and tortuous vessels with areas of hemorrhage and/or capillary dropout. Late changes include arborization of the capillaries.

Sclerosis of the skin is another common feature of jSSc. Edema predominates initially, but it is replaced by shiny, indurated, thickened skin. The fingers become tapered and the skin thickening causes loss of mobility over time. Skin sclerosis is limited to the face, upper torso, and distal extremities in lcSSc, while rapidly progressive proximal involvement occurs in dcSSc. A scleroderma facies can develop with a small pursed mouth, pinched nose, and loss of facial folds.

Matted telangiectasias of the face, chest, and upper extremities can be a feature of lcSSc. Calcinosis cutis is typically seen as sequelae of chronic disease, and painful ulcerations can develop at the site of calcium deposits in areas of trauma.

6.6.1.2 Systemic Manifestations

Musculoskeletal disease is more frequent in jSSc compared to adult-onset SSc. Sclerodactyly and skin thickening result in flexion and extension contractures of the fingers and other affected joints. Tendon friction rubs can be heard or palpated with extension or flexion of a joint, described as a "leathery" crepitus, due to tendon inflammation and thickening. Arthralgias and arthritis are common. A mild myopathy is often present in jSSc. Additionally, myositis similar to that of juvenile dermatomyositis is seen and can represent an overlap syndrome [136].

Gastrointestinal manifestations in the form of dysmotility are present in some children. Esophageal dysmotility can cause dysphagia, whereas gastroparesis in addition to esophageal dysfunction contribute to symptoms of gastroesophageal reflux. The small and large intestines may be involved, with symptoms of abdominal pain, diarrhea, and constipation and with severe manifestations such as small intestinal bacterial overgrowth causing malabsorption, ileus, volvulus, and even perforation. Acute gastrointestinal bleeding due to gastric antral venous ectasia is rare in children.

Dyspnea suggests pulmonary involvement, either in the form of interstitial lung disease or pulmonary arterial hypertension. Pulmonary function testing may show decreased forced vital capacity and diffusion capacity (DLCO). Ground glass opacities are seen on chest radiographs and high-resolution computed tomography. Increased neutrophils, eosinophils, and alveolar macrophages are seen on bronchoalveolar lavage.

Other organ system involvement is less likely and includes cardiac, renal, and neurological manifestations (see Table 6.5 for the full list). While rare, cardiac involvement is a major cause of morbidity and mortality in jSSc. Fortunately, the scleroderma renal crisis that is more common in adult SSc is extremely rare in children.

6.6.2 Candidates for Systemic Therapy

All children with jSSc should be referred to a pediatric rheumatologist for management, and nearly all will be started on systemic therapy. A multidisciplinary team is often necessary to manage the various disease manifestations. The

dermatologist may be called upon to treat the cutaneous manifestations of jSSc through adjunctive therapy.

6.6.3 Treatment

Treatment of jSSc is complicated by the fact that it is a rare and heterogenous disease for which evidence-based treatments are lacking. All treatments are off-label, and treatment of jSSc is often extrapolated from trials performed in adult patients. Consensus-derived treatment recommendations for the treatment of adult SSc and jSSC were published in 2009 by the European League Against Rheumatism Scleroderma Trials and Research (EUSTAR) group [137]. The group developed 14 treatment recommendations for SSc based on published literature combined with expert opinion. It should be noted that these treatment recommendations are not specific to jSSc. Those aspects of jSSc treatment of most interest to a dermatologist are described below.

6.6.3.1 Systemic Therapy for Raynaud's Phenomenon and Digital Ulcers

The EUSTAR guidelines call for dihydropyridine-type calcium channel blockers as first-line treatment for RP and digital ulcers [137]. A meta-analysis of eight randomized controlled trials found a clinically significant reduction in the frequency and severity of ischemic attacks [138]. Oral nifedipine is the calcium channel blocker with the most evidence for its use. The most commonly prescribed formulations include nifedipine extended-release tablets, which can be used for ease of once-daily dosing, and immediate-release capsules taken three times daily. Doses of 0.25–0.5 mg/kg/day are used initially and titrated to effect up to a maximum of 3 mg/kg/day or 120 mg per day. Amlodipine tablets can be crushed in food and given once daily for younger children at a dose of 0.05–0.1 mg/kg/day (maximum of 5 mg/day). Adverse effects of calcium channel blockers include flushing, tachycardia, hypotension, and headache.

Intravenous prostanoids are considered second-line treatment for RP when calcium channel blockers have failed and first-line treatment for severe digital ulcers. These agents act primarily as vasodilators, although they may have effects on platelet aggregation, fibrosis, and vascular remodeling. There is the most evidence for intravenous iloprost, yet this medication is not available in intravenous form in the United States. Alprostadil is an alternative that showed equal efficacy to iloprost in one study, yet was not found to have clear benefit in another [139, 140]. Alprostadil is administered as a continuous intravenous infusion at 20 μg/h for 3 h a day for 5 days and then repeated for 1 day each month. The difficulties in administering the intravenous prostanoids limit their use.

Bosentan is an oral dual endothelin receptor antagonist. In contrast to calcium channel blockers and intravenous prostanoids, bosentan cannot improve the healing of digital ulcers; however, there is evidence from randomized controlled trials that bosentan can prevent and reduce the number of digital ulcers [137, 141, 142]. The evidence for using bosentan to prevent RP is mixed, with a randomized controlled trial showing no benefit [143, 144]. There is no published literature on the use of bosentan in the treatment of pediatric RP and digital ulcers; a trial in pediatric pulmonary hypertension used doses of 31.25 mg bid for those weighing 10–20 kg, 62.5 mg bid for those weighing 20–40 kg, and 125 mg bid for those weighing >40 kg [145]. Liver toxicity and teratogenicity are the most serious adverse effects with this drug.

Sildenafil and other phosphodiesterase inhibitors may also be used to prevent RP and treat digital ulcers, though the results from the published literature are mixed. Doses in children are not well established, with reports of 0.5–2 mg/kg/dose administered every 4–8 h [146, 147]. Adverse effects include flushing, headache, hypotension, vision changes, and sudden hearing loss.

Nitrates, which act as vasodilators, have been used in a variety of oral, transdermal, and topical formulations to treat RP and systemic

sclerosis [148–152]. Other agents with limited evidence but potential efficacy in treating RP and digital ulcers include α-adrenergic blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, selective serotonin receptor inhibitors, pentoxifylline, probucol, and aspirin. Extreme caution should be exercised when combining therapies for RP and digital ulcers as the risk of symptomatic hypotension and other adverse events is increased.

6.6.3.2 Systemic Therapy for Skin Sclerosis

Methotrexate is recommended by the EUSTAR guidelines for the treatment of cutaneous sclerosis in early jSSc [137]. Data are limited in children, but randomized controlled trials have demonstrated efficacy of this drug in improving skin scores in early adult SSc disease [153–155].

Other disease-modifying agents are used for severe jSSc. Cyclophosphamide is often beneficial for the lung disease of jSSc [156, 157]. Mycophenolate mofetil, azathioprine (as an adjunctive agent), intravenous immunoglobulin, and plasmapheresis also have reported efficacy [158–168]. Novel agents with promise include B-cell depletion with rituximab and the tyrosine kinase inhibitor, imatinib [169–177].

6.6.3.3 Supportive Care

Optimal skin care is important for children with jSSc. Daily moisturization to prevent xerosis and skin breakdown is important. If ulcers form, meticulous wound care can prevent further complications. Because the sclerotic skin affects thermoregulation, temperature extremes should be avoided; in addition, avoidance of cold can minimize Raynaud's episodes. Trauma avoidance can also minimize the risk of calcinosis cutis in those children who are predisposed.

Maintenance of mobility is another essential component in the care of a jSSc patient. Children should be encouraged to stay active as much as possible. Physical therapy is helpful for maintaining joint mobility, and splinting may be necessary to prevent or treat contractures.

6.7 Juvenile Dermatomyositis

Juvenile dermatomyositis (JDM) is the most common idiopathic inflammatory myopathy of childhood. The average annual incidence in the United States is 3.7 per 1 million children [178]. The female to male ratio may be as high as 5:1 [179].

6.7.1 Clinical Presentation

6.7.1.1 Cutaneous Manifestations

Cutaneous manifestations are extremely common in JDM, with over 90 % of children having skin involvement at disease onset [180]. The skin disease may arise before or after muscle symptoms. JDM is a photosensitive dermatosis, and lesions are often triggered after UV exposure in sun-exposed areas. Pruritus of involved areas may be a prominent feature of the disease. The characteristic heliotrope rash is a pink-purple discoloration of the upper eyelids, often with associated eyelid edema. Pink-red, scaly patches and plaques may be present on the scalp, malar region, upper chest, shoulders, upper back, and other sun-exposed areas. Pathognomonic Gottron's papules are pink-purple, flat-topped, sometimes scaly papules seen on the elbows, knees, and dorsal surfaces of the hands and feet overlying joints (Fig. 6.7). When patches or plaques arise in the same locations, it is called Gottron's sign. Periungual erythema is another characteristic feature, and capillaroscopy can show dilated and tortuous vessels with areas of dropout. Cutaneous ulcers and calcinosis cutis are less commonly seen but may cause more severe disease morbidity. Papules on the palms are a rare manifestation of JDM, and reports suggest that their presence may predict interstitial lung disease [181].

6.7.1.2 Extracutaneous Manifestations

The myopathy of JDM presents as proximal muscle weakness, although younger children may have nonspecific fatigue and lethargy. Arthritis and arthralgias may also be present.

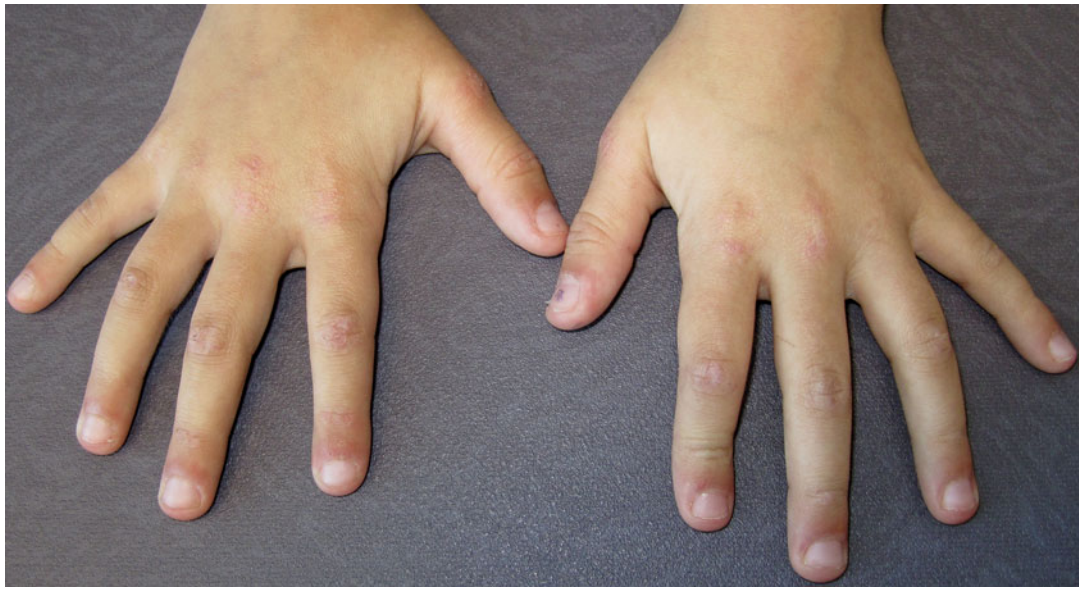

Fig. 6.7 Gottron's papules on the hand

Gastrointestinal involvement can include dysphagia, esophageal dysmotility, gastrointestinal tract ulceration, or malabsorption. Interstitial lung disease is rare in children, although respiratory weakness may cause reduced ventilation. Lipodystrophy and associated metabolic abnormalities such as hypertriglyceridemia, insulin resistance, and diabetes mellitus are a recently recognized complication of JDM [182]. Unlike in adult dermatomyositis, JDM is not associated with an increased malignancy risk.

6.7.2 Candidates for Systemic Therapy

All children with JDM should be referred to a pediatric rheumatologist for comanagement, and nearly all will be started on systemic therapy. A multidisciplinary team may be necessary if there are other organs involved. The dermatologist plays a role in treating the cutaneous manifestations of JDM through adjunctive therapy.

Some children with JDM do not have clinical, laboratory, or radiologic evidence of muscle inflammation at diagnosis, and the terms amyopathic dermatomyositis, clinically amyopathic dermatomyositis, hypomyopathic dermatomyositis, and dermatomyositis sine myositis are variably used to describe this category of patients. In a review of clinically amyopathic dermatomyositis, 74 % of those children presenting with cutaneous JDM alone for at least 6 months did not develop clinical evidence of muscle disease in subsequent follow-up [183]. Whether systemic therapy should be instituted in these children is controversial, with some advocating early aggressive therapy while others prefer an expectant approach [184].

6.7.3 Treatment

6.7.3.1 Prevention

JDM is a photosensitive disease where UV irradiation can exacerbate cutaneous disease. Both UVA and UVB light have been shown to trigger flares, and even indoor lighting sources may emit these wavelengths [185–187]. Sun avoidance and photo-protection are mainstays of

preventive therapy. JDM patients should avoid indoor and natural tanning and seek shade whenever possible. A broad-spectrum, SPF 30+ sunscreen should be used daily with reapplication every 2 h.

6.7.3.2 Adjunctive Therapy

Topical agents are mainly used as adjunctive agents in the treatment of children with recalcitrant skin manifestations of JDM. Topical corticosteroids are first-line agents to treat the erythema and pruritus of the disease, although evidence from prospective trials are lacking. Anecdotal reports also suggest that topical calcineurin inhibitors may be helpful as well [188, 189].

Pruritus may be a prominent complaint in patients with JDM. Supportive agents for the pruritus include moisturizers that contain menthol, phenol, or camphor. Topical antihistamines such as doxepin cream or diphenhydramine cream may be tried for severe pruritus, though these agents have high sensitization potential and a contact dermatitis may result. Topical analgesics such as pramoxine may be tried for symptomatic relief of the pruritus as well. Sedating antihistamines are generally more useful than the nonsedating antihistamines. Hydroxyzine 1 mg/kg at bedtime or 2 mg/kg/day divided into two to four doses is one option (maximum of 25 mg per dose). Doxepin 1 mg/kg (maximum dose of 10–25 mg) can be used for severe pruritus.

Hydroxychloroquine can be used to treat the cutaneous manifestations of JDM that are not responsive to other systemic therapy. In a retrospective review, 9 children were treated with hydroxychloroquine 2–5 mg/kg/day in addition to corticosteroid therapy and had improvement in their cutaneous and muscle symptoms [190]. Not all children will respond to hydroxychloroquine, and the experience with other antimalarials is limited in children. Data from adults suggest that combination therapy of hydroxychloroquine and quinacrine may be more effective than monotherapy, though the data for JDM is lacking [191]. Interestingly, hydroxychloroquine use has also been associated with worsening rash when used for JDM [192].

6.7.3.3 Adjunctive Therapy for Calcinosis Cutis

Supportive care is generally sufficient for lesions of calcinosis cutis. Avoidance of trauma may minimize new lesions or prevent exacerbation of existing ones. Local wound care is essential to prevent secondary complications such as infections. Surgical excision of isolated lesions may be considered, though children with JDM may be predisposed to poor wound healing and other postoperative complications as a result of their immunosuppression.

There are anecdotal reports of specific medical therapy for the calcinosis cutis of JDM. Diltiazem, bisphosphonates such as alendronate and pamidronate, oral aluminum hydroxide, probenecid, and colchicine have been reported efficacious [193–210].

6.7.3.4 Systemic Therapy

Systemic therapy for JDM is primarily guided by the extent of systemic inflammation and managed by the pediatric rheumatologist. In a survey of North American pediatric rheumatologists, systemic corticosteroids and methotrexate were the mainstay of therapy for JDM [211]. The Childhood Arthritis and Rheumatology Research Alliance has developed treatment protocols for children with moderately severe JDM who meet specific inclusion and exclusion criteria [212, 213]. These protocols summarized in Fig. 6.8 describe treatment plans for the first 4 weeks, followed by adjustments based on patient response.

Additional systemic agents used for JDM include cyclosporine, mycophenolate mofetil, cyclophosphamide (especially for ulcerative disease), and systemic tacrolimus [214–217]. Infliximab has been successfully used to treat JDM, but there are also reports of tumor necrosis factor-α agents promoting JDM flares [193, 218]. B-cell depletion with rituximab also has reported efficacy in some children [219].

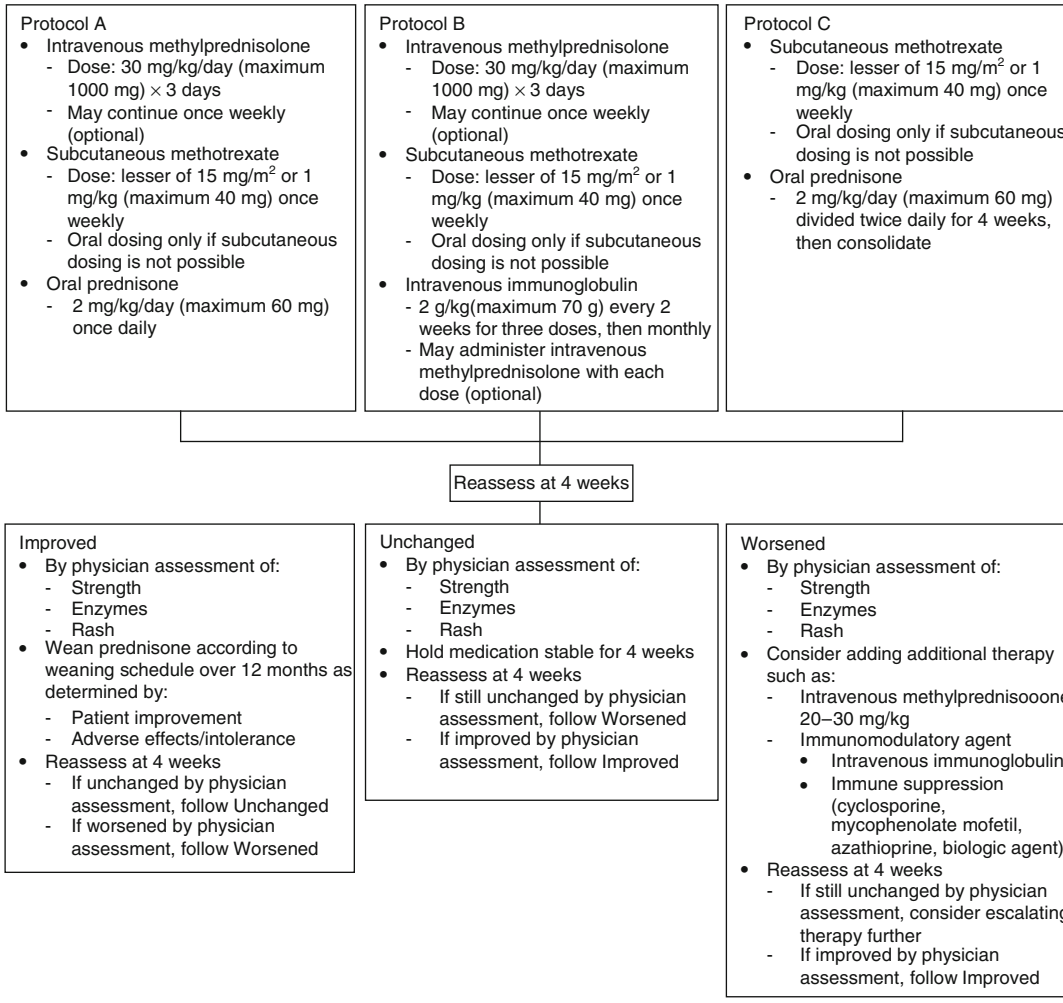

Fig. 6.8 Childhood Arthritis and Rheumatology Research Alliance treatment protocols for children with moderately severe JDM. Adapted from Huber et al. [213], copyright 2012, with permission from Wiley

Conclusion

Children with connective tissue disease will often require treatment with systemic therapy for their disease. Factors such as internal organ involvement, potential to cause functional deficits, and likelihood of permanent disfigurement guide management decisions. Children with these disorders may also be managed by a pediatric rheumatologist, but the dermatologist still plays an important role in addressing the cutaneous components of the disease, either with topical or systemic therapy.

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Autoinflammatory Syndromes

7

Tien V. Nguyen and Kieron S. Leslie

Key Points

- Autoinflammatory syndromes are a relatively new category of diseases that are due to aberrant regulation of the innate immune system.
- The genetic basis for many of these syndromes has recently been elucidated, though some still require further study.
- Early recognition and diagnosis are of great importance to enable effective treatment and prevent long-term complications such as amyloidosis.
- A chronic urticarial eruption is a prominent feature of these disorders, and such lesions in the presence of signs of systemic inflammation (e.g., fever, arthralgia, arthritis, repeatedly elevated inflammatory markers such as CRP, ESR, and a neutrophilic leukocytosis) should prompt consideration of autoinflammation and further work-up.

Abbreviations

AD	Atopic dermatitis
ASC	Apoptosis-associated speck-like protein
CANDLE	Chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature
CAPS	Cryopyrin-associated periodic syndrome
CARD	Caspase-recruiting domain
CINCA	Chronic infantile neurologic cutaneous and articular
CRP	C-reactive protein
DAMP	Danger-associated molecular pattern
DIRA	Deficiency of the interleukin-1 receptor antagonist
ESR	Erythrocyte sedimentation rate
FCAS	Familial cold-associated syndrome
FMF	Familial Mediterranean fever
HIDS	Hyper immunoglobulin D syndrome
H&P	History and physical examination
Ig (A D, E, M, or G)	Immunoglobulin (type A, D, E, M, or G)
IL	Interleukin

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IL-1β	Interleukin-1 beta
IL-RA	Interleukin receptor antagonist
MKD	Mevalonate kinase deficiency
MWS	Muckle-Wells syndrome
NLR	Nucleotide-binding domain leucine-rich repeat-containing
NLRP	Nucleotide-binding domain leucine-rich repeat-containing protein
NOD	Nucleotide-binding oligomerization domain
NOMID	Neonatal onset multisystem inflammatory disorder
NSAID	Nonsteroidal anti-inflammatory drug
PAMP	Pathogen-associated molecular pattern
PAPA	Pyogenic arthritis, pyoderma gangrenosum, and acne
PG	Pyoderma gangrenosum
PRR	Pattern recognition receptor
SAA	Serum amyloid A
SAPHO	Synovitis acne, pustulosis, hyperostosis, and osteitis
SLE	Systemic lupus erythematosus
SNP	Single nucleotide polymorphism
SOJIA	Systemic-onset juvenile idiopathic arthritis
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor alpha
TRAPS	Tumor necrosis factor receptor-associated periodic syndrome

The discovery of monogenic origins for seemingly unprovoked inflammatory episodes in patients with periodic fever syndromes has led to a new disease pathogenesis model known as autoinflammation. This concept is distinct from autoimmunity, in which lymphocyte-mediated immune responses are directed against specific self-antigens. Autoinflammation, by contrast, is characterized by aberrant regulation of the innate immune system, and as such, therapies targeting key factors in innate immune pathways have become the gold standard treatment for several familial inflammatory conditions.

Understanding the role of nucleotide-binding domain leucine-rich repeat-containing (*NLR*) genes and their protein products NLRPs in mediating inflammatory responses can help explain the basic etiopathogenesis of autoinflammation [1]. Thus far, 22 human *NLRs* have been identified [2]. Each *NLR* encodes a NLR protein (NLRP), which interacts with two other proteins called the apoptosis-associated speck-like protein (ASC) and pro-caspase-1 to form a complex known as an inflammasome. Inflammasome assembly allows caspase-1 to become activated, leading to hydrolysis and activation of pro-inflammatory cytokines, primarily interleukin-1 beta (IL-1ß), IL-6, and IL-18 [3]. Caspase-1 can also mediate secretion of IL-1 alpha (IL-1α) and fibroblast growth factor 2 [4].

NLRPs are cytosolic pattern recognition receptors (PRRs) responsible for detecting pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), respectively, representing exogenous and endogenous stimuli (e.g., microbial pathogens, products of cellular stress). Binding of NLRPs to PAMPs and DAMPs begins the process of inflammasome assembly. Toll-like receptors on cell surfaces bear equivalent function to NLRPs as innate sensors of inflammatory signals; however, these receptors stimulate cytokine production by turning on transcription factors (e.g., nuclear factor kappa B or NF-kB) instead of inflammasome formation.

NLR mutations may lead to inappropriate activation of or failure to inhibit inflammasomes, resulting in abnormal secretion of pro-inflammatory cytokines [5]. Although incompletely understood, active IL-1ß appears to prime the production of its own precursor pro-IL-1ß, thereby perpetuating autoinflammatory responses [6, 7]. Alternative pathways have also been suggested, including inflammasome activation via mitochondria-derived reactive oxygen species in response to exogenous pathogens or endogenous danger signals [8], but the literature lacks substantial evidence to support these hypotheses.

7.1 Cryopyrin-Associated Periodic Syndrome (CAPS)

Cryopyrin-associated periodic syndrome (CAPS) is the new preferred name for a syndrome that encompasses three distinct phenotypes, listed in the order of increasing severity: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells

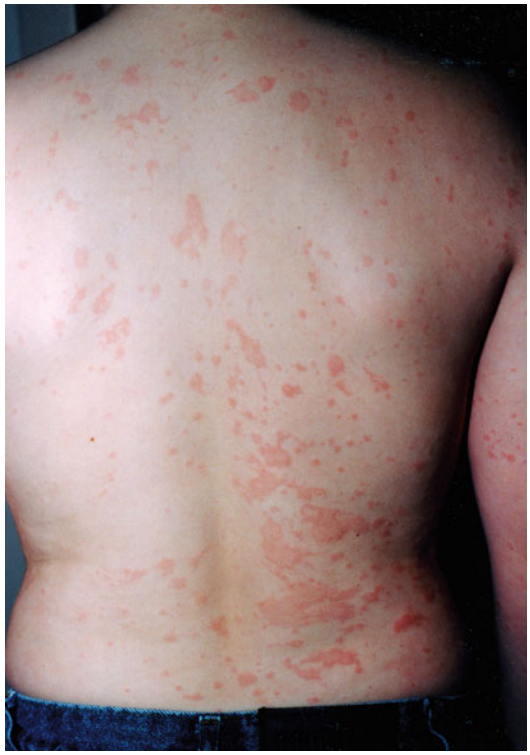

Fig. 7.1 Cryopyrin-associated periodic syndrome (CAPS). A widespread urticarial-like eruption on a patient's back

syndrome (MWS), and neonatal onset multisystem inflammatory disorder (NOMID), also called chronic infantile neurologic cutaneous and articular (CINCA) syndrome. Symptoms typically begin in the neonatal period and persist throughout life. However, due to the rarity of the syndrome, correct diagnosis is frequently delayed until adulthood. Stress and exposure to low ambient temperatures have been described as triggers – this is especially true for FCAS [9, 10].

CAPS typically presents as episodes of evanescent, urticarial-like macules, papules, and geographic plaques on the trunk (Fig. 7.1), on extremities, and, less frequently, on the face, along with periodic fevers and distal arthralgia [9, 11, 12]. The eruption is generally more subtle than acute urticaria, although at times it may be indistinguishable from typical urticaria. In contrast to true chronic urticaria, the lesions of CAPS are usually non-pruritic, though patients might complain of tightness and a burning sensation in the skin. It is generally characterized by little to no rash in the morning with worsening of cutaneous findings and other febrile symptoms as the day progresses. Skin biopsy reveals a sparse interstitial, perivascular, or perieccrine neutrophilic infiltrate.

Ocular involvement, including conjunctivitis, episcleritis, and uveitis, and neurological manifestations, including headaches, sensorineural hearing impairment, and chronic meningitis, are less common manifestations [13, 14]. Secondary amyloid A (AA) amyloidosis can develop in approximately 25 % of CAPS patients and most frequently affects the kidney, potentially leading to nephrotic syndrome. One case series reported six cases of reactive amyloidosis out of 22 patients [13]. There are no known susceptibility markers for the development of amyloidosis. During active disease, leukocytosis and elevation of C-reactive protein (CRP) and serum protein AA (SAA) are almost always present, whereas the erythrocyte sedimentation rate (ESR) is variably elevated [15]. Normalization of the aforementioned inflammatory markers appears to lower the risk of systemic amyloidosis.

Expression of the pro-inflammatory cytokine IL-1ß is upregulated in CAPS [7, 13, 16]. In most patients, mutations in the *NLRP3* gene (also referred to as the *CIAS1* or *NALP3* gene) have been found to cause a gain of function in the protein product, cryopyrin. The mutated cryopyrin participates with other structural components to form a permanently active inflammasome [17–19]. In addition, there have been patients with NALP12 (also known as NLRP12) mutations presenting with a CAPS phenotype, and such mutations have been shown to cause excessive production of IL-1ß [20, 21].

As such, targeted inhibition of IL-1ß has revolutionized the management of CAPS patients. Anakinra, a recombinant DNA analog of the human IL-1 receptor antagonist (IL-1RA), is an effective treatment and has been found to improve amyloidosis-induced nephrotic syndrome [22–26]. Administered subcutaneously once every day, anakinra is dosed at 100 mg for adults and 1–2 mg/kg for pediatric patients. Common adverse events include injection site reactions and upper respiratory tract infections, whereas neutropenia is a rare

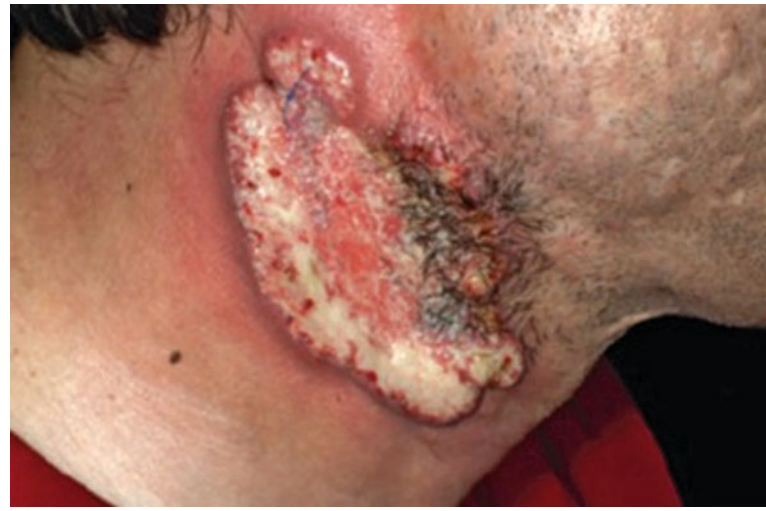

Fig. 7.2 Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome. A "beefy red" ulcer with some granulation tissue and a sharply demarcated, bluish, undermined border consistent with pyoderma gangrenosum (Reprinted with permission from Brenner et al. [33])

adverse event. The concomitant use of anakinra and tumor necrosis factor alpha (TNF-α) inhibitors (e.g., etanercept) is contraindicated due to an increased risk of infections [27]. Prior to instituting therapy, it is important to rule out preexisting infectious diseases, such as tuberculosis (TB), hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) infection. With respect to laboratory monitoring, CRP, ESR, blood urea nitrogen, and creatinine should be measured every 2 weeks until clinical remission is achieved, after which measurement once every 3 months, along with blood cell counts (CBC), is appropriate.

The use of anakinra for CAPS is off-label in the USA, as it is FDA-approved solely for rheumatoid arthritis; however, canakinumab and rilonacept are licensed for CAPS (for FCAS and MWS phenotypes). Canakinumab, a fully human monoclonal antibody against IL-1ß, demonstrated a 97 % complete response rate in a recent clinical trial [28]. Standard dosing is 150 mg for adults and 2 mg/kg for pediatric patients, administered subcutaneously once every 8 weeks. If response is suboptimal, dosing may be titrated up to 600 mg for adults and 8 mg/kg for children. Reported side effects include an increased risk of infections and vertigo. Live vaccinations should be avoided in patients receiving canakinumab.

Rilonacept, a "cytokine trap" antibody with high affinity for anti-IL-1, represents a third highly effective treatment option [29–31]. It is administered subcutaneously once weekly, starting with a loading dose of 320 mg for adults and 4.4 mg/kg for pediatric patients and continuing with 160 mg for adults and 2.2 mg/kg for children. Common adverse effects are similar to those of anakinra and canakinumab.

7.2 Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne (PAPA) Syndrome

PAPA syndrome is a dominantly inherited disorder characterized by pyoderma gangrenosum (PG), acne vulgaris, and pyogenic arthritis primarily involving the appendicular skeleton [32]. PG and arthritis typically present in early childhood, whereas acne often begins during puberty (also see Chap. 3). PG lesions are characterized as single or multiple deep, "beefy red" ulcers with bluish, undermined borders (Fig. 7.2). Common locations are the legs and face and occasionally the intertriginous regions. Skin ulcers in PAPA are indistinguishable from PG lesions secondary to other causes.

Mutations in *PSTPIP1* (also known as *CD2BP1*) cause increased binding of the protein pyrin to the pyrin domain of NLRP, leading to inflammasome formation [34]. Laboratory findings include elevated CRP and ESR levels, as well as hypogammaglobulinemia [35–37]. Acne

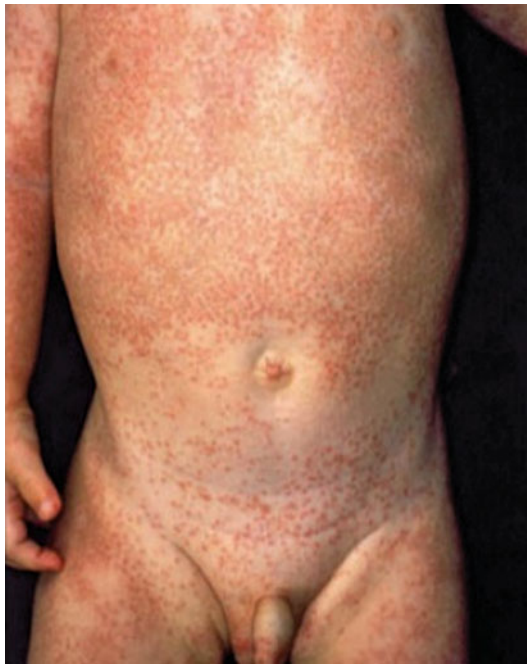

Fig. 7.3 Blau syndrome. Densely populated, *yellowish* to *red-brown* pinhead papules (Reprinted with permission from Stoevesandt et al. [46])

and PG typically respond to infliximab and etanercept, respectively, whereas response to anakinra is variable [33, 38–40]. Control of inflammation can sometimes be achieved with prednisone (15–60 mg/day) [41].

7.3 Blau Syndrome

Blau syndrome is a childhood-onset, dominantly inherited disorder with a triad of cutaneous granulomata, symmetric polyarthritis (with or without camptodactyly), and ocular manifestations, including uveitis, iritis, vitritis, and closed-angle glaucoma [42–45]. Family history is frequently positive; however, a lack of contributory family history does not exclude the diagnosis, since spontaneous mutations may occur. The rash tends to be asymptomatic with episodes of flaring and spontaneous resolution. Skin examination reveals generalized, discrete, pinhead, yellowish to red-brown papules with a densely populated, perifollicular distribution (Fig. 7.3) [47, 48]. Recalcitrant, tender leg ulcers with granulating bases and poorly demarcated flat borders have been described, in contrast to the well-defined undermined borders of PG ulcers [49]. Arthritis often is symmetric and affects the wrists, knees, and ankles.

Skin biopsy is very helpful in establishing a diagnosis and reveals perifollicular noncaseating granulomata in the dermis [46–48]. Lichen scrofulosorum, a tuberculid, can also present in a similar fashion; thus, a tuberculin skin test or QuantiFERON® measurement should be performed to assess for tuberculosis. In Blau syndrome, granulomatous infiltration of the lungs, kidneys, liver, and of the arterial and nervous systems has been anecdotally reported [50–54]. It appears that lung involvement is rare, and mediastinal lymphadenopathy has yet to be documented. This information can be useful to a clinician wishing to distinguish Blau syndrome from childhood-onset sarcoidosis.

Missense mutations in the *CARD15* (also known as *NOD2 – nucleotide-binding oligomerization domain*) gene are responsible for abnormal innate immunity in affected patients [44, 55]. CARD15 serves as an activator of the nuclear factor kappa B (NF-kB) pathway in monocytes, leading to expression of inflammatory cytokines that in turn contribute to the development of granulomata [56, 57]. Increased immunoglobulin (Ig) A, IgG, ESR, and angiotensin-converting enzyme levels have been documented [43].

Genetic counseling and management with a multidisciplinary team approach involving dermatology, rheumatology, and ophthalmology may be needed. Since the rash often resolves spontaneously, systemic medications are usually reserved for recalcitrant arthritis and ocular inflammation. Response to targeted anti-IL-1 therapy is inconsistent, and serum IL-1ß levels do not necessarily correlate with disease severity [58, 59]. Infliximab and thalidomide have been used with moderate success [60, 61], whereas treatment with prednisone 2 mg/kg/day may be necessary to control ocular inflammation [42, 45]. Surgical intervention is an option for advanced glaucoma [45].

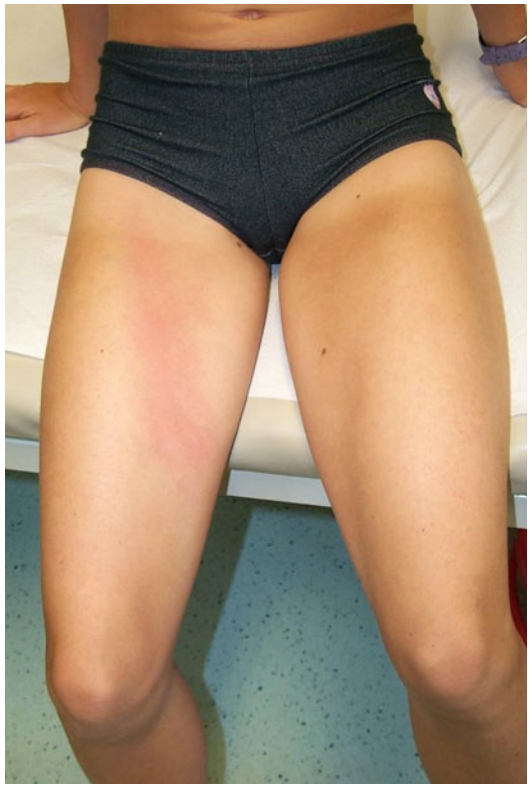

Fig. 7.4 Tumor necrosis factor-associated periodic fever syndrome (TRAPS). A large, ill-defined, erythematous patch on a patient's thigh (Reprinted with permission from Morbach et al. [64])

7.4 TNF Receptor-Associated Periodic Fever Syndrome (TRAPS)

TRAPS is a dominantly inherited disorder that presents with prolonged periodic fevers (typically 7–21 days), macules and patches overlying focal myalgia, abdominal pain, conjunctivitis, unilateral periorbital edema, and occasional lymphadenopathy [62, 63]. Most patients develop skin manifestations during early childhood: warm, blanchable, erythematous macules, and patches with a tendency to migrate from the trunk to distal extremities (Fig. 7.4). Other morphologies include widespread reticulate erythema or annular edematous plaques [63, 65].

Mutations in the *TNFRSF1A* gene coding for a TNF receptor are associated with reduced concentrations of the cytosolic, soluble form of the receptor [66]. This may be a result of "defective shedding" of the receptor from its position on the cell surface. However, some TRAPS patients manifest normal levels of the membrane-bound TNF receptor [67]. Plasma levels of ESR, CRP, haptoglobin, fibrinogen, and ferritin may be elevated during inflammatory attacks [64]. Histopathology of skin specimens reveals perivascular and interstitial infiltrate of lymphocytes and monocytes – distinct from the neutrophilic infiltrate observed in CAPS [63].

With regard to treatment, NSAIDs and corticosteroids have been effective as on-demand agents during inflammatory attacks [68]. According to the results of the Eurofever Registry, anakinra is "a promising therapy" with a 79 % rate of complete response [68], and its efficacy has been corroborated by another study [69]. Colchicine and etanercept have been used with moderate success, but complete response is less commonly observed compared with anakinra [68, 70]. There are a few reports of etanercept not being effective in reducing symptoms or normalizing lab parameters for TRAPS patients; however, it reduced corticosteroid requirements in corticosteroid-responsive patients [71, 72]. One study has documented increased IL-6, IL-8, and IL-12 signaling and no symptomatic relief with infliximab [73]. Tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, was reported as beneficial in one case [74].

7.5 Hyper-IgD Syndrome (HIDS)

Hyper immunoglobulin D syndrome (HIDS), or mevalonate kinase deficiency (MKD), is an autosomal recessive disorder characterized by periodic fevers, a morbilliform exanthem, arthralgia, GI disturbances, lymphadenopathy, and splenomegaly [75–77]. It was first described in the Netherlands with six patients affected by recurrent fevers and high serum IgD levels. Symptoms typically present within the first year

of life, are exacerbated by physical/emotional stressors, and sometimes coincide with childhood vaccinations.

A child with HIDS frequently appears febrile and ill. Skin findings range from intermittent, painful, ill-defined erythematous macules and papules to edematous, erythematous plaques with prominent borders and occasionally central clearing. Common areas of involvement are the trunk and extremities but it can extend to the face, neck, and buttocks. Amyloidosis can be found in severe cases [76]. Immunohistology of lesional skin reveals perivascular deposition of IgD and C3 complexes [78].

Elevated serum IgD is a unique feature lending the syndrome its name [76, 79], whereas the IgA level is sometimes elevated [80]. Levels of acute-phase reactants (e.g., ESR, CRP, leukocytosis) are frequently increased during attacks and may persist with lower intensity or normalize between attacks. Urinary mevalonate can be normal or elevated and thus is not a reliable diagnostic criterion. The gold standard for diagnosis is genetic testing. Mutations in the *MVK* gene coding for the enzyme mevalonate kinase disrupt cholesterol synthesis, resulting in decreased serum cholesterol levels and an episodic increase in urinary mevalonic acid [81]. The shortage of some of the mevalonate pathway intermediates has been linked with upregulation of the inflammasome gene *NALP3* [82, 83], and this might explain the increase in TNF-α and IL-1ß activity in affected patients [84].

The Eurofever Registry reports reasonable responses to on-demand therapy (during an attack) of NSAIDS and corticosteroids [68]. There are reports of simvastatin (dose range 20–80 mg daily) being modestly helpful for patients with HIDS, possibly via inhibition of mevalonic acid production [85–89]. Response to anakinra (20–100 mg/day) and canakinumab, respectively, has also been documented [68, 77, 89–92]. TNF inhibition may yield mixed results, with etanercept being the agent of choice, while colchicine is often ineffective [68, 85–88]. As there are no randomized clinical trials guiding management for HIDS, it is unclear if therapy should be instituted on a continuous or on-demand basis.

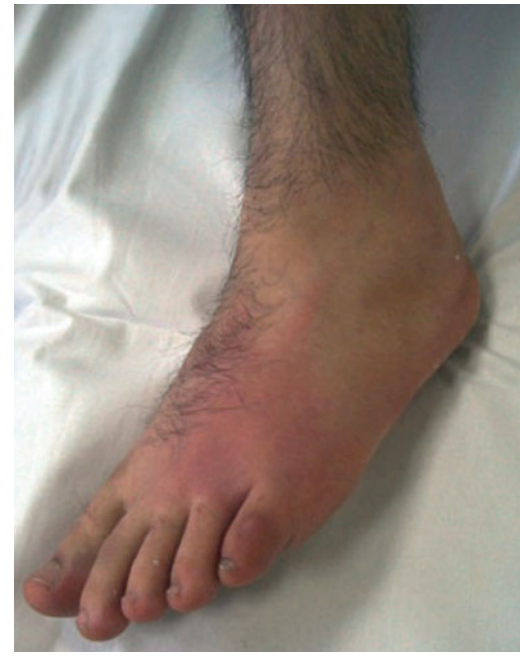

Fig. 7.5 Familial Mediterranean fever (FMF) syndrome. Erysipelas-like erythema on the dorsal surface of a patient's foot (Reprinted with permission from Aydin et al. [95])

7.6 Familial Mediterranean Fever (FMF) Syndrome

FMF syndrome is an early-onset, autosomal recessive disorder presenting mainly in patients of Mediterranean descent with periodic bouts of fevers lasting 1–3 days, synovitis, serositis, and less commonly an erysipelas-like erythema. Other reported features include Henoch-Schönlein purpura, polyarteritis nodosa, and protracted febrile myalgia [93–103]. Amyloidosis is a rare complication of FMF [93, 104]. Although attacks can occur on a weekly basis, some patients experience them much less frequently (e.g., one per year). Precipitating factors range from stress and strenuous physical activity to menstruation. Nevertheless, the majority of patients report no obvious inciting events.

In patients presenting with skin manifestations of FMF, physical examination typically reveals tender, erythematous plaques with sharply demarcated, advancing borders localized to the bilateral legs, consistent with erysipelas-like erythema (Fig. 7.5). Histopathologic findings consist of dermal edema and sparse perivascular

infiltrates of lymphocytes, neutrophils, and histiocytes. This erysipeloid skin eruption is only seen in 15–40 % of patients, and other possible skin morphologies range from urticarial-like eruptions, purpura, and angioneurotic edema to Raynaud's phenomenon, PG, and subcutaneous nodules.

FMF is caused by mutations in the *MEFV* (*ME*diterranean *Fe*V*er*) gene encoding pyrin, a key protein involved in inflammasome activation [105–107]. Patients with homozygous *MEFV* mutations from Armenia, Turkey, and Arabian countries are at high risk of developing amyloidosis and should be placed on long-term prophylactic colchicine [108]. Urinalysis should be performed regularly to look for evidence of compromised renal function, e.g., proteinuria and impaired creatinine clearance. A renal biopsy may reveal amyloidosis in patients with nephrotic syndrome. Other useful measurements include serum levels of CPR and SAA.

Three randomized controlled trials have established the efficacy of colchicine in reducing the severity of the acute inflammatory episodes and reducing the number of attacks [109–111]. It works by inhibiting microtubule assembly and halting neutrophil migration. Side effects include gastrointestinal disturbances, fatigue, headaches, and rarely, bone marrow suppression, myopathy, rhabdomyolysis, nephrotoxicity, hepatotoxicity, and hypersensitivity reactions. IL-1 blockade represents an alternative option for the treatment of FMF [112–116]. Etanercept and sulfasalazine may be helpful, whereas thalidomide administration has yielded conflicting results [117–122].

7.7 Deficiency of IL-1 Receptor Antagonist (DIRA) Syndrome

In 2009, Aksentijivech et al. described a novel autoinflammatory syndrome characterized by neonatal-onset, mild-to-severe generalized pustulosis, periostitis, and osteomyelitis with negative bone tissue culture findings [123]. Abnormal radiographic skeletal features were commonly observed, whereas nail changes and hepatosplenomegaly were found in 4 of the 9 patients in this report. Therapy with disease-modifying antirheumatic drugs and prednisone at 2 mg/kg/day did not diminish symptoms or normalize levels of acute-phase reactants [123]. Two of the nine reported children died of multiorgan failure secondary to severe inflammation, and another died from complications of pulmonary hemosiderosis.

The new entity was named "deficiency of the IL-1 receptor antagonist" (DIRA) based on the discovery of mutations in the *IL1RN* gene, which encodes a circulating antagonist to IL-1 signaling [123]. Monocytes of patients with DIRA produce a truncated, nonfunctional version of the IL-1 receptor antagonist, correlating with hyperresponsiveness of inflammatory cells to IL-1ß stimulation. Anakinra has been reported as a highly effective treatment with most patients achieving complete remission [123].

7.8 Chronic Atypical Neutrophilic Dermatitis with Lipodystrophy and Elevated Temperature (CANDLE) Syndrome

CANDLE syndrome, first described by Torrelo et al. in 2010, is characterized by generalized annular erythematous/violaceous plaques, edematous eyelids, progressive facial lipodystrophy, arthralgia, early-onset periodic fevers, and delayed physical development [124, 125]. Homozygous and heterozygous mutations in the proteasome subunit ß type 8 (*PSMB8*) gene have been identified [126]. Impaired proteasome function means that damaged proteins serving as signals of cellular stress are not adequately degraded, leading to chronic inflammation [126]. ESR and hepatic transaminase levels are consistently elevated in patients with CANDLE syndrome. Skin biopsy reveals mature neutrophils and a perivascular/interstitial infiltrate rich in myeloid cells [124]. Lipodystrophy may be a result of chronic inflammation involving adipose tissue [127, 128]. Patients generally respond poorly to anakinra, intravenous immunoglobulin, infliximab, etanercept, cyclosporine, and prednisone [124, 125]. Partial response to methotrexate has been reported [124].

7.9 Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis (SAPHO) Syndrome

SAPHO syndrome is characterized by severe acne, palmoplantar pustulosis or palmoplantar pustular psoriasis, chronic inflammation of sternoclavicular and sternocostal synchondroses, osteosclerosis, and hypertrophic osteitis of the vertebrae and femurs, as well as synovitis involving the elbows, knees, metacarpophalangeal, and proximal interphalangeal joints [129–134]. Sterile pustules measuring 2–4 mm in diameter are localized to the palms and soles, sometimes studding scaly erythematous plaques. Inflamed comedones and pustules of acne vulgaris can be found on the face and upper trunk. Acne conglobata, acne fulminans, and acne inversa appear as suppurating cysts, nodules, abscesses, and sinus tracts [129, 135]. Dermatologic and rheumatologic manifestations are not temporally related [136].

Both *Staphylococcus aureus* and *Propionibacterium acnes* have been implicated in triggering the inflammatory attacks of SAPHO. *P. acnes* has been cultured from bone specimens, a sternal osteosclerotic lesion, and intervertebral material from affected individuals [137]. This has led to the hypothesis that the inflammation may be a result of multiple failed attempts to clear the bacterium [137]. Serum levels of ESR and CRP are elevated. Successful treatment with anakinra has been reported [138, 139]. TNF-α blockade with infliximab, etanercept, or adalimumab can be helpful for some patients [140]. Several case reports have documented response of skin manifestations to colchicine 1–1.5 mg/day, prednisone 5 mg/day, etretinate 20–50 mg/day, dapsone, and tonsillectomy [140–148].

7.10 Schnitzler Syndrome

Schnitzler syndrome is a rare disorder characterized by recurrent fevers, urticaria, arthritis, hyperostosis, osteosclerosis, and IgM gammopathy [149–151]. Skin findings consist of asymptomatic erythematous, edematous plaques with prominent borders, primarily found on the trunk and lower extremities. Lymphadenopathy, hepatomegaly, polyclonal lymphoplasmacytic infiltration of the bone marrow, and rarely severe anemia and life-threatening thrombophilia have been reported [152, 153]. Impaired renal function and Waldenstrom's macroglobulinemia may occur as late sequelae [154–159].

No genetic basis for Schnitzler syndrome has been found. Laboratory investigations reveal elevation of IL-1ß, IL-6, IL-18, ESR, and CRP levels [160–162]. Histopathology of lesional skin demonstrates perivascular infiltrate consisting of lymphocytes, histiocytes, and neutrophils [151]. Immunofluorescence staining shows IgM deposits in the superficial dermis or at the basement membrane [151]. Daily administration of anakinra has provided long-term control [163–166]. Psoralen combined with ultraviolet A therapy and IL-6 blockade with tocilizumab may be effective, respectively [167, 168]. Other treatments that have been used with variable success include TNF-α inhibition, thalidomide, colchicine, systemic steroids, and interferon α-2b [169–177].

7.11 Systemic-Onset Juvenile Idiopathic Arthritis (SOJIA)

Systemic-onset juvenile idiopathic arthritis (SOJIA) is a relapsing systemic inflammatory disorder with an onset in childhood. Characteristic features consist of spiking fevers, an evanescent morbilliform rash occurring daily and polyarticular arthritis [178, 179]. Skin examination reveals diffuse erythematous macules and papules closely distributed on the trunk and upper extremities, and less frequently on the face [179–182]. Histopathology of lesional skin shows perivascular and interstitial infiltrate composed of (in order of decreasing frequency) neutrophils, monocytes, lymphocytes, and eosinophils [183]. Neutrophils can also be visualized in perieccrine tissues and at the epidermal-dermal junction [183].

Elevated IL-6 levels, which have been found to parallel febrile episodes, suggest a possible role for IL-6 blockade therapy [178]. No genetic mutations have been found in patients with SOJIA.

In clinical trials, anakinra and canakinumab have demonstrated efficacy in controlling inflammatory attacks [184–186].

7.12 Chronic Urticaria and Differentiation from Autoinflammatory Syndromes

Chronic urticaria is urticaria typically lasting 2–24 hours and occurring twice weekly for more than 6 weeks [187]. Although acute urticaria is common in young children, chronic urticaria is more likely to present in adults, with peak incidence in the fourth decade [188]. Basic morphology consists of evanescent wheals of various sizes. Dermographism and other types of physical urticaria may also be seen in patients with chronic idiopathic urticaria. Pruritus and irritation are most noticeable at night, causing loss of sleep and significant distress. Degranulation of mast cells with release of histamine is the main disease-mediating process, and there has been an association with aberrant autoimmunity [187, 189, 190].

The differential diagnosis for chronic urticaria consists of chronic idiopathic urticaria, physical urticaria, contact urticaria, cholinergic urticaria, angioedema, urticarial vasculitis, and urticarial-like eruption of an autoinflammatory process (e.g., CAPS, SOJIA). A thorough history and physical exam (H&P) are the best tools to establish a diagnosis and identify potential triggers and possible contributing infections [191]. Without meaningful diagnostic clues in the H&P, indiscriminate investigations involving food allergy tests as well as occult infection and malignancy work-ups are unwarranted [191]. Provocation and contact allergy tests are appropriate when the H&P points toward physical, cholinergic, or contact urticaria. For severe or antihistamine-unresponsive disease, obtaining a complete blood count, ESR, CRP, thyroid function studies, an autoantibody panel, and a urinalysis might be helpful [191, 192].

If the wheals last longer than 24 hours, are painful and/or purpuric suggesting vasculitis, or the patient has signs of systemic inflammation (e.g., fever, arthralgia, arthritis, repeatedly elevated markers of inflammation such as CRP, ESR, and a neutrophilic leukocytosis), then urticarial vasculitis or an autoinflammatory process should be considered, respectively. In these patients lesional skin biopsies may be very helpful. Chronic urticarial wheals are marked by prominent dermal edema and a scant perivascular infiltrate of lymphocytes, eosinophils, and neutrophils, whereas urticarial vasculitis lesions show leukocytoclasis and intravascular/perivascular fibrin deposits. Direct immunofluorescence in chronic urticaria frequently reveals immunoglobulin and complement C3 deposits within blood vessels [193]. Classic urticarial lesions respond to antihistamines (H1 ± H2 blockers) and in part to leukotriene antagonists, whereas autoinflammatory disorders do not [194].

Conclusion

Awareness of autoinflammatory syndromes can lead to earlier diagnosis of undetected cases as well as proper management of febrile episodes and multiorgan inflammatory symptoms in both pediatric and adult patients. Our understanding of aberrant pathways in the innate immune system has expanded significantly in the past decade, but much is still unknown about recently discovered conditions such as DIRA and CANDLE syndromes. This has opened up avenues for the development of new, targeted therapies for the treatment of these complex inflammatory conditions.

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Part III

Vascular Lesions and Tumors

Infantile Hemangiomas

8

Denise W. Metry

Abbreviations

AIS	Arterial ischemic stroke
IH	Infantile hemangioma
MRA	Magnetic resonance angiography
PHACE syndrome	Posterior fossa brain malformations, Hemangioma, Arterial lesions, Cardiac abnormalities, and Eye abnormalities
VEGF-A	Vascular endothelial growth factor A

Infantile hemangiomas (IH), the most common tumors of childhood, are benign growths of vascular endothelial-like cells that are characterized by a proliferative phase followed by involution. Despite their benign pathology and self-limited nature, a significant minority of IH do not follow an uneventful course. Complications range from minor to serious, and include ulceration, permanent disfigurement, bleeding, loss of vision, airway obstruction, hepatic compromise, congestive heart failure, and associated developmental anomalies (Table 8.1). Many of these complications can be life altering, and occasionally, life threatening. A Hemangioma Severity Scale has been developed as a tool to reliably assess relative severity of complications [1]. Goals of IH treatment include control of ulceration to limit scarring, bleeding, infection, and pain, prevention or reversal of function-threatening complications, avoidance or minimization of disfigurement, and minimization of psychosocial distress for the patient and family [2].

The approach to IH treatment is highly individualized and dependent on a number of variables not limited to tumor size, morphology, location, stage, severity of potential or actual complications, patient age and comorbidities, and parental level of concern. Furthermore, much of IH care is based on case reports, observational studies, and clinical experience; there is a clear lack of evidence-based standards for the treatment of IH, and no FDA-approved agents currently exist. While most IH can be managed conservatively with parental education, reassurance, and observation alone, treatment of complicated IH may include any combination of the following: wound care, topical medications, pain control, pulsed-dye laser, surgery, or systemic therapy. Of these, systemic therapy is the most commonly utilized modality and, depending on the individual case, is often the most efficacious. Consultation with or referral to a pediatric dermatologist, vascular anomalies center, or other knowledgeable specialist is recommended when treatment is being considered for a complicated IH [2]. Such action must be timely, since therapy, particularly systemic, is usually most effective when initiated

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Table 8.1 Hemangioma complications: candidates for systemic therapy

Risk of disfigurement	Any moderately sized superficial or deep hemangioma on the face[a], especially when central and/or involving the lip, nasal tip, ear or periocular skin
	Any lesser hemangioma in other cosmetically concerning locations, especially when at risk of distorting anatomic landmarks (e.g., breast[b])
	Milder hemangiomas in cosmetically concerning locations that are failing to respond adequately to nonsystemic therapy[c]
Ulceration	Superficial or deep ulceration that is interfering with daily living (diaper changes, bathing, feeding, sleeping)
	Cosmetically concerning locations for scarring/disfigurement
	Failure to respond adequately to standard wound care, other nonsystemic therapies[c], pain and/or infection control
Vital organ compromise	Airway involvement—asymptomatic or symptomatic (noisy airway breathing, hoarse cry, stridor)
	Visual compromise—partial or complete visual axis occlusion, eyelid distortion, astigmatism, proptosis, amblyopia, anisometropia
	Hepatic dysfunction—hepatomegaly especially in presence of hepatic dysfunction (elevated bilirubin/liver enzymes, abnormal synthetic function, hypothyroidism requiring oral replacement)
	High-output cardiac failure due to a significant hepatic or very large cutaneous hemangioma
	Gastrointestinal bleeding with or without symptomatic anemia
	Neurologic abnormalities due to an intraspinal hemangioma
	Torticollis due to large neck hemangioma, especially when persistent (e.g., abnormal head posture maintained most of the day)
	Hearing loss due to an intra-auditory hemangioma[d]

[a]Infants with large, segmental hemangiomas of the face should be evaluated for PHACE syndrome prior to considering propranolol therapy (see Section on Propranolol Use in PHACE syndrome)
[b]Breast hemangiomas, especially those with a significant deep component, can potentially interfere with normal breast bud development in girls in the future
[c]Smaller, superficial hemangiomas of minor cosmetic or functional concern or non-severely ulcerated hemangiomas can be candidates for topical therapy (e.g., timolol, corticosteroids, imiquimod), intralesional corticosteroid therapy and/or laser therapy
[d]This is most commonly observed in the setting of a segmental scalp, periauricular hemangioma in association with PHACE syndrome

early during the proliferative phase (e.g., within the first few months of life) [3]. Propranolol and glucocorticoids (prednisolone or prednisone) are first-line agents for the majority of complicated IH that require systemic intervention. Alternative systemic agents such as vincristine and interferon are uncommonly used, especially since the introduction of propranolol.

8.1 Treatments Used: Systemic Pharmacotherapy

8.1.1 Propranolol

Propranolol hydrochloride, a nonselective beta-adrenergic blocking agent, is rapidly becoming the standard of care for complicated IH due to its reputation of superior efficacy and lower side effect profile compared to alternative systemic agents. Potential mechanisms of action include vasoconstriction, inhibition of angiogenesis, and/or stimulation of apoptosis. Recent data supports effects on growth via inhibited expression of eNOS protein and subsequent production of nitric oxide [4] and/or inhibition of vascular endothelial growth factor A (VEGF-A) through the hypoxia-inducible factor (HIF)-1a angiogenesis axis [5]. The efficacy of propranolol was serendipitously discovered when two infants with IH on propranolol for heart failure were noted to have a change in color, softening, and decreased size of their tumors. This observation was then replicated in an open trial of propranolol in nine children with disfiguring IH, results of which were published in the *New England Journal of Medicine* in 2008 [6]. Numerous case reports and larger observational studies have since been written,

the vast majority of which demonstrate marked improvement with propranolol. However, most of these studies are not prospective, randomized, or controlled.

While propranolol has been used in children for nearly 40 years for both cardiac and noncardiac disease, pediatric experience has been largely anecdotal and there are currently no FDA-approved indications for propranolol in pediatric patients in the USA. Propranolol contraindications, side effects, and current guidelines regarding pretreatment evaluation and dosing are listed in Table 8.2. The most common effects of propranolol include hypotension and bradycardia, effects of which peak 1–3 hours after an oral dose in children [7]. Other serious side effects include

Table 8.2 Overview of propranolol guidelines

Contraindications to propranolol	Cardiogenic shock Sinus bradycardia: Newborns (< 1 month old): <70 beats per minute Infants (1–12 months old): <80 beats per minute Children (over 12 months old): <70 beats per minute Greater than first-degree heart block Bronchial asthma Known hypersensitivity to propranolol hydrochloride
Side effects	Hypotension Bradycardia Hypoglycemia Bronchospasm Sleep disturbance (crying episodes, nightmares, insomnia, restlessness) Congestive heart failure Gastrointestinal complications (nausea, vomiting, abdominal cramping, reflux, constipation) Cool or mottled extremities Hyperkalemia Rash/dry skin Depression Dental caries Drug interactions
Pretreatment evaluation	History and physical examination including cardiac auscultation Heart rate Blood pressure EKG +/− cardiology consultation when: Bradycardia Arrhythmia detected on cardiac auscultation Family history of arrhythmias or maternal history of connective tissue disease Large, facial IH at risk for PHACE syndrome should be evaluated with: MRI and MRA imaging of the head and neck Echocardiogram to include the aortic arch Ophthalmologic examination Consider hospital admission to initiate propranolol for: Newborns <6–8 weeks of age Extreme prematurity Significant comorbidity PHACE syndrome Airway IH Suboptimal social situations

(continued)

Table 8.2 (continued)

Dosing	20 mg/5 mL preparation is preferred Initiate dose at 0.5–1.0 mg/kg/day Gradually taper upward over days to weeks to peak dose of 2.0 mg/kg/day Three times daily dosing is preferred over twice daily when feasible Effective dose often at 2.0–3.0 mg/kg/day, though sometimes lower doses adequate To minimize risk of hypoglycemia: Administer during daytime hours with a feeding shortly after dose Children should be fed regularly; prolonged fasts should be avoided Discontinue propranolol during intercurrent illness, especially in setting of restricted oral intake Children requiring fasting for sedation due to procedures or imaging should be supported with oral rehydration solutions (such as Pedialyte®) or glucose-containing IV fluids

hypoglycemia and bronchospasm. The latter is relevant particularly for patients with reactive airway disease, in whom propranolol should be considered cautiously, or during an acute respiratory illness, when bronchial hyperreactivity may require temporary discontinuation of the drug [8]. Other adverse effects include congestive heart failure, gastrointestinal complications (nausea, vomiting, abdominal cramping, reflux, constipation), sleep disturbance (crying episodes, nightmares, insomnia, restlessness), cool or mottled extremities, hyperkalemia [9], rash or dry skin, and depression in older patients. Dental caries have been reported in two IH patients treated with propranolol, which may be related to the sucrose-containing formula suspension or decreased salivation due to beta-adrenergic blockage of salivary gland function [10, 11]. Lastly, propranolol's metabolism involves multiple pathways within the cytochrome P-450 system, rendering clinically important drug interactions an important issue [8, 12, 13].

Although reports of serious side effects among children treated with propranolol for IH have been rare to date, it appears that hypoglycemia may be the most serious potential complication. Hypoglycemia is usually related to decreased oral intake or an overnight fast, such as might occur with an intercurrent illness or prior to general anesthesia, and it is thus recommended that propranolol be discontinued in such circumstances until normal oral intake is resumed. Children and infants appear to be at higher risk for hypoglycemia due to an increased rate of glucose utilization in the fasting state, which is nearly tripled in infants, attributed partly to a greater ratio of brain mass to body weight [14, 15]. Most reported children who developed hypoglycemia were on relatively low doses of propranolol, which suggests that risk is not dose-dependent. While clinical manifestations of hypoglycemia in infants vary widely, mild early symptoms include sweating, tremors, tachycardia, anxiety, and hunger; however, such symptoms may be masked by propranolol-induced beta-adrenergic blockage. The exception to this is sweating, and thus, this may be the most reliable early symptom of hypoglycemia to observe for. More severe manifestations include lethargy, stupor, poor feeding, seizures, apnea, loss of consciousness, and hypothermia [14, 16].

In a randomized, controlled trial, 39 children aged 11 weeks to 4 years with IH complicated by potential functional or cosmetic concerns were randomly assigned to propranolol 2 mg/kg per day or placebo for 24 weeks [11]. Response to therapy was measured by blinded estimation of tumor volume at baseline and then every 4 weeks. In the propranolol-assigned group, IH involution started after 4 weeks and continued steadily until study completion. After 24 weeks, average tumor volume had decreased from baseline by 60 % in the propranolol group compared to 14 % in the placebo group. Side effects were reported commonly in the propranolol group (68 %) versus 25 % in the placebo group, and those that could be directly attributed to propranolol included sleep disturbance and

bronchiolitis. Small case series have also reported propranolol benefit for IH ulceration. In two studies, propranolol dosed at 2.0–2.5 mg/kg per day was associated with a shorter time to pain control and healing, with a mean time to healing of 4.3 and 8.7 weeks compared with 22.4 weeks in a group of historical controls treated with only supportive measures [17, 18]. In addition, oral propranolol has been used to treat IH beyond the proliferative phase, a timeframe in which corticosteroids are historically known to be minimally, if at all, efficacious. In a multicenter, retrospective study, 42 children ages 7 months to 10 years with documented completion of IH growth were treated with propranolol dosed at 1.5–3 mg/kg per day for 1–8 months. In all treated children, rates of involution increased with propranolol compared to those observed with nonintervention [19].

While no randomized trials have been published that compare propranolol to systemic glucocorticoids in the treatment of IH, results from a retrospective multicenter study suggest that propranolol may be both safer and more effective. In this trial [20], 68 children treated with propranolol dosed at 2 mg/kg per day for 3.5–14 months were compared to 42 children treated with oral prednisone dosed at 2–4 mg/kg per day for 2.5–8 months. Outcome measures included the percentage of IH improvement measured by clinical examination and serial photographs, documentation of adverse effects including ulceration, and whether surgical referral was needed after treatment. A ≥75 % improvement in IH size was achieved in 82 % of patients in the propranolol group and 29 % of the glucocorticoid groups. Side effects were reported in only 2 of 68 patients treated with propranolol, which included transient hypoglycemia and a nonspecific skin eruption. In comparison, all the patients treated with oral glucocorticoids developed adverse effects, including cushingoid features, hypertension, and gastroesophageal reflux. Ulceration during treatment occurred in 6 % versus 26 % of patients in the propranolol versus glucocorticoid groups. Patients were referred to surgery after treatment in 12 % of the propranolol group versus 29 % of the glucocorticoid group.

A multinational, randomized, double-blind, phase II/III propranolol study is currently being conducted, the results of which are likely to provide propranolol safety and efficacy data in the near future. Until then, there is much uncertainty and difference of opinion among specialists regarding monitoring of the drug, dose escalation, and use in PHACE (Posterior fossa brain malformations, Hemangioma, Arterial lesions, Cardiac abnormalities, and Eye abnormalities) syndrome (see below). Significant inconsistency in treatment protocols also exists between institutions. A multidisciplinary consensus conference was recently held in an effort to establish guidelines for the initiation and use of propranolol for IH [12]. Pertaining to baseline evaluation and monitoring, it was determined that bradycardia may be the most reliable measurement of toxicity, given the challenge of obtaining accurate blood pressures in infants and better-established normal data ranges for bradycardia [21]. An electrocardiogram was recommended as part of the baseline evaluation under the following circumstances: below normal heart rate, arrhythmia detected on cardiac auscultation, or a family history of arrhythmias or maternal history of connective tissue disease [12, 22, 23]. Echocardiography was determined unnecessary in the otherwise healthy infant without concern for PHACE syndrome. No evidence exists to support the routine screening of serum glucose, as the timing of hypoglycemic events reported in the literature has been varied and unpredictable.

Results from an unpublished survey of pediatric dermatologists who frequently prescribe propranolol for IH showed that the majority admits patients to the hospital for initiation only under special situations, which include young age less than 6–8 weeks, extreme prematurity, significant comorbidity, PHACE syndrome, airway IH, and/or suboptimal social situations. The majority prescribes the 20 mg/5 mL preparation of propranolol, given the small volumes needed for dosing and to minimize the potential risk of overdose. Most initiate propranolol at an average dose of 0.5 mg/kg/day, divided three times daily and slowly titrated up over days to weeks to an average peak dose of 2.0 mg/kg/day. Such

measures are undertaken to minimize side effects, particularly abrupt changes in blood pressure. The majority continues propranolol until completion of the IH growth phase, up to 1 year or longer, given the observed risk of rebound growth when propranolol is discontinued earlier [11].

8.1.2 Systemic Glucocorticoids

Prior to the introduction of propranolol, systemic glucocorticoids had been the "gold standard" of IH therapy since the 1960s. While their mechanism of action for IH remains incompletely understood, a direct inhibitory effect on the production of factors that promote vasculogenesis has been postulated. IH-derived stem cells are capable of inducing *de novo* blood vessel formation. These cells and one of their products, VEGF-A, have been identified in proliferating IH [24, 25]

In an investigative study of the effects of glucocorticoids on IH, dexamethasone suppressed VEGF-A production by IH-derived stem cells *in vitro* and inhibited vasculogenesis in a murine model of IH. In the absence of dexamethasone, preventing the production of VEGF-A by IH-derived stem cells also led to reduced vasculogenesis in the murine model. The combined results of this study suggest that glucocorticoid-mediated inhibition of VEGF-A production by stem cells in IH may be at least partly responsible for the efficacy of glucocorticoids in IH. The suppression of other pro-angiogenic factors may also play a role. In this same study, dexamethasone also suppressed urokinase plasminogen activator receptor, monocyte chemoattractant protein 1, interleukin-6, and matrix metalloproteinase in IH-derived stem cells [24].

The typical prednisolone (20 mg/5 mL) starting dose is 2–3 mg/kg per day, administered as a single morning dose in order to minimize adrenal suppression. IH response (either stabilization or regression) can usually be observed within the first few weeks of treatment. Therapy is generally continued for several months or longer, depending upon the indications for treatment, IH response, and child's age at initiation. Glucocorticosteroids should be slowly tapered since abrupt discontinuation or rapid tapering of medication while an IH is still in its active growth phase often results in rebound proliferation [26, 27]. Supraphysiologic doses of glucocorticoids suppress the hypothalamic-pituitary-adrenal axis; thus, "stress doses" of glucocorticoids may be required for infants undergoing steroid therapy for IH who require medical or surgical hospitalization [28].

When used during the growth phase, systemic glucocorticoids often halt IH growth and may stimulate regression. In a meta-analysis of 24 publications, which included case series of more than five patients who were treated for IH with systemic glucocorticoids, patients were administered a mean prednisone equivalent daily dose of 2.9 mg/kg for an average of 1.8 months [29]. The rate of response was 84 % (95 % CI 78–89 %). A 3 mg/kg daily dose of prednisolone was determined to be more effective than 2 mg/kg/day. In another small, randomized trial, the safety and efficacy of high-dose intravenous pulse glucocorticoids was compared to oral glucocorticoids for the treatment of complicated IH [30]. Infants treated orally had greater reduction in hemangioma size at 3 and 12 months than those who were treated with pulse therapy, suggesting that continuous use of oral glucocorticoids is preferred.

Glucocorticoid use for IH often results in minor, temporary side effects, while long-term consequences are more rare. Short-term effects are more likely with higher doses and courses of 6 months or longer. The most common adverse effect, usually observed within the first 1–2 months of treatment, is the development of a cushingoid facies. Personality changes (e.g., depressed mood, agitation, insomnia, restlessness) develop sooner, usually during the first 2 weeks of therapy and in about one-third of infants. Delayed skeletal growth, which is commonly noted within the first year of life, results from a temporary inhibition of collagen synthesis, but almost all recover by age 2 years. Gastrointestinal upset occurs in at least 20% of infants and can be relieved with histamine 2 (H2)

blockers such as ranitidine hydrochloride, which many practitioners initiate routinely along with glucocorticoids. Serious glucocorticoid complications, such as aseptic necrosis of the femoral head, hypertension, osteoporosis, and cataracts, are very rare in children [31, 32].

Glucocorticoids have immunosuppressive effects and can increase risk for infections. In an uncontrolled study of 16 infants who received systemic glucocorticoids for IH, significant reductions in both T and B lymphocyte counts were detected during treatment [33] Glucocorticoids also suppress the immune system by reducing neutrophil migration to sites of inflammation. At least two cases of Pneumocystis carinii pneumonia (PCP, but officially renamed Pneumocystis jirovecii pneumonia) developing in infants treated with glucocorticoids for IH have been reported [34, 35]. While the true risk of PCP and the utility of antibiotic prophylaxis in this population is not known, some advocate routine administration of trimethoprim-sulfamethoxazole [33], particularly in infants with airway involvement or other airway abnormalities [34]. PCP prophylaxis may especially be warranted in infants who have other risk factors for PCP, such as premature infants with significant comorbid medical conditions.

Regarding immunizations, vaccines containing live or live-attenuated virus (e.g., measles, mumps, rubella [MMR], varicella, rotavirus) should not be administered to infants on supraphysiologic doses of glucocorticoids. In addition, because the varicella vaccine is not administered until children are at least 1 year of age, infants receiving glucocorticoid therapy should also avoid exposure to persons with varicella infection. Lastly, it should be noted that immunizations for diphtheria and tetanus may not be as effective in some patients on systemic glucocorticoid therapy. When concern exists, diphtheria and tetanus titers can be used to confirm protection. In a study of 16 patients with IH who were immunized against tetanus and diphtheria while taking systemic glucocorticoids, 5 had protective tetanus titers and 13 had protective diphtheria titers 3 months after glucocorticoid therapy was completed [33]. Additional studies are necessary to determine whether routine testing of diphtheria and tetanus titers should be performed following systemic glucocorticoid therapy.

8.1.3 Alternative Medical Therapies

For severe IH that fail to respond sufficiently to propranolol or corticosteroids, vincristine is generally the preferred second-line agent. Vincristine is a vinca alkaloid chemotherapy agent widely used by oncologists to treat hematological and solid tumor malignancies. However, it has been most commonly used in combination with other systemic therapies, and its use in IH has not been extensively studied. Vincristine is generally administered intravenously by a central venous catheter at a dose of 1.0–1.5 mg/m^2 weekly for IH, and therapy is most commonly overseen by a pediatric hematologist-oncologist. Toxicities include immunosuppression, peripheral neuropathy, constipation, jaw pain, and rarely leukopenia and anemia [36–38].

Other alternative systemic medications that have been reported useful in severe IH include interferon alpha, which has good efficacy for IH, but because of the potential side effect of permanent spastic diplegia in infants, it is now rarely used. The initial subcutaneous dose of interferon alpha for IH is 3 million units/m^2 per day, and the interval between administration and response can be relatively long, ranging from a few weeks to several months. Other common side effects, usually transient, include fever, irritability, neutropenia, and liver enzyme abnormalities [26, 39–41]. Use of cyclophosphamide has been reported, particularly for life-threatening hepatic IH; however, the development of acute myelogenous leukemia following use for IH treatment has been described [42]. Lastly, thalidomide is an inhibitor of angiogenesis that has been rarely reported in the treatment of IH, but its use is also limited by significant side effects [43, 44]. The role of these alternative agents for IH therapy in the future remains uncertain, particularly given the introduction of propranolol.

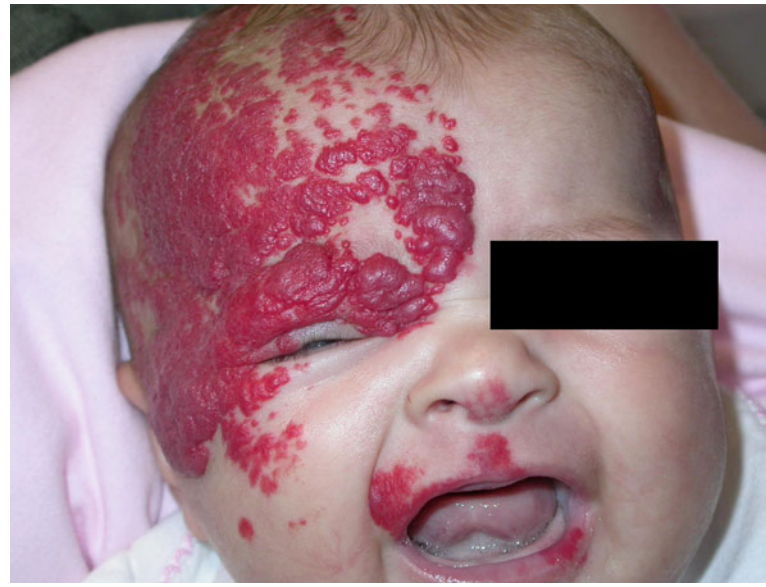

Fig. 8.1 Infant with large, segmental facial hemangioma and cerebrovascular anomalies in association with PHACE Syndrome

8.2 Particular Subtypes of Disease, Approaches, and Pitfalls

Particular subtypes of hemangioma complications that warrant consideration of systemic therapy are listed in Table 8.1. For the majority of these complications, propranolol may be considered first line, with the following possible exceptions:

8.2.1 PHACE Syndrome with Associated Vascular Anomalies

PHACE (OMIM 606519) is a cutaneous neurovascular syndrome characterized by large, segmental IH of the face in association with congenital anomalies of the brain, heart, eyes, and chest wall (Fig. 8.1) [45]. Infants with PHACE represent a unique treatment challenge in that most have extensive facial IH with both potential medical morbidities (e.g., periocular disease, airway disease, and/or risk of ulceration) and a high risk of facial scarring and disfigurement and are thus prime candidates for propranolol therapy. However, experts have advised particular caution when using propranolol in PHACE infants with cervical or cerebral arteriopathy, as systemic hypotension is a known risk factor for stroke [46] and carries the theoretical risk of reducing blood flow through narrowed or occluded arteries supplying the brain [47, 48]. Cerebrovascular anomalies are the predominant extracutaneous features of PHACE, and it is known that a small proportion of PHACE patients with anomalies of major cervical and cerebral vessels develop arterial stenoses and occlusions that may lead to acute arterial ischemic stroke (AIS). While the mechanism of AIS in PHACE remains unknown, it is likely complex and related to several factors that include severity of arterial stenosis, presence or absence of an intact circle of Willis, degree to which collateral circulation is developed, and coexisting cardiac and aortic arch anomalies that could lead to cardioembolic events [49]. The potential for hypoperfusion in PHACE is underscored by recent reports of transient ischemic attacks in two adult PHACE patients with severe cerebrovascular anomalies [50, 51].

In a retrospective study of propranolol use in 32 infants with definite PHACE syndrome and cervical and intracranial arterial anomalies, 7 of 32 (22 %) patients were categorized as higher risk for stroke, defined on magnetic resonance angiography (MRA) as severe, long-segment

Table 8.3 Comparison of head and neck MRA imaging features to stroke risk in PHACE syndrome

Risk category	Cerebrovascular anomalies
Higher[a]	Severe narrowing/stenosis[b] or nonvisualization of major vessels[c] without adequate anatomic evidence of collateral circulation[d]
Standard	Severe narrowing/stenosis[b] of major vessels[c] *with* adequate anatomic evidence of collateral circulation
	Mild narrowing/stenosis[e] of major vessels[c]
	Hypoplasia, dysplasia, aberrant origin or course of major vessels[c, f]
	Aberrant subclavian artery
	Persistent embryonic arteries

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[a]Risk further increased if coexistent cardiac or aortic arch anomalies

[b]Defined as vessel narrowing >75 %

[c]Internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, basilar artery, and vertebral artery

[d]There are limitations to the ability of MRA to detect collateral vasculature because the imaging is done without a hemodynamic challenge; e.g., some collaterals may only be dynamically recruited when a stressor to perfusion, such as hypotension, is introduced. For questionable cases, follow-up perfusion studies can prove beneficial

[e]Defined as vessel narrowing <75 %, and categorized as standard risk given known tendency to overestimate stenosis on time of flight MRA

[f]Any degree of severity

narrowing, or nonvisualization of major cerebral or cervical vessels without anatomic evidence for collateral circulation, often in the presence of concomitant cardiovascular comorbidities ([51] and Table 8.3). While no patients developed serious neurologic consequences related to propranolol, the authors concluded the following:

1. Infants with large, facial IH should be thoroughly investigated for potential vasculopathy associated with PHACE syndrome, with MRA of the head and neck and cardiac imaging to include the aortic arch, prior to considering propranolol therapy.
2. Physicians should be aware of the imaging features that may portend a higher risk for developing arterial ischemic stroke while at the same time acknowledging that the presence of "standard" imaging features does not eliminate risk of hypoperfusion injury. In cases in which MRA features demonstrate severely compromised vessels, but the presence of collateral, compensatory flow is questionable, follow-up perfusion studies may prove helpful in assessing risk.
3. Physicians should utilize the most conservative approach to control the target signs and symptoms of the IH being treated. Consultation with neurology and/or cardiology should be considered, as appropriate. In order to minimize abrupt changes of blood pressure, use of the lowest possible propranolol dosage, slow upward dosage titration, and three times daily dosing should be utilized. It should be noted that while propranolol is not contraindicated in the majority of PHACE infants, for some high-risk cases, the risk to benefit ratio might justify use of systemic corticosteroids over propranolol.

8.2.2 Symptomatic Hepatic IH

Similar to cutaneous IH, hepatic IH is the most common benign tumor of the liver in infancy. Most remain clinically silent and thus treatment is not generally required [52]. However, a small minority can be serious and even life threatening. An understanding of the categories of infantile hepatic vascular tumors, which have been classified into three patterns, focal, multifocal, and diffuse, is critical for risk stratification and management. Focal hepatic "hemangiomas," which tend to be large, solitary, GLUT-1 negative tumors, have now been determined the hepatic equivalent of "congenital hemangiomas" of the skin. The majority thus involutes relatively quickly without treatment, akin to RICH (rapidly involuting congenital hemangioma), although a minority may persist, similar to its non-involuting congenital hemangioma (NICH) counterpart. In contrast, multifocal and diffuse hepatic hemangiomas represent true IH, with the diffuse variant representing the severe end of the spectrum, with near-total replacement of the liver parenchyma [53, 54]. Notably, associated cutaneous IH in such cases may be clinically unusual, having

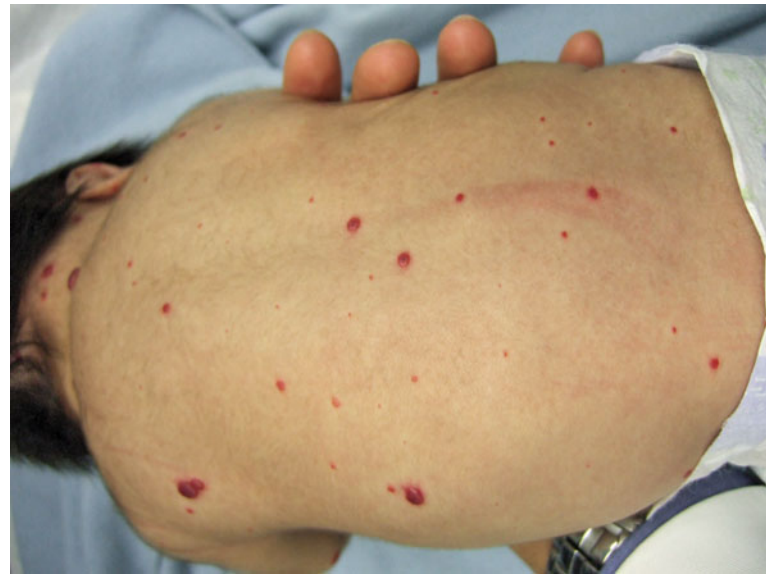

Fig. 8.2 Infant with multifocal cutaneous hemangiomas at-risk for hepatic involvement

been described as firm, thick, dome-shaped and red violaceous in color (Fig. 8.2). Complications of both multifocal and diffuse liver IH include acquired hypothyroidism due to hemangioma expression of type III thyronine deiodinase [55] and macrovascular high-flow shunting, which can lead to low- or high-output cardiac failure. An additional complication of diffuse hepatic IH, the most feared subtype, includes compression of the inferior vena cava, renal veins, and thoracic cavity, leading to abdominal compartment syndrome, respiratory distress, and multiorgan failure. Early and aggressive medical management with propranolol and/or corticosteroids, with vincristine as second line, is generally needed for symptomatic multifocal and diffuse hepatic IH in order to accelerate tumor involution and treat hypothyroidism. Consultation with endocrinology in cases of hypothyroidism is also advisable, as is consultation with a liver transplant service for diffuse cases, in the event medical therapies prove ineffective or for emergent cases in which there is no time to await a response to medical treatment. Notably, it has been suggested that even asymptomatic multifocal hepatic IH be followed with serial ultrasound during infancy, given the rare potential of progression to the diffuse subtype [54, 56].

8.2.3 Symptomatic Airway IH

While there are many successful reports of propranolol use for symptomatic airway IH (Fig. 8.3), several failures have also been described [57–59], in which case oral corticosteroids +/– vincristine can be options. Comanagement with otolaryngology is essential in such cases, as intralesional corticosteroids, laser, or tracheotomy may also warrant consideration.

It should also be noted that some experienced practitioners use both low-dose systemic propranolol and corticosteroids for severe hemangioma cases, with the rationale of combining mechanisms of action and minimizing side effects from either. While there is no evidence yet to support a synergistic effect, this may be a reasonable approach for select cases such as those listed above [56]. Importantly, local pharmacotherapy, including topical therapy with corticosteroids, imiquimod, and beta-blockers, and the pulsed-dye laser, are used primarily in the treatment of small, superficial hemangiomas in the absence of serious complications and are generally not appropriate as primary therapy for severely complicated hemangiomas. Intralesional corticosteroids, originally used by

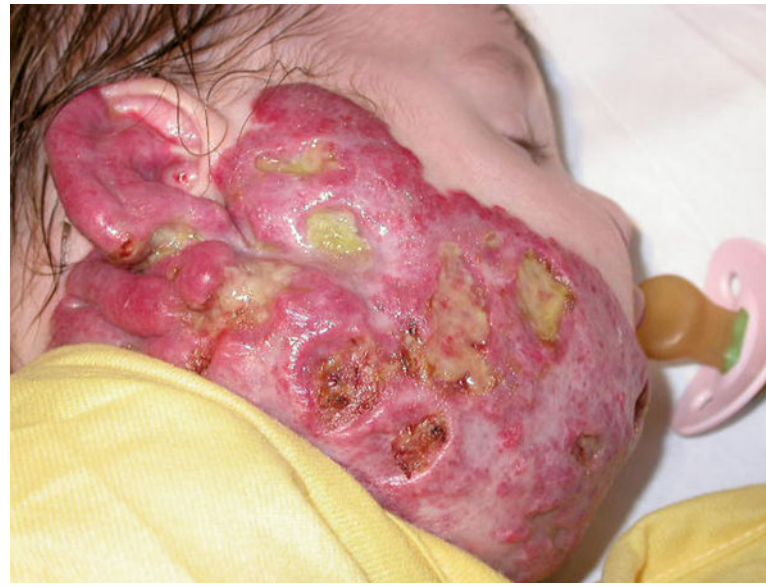

Fig. 8.3 Infant with large, segmental facial hemangioma complicated by ulceration and at-risk for PHACE Syndrome and concomitant airway hemangioma

ophthalmologists for vision-threatening periorbital hemangiomas, are now less commonly used for this indication due to risks of retinal artery damage and blindness [60]. However, this modality can be beneficial for reducing hemangioma bulk in other locations such as the lip and nasal tip at risk for permanent disfigurement. Typically triamcinolone 10 mg/ml is used, with less than 1–2 mg/kg per injection. Serial treatments may be required [61].

Conclusion

While infantile hemangiomas are characterized by benign histopathology and clinical improvement over time, a small but significant subset can be complicated by ulceration, organ compromise, associated congenital anomalies, and/or permanent disfigurement. Systemic medications are the mainstay of therapy for most problematic tumors, with propranolol hydrochloride having become the standard of care due to its reputation of superior efficacy and low side effect profile. Nevertheless, it should be used with appropriate caution and after assessment for potential contraindications. Hemangioma management remains highly individualized and dependent on a number of case-by-case variables.

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Complex Vascular Malformations

9

Diana Camarillo, Christopher P. Hess, and Ilona J. Frieden

Key Points

- Vascular malformations have particular clinical features, associated complications, and treatment options dependent on the type of vessel(s) involved.
- A multidisciplinary approach to children with extensive or complex vascular malformations provides the best approach to management, as complications may span the expertise of many different specialties.
- Imaging, particularly magnetic resonance imaging (MRI), is helpful and sometimes necessary to confirm diagnosis and evaluate extent of vascular malformations.
- Need for and type of intervention is dependent on factors that include extent and depth of lesion, compression of vital structures, pain, functional impact, and hematologic abnormalities.

Abbreviations

AVM	Arteriovenous malformation
CM	Capillary malformation
LIC	Localized intravascular coagulopathy
LM	Lymphatic malformations
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography
Nd:YAG	Neodymium YAG
PE	Pulmonary embolism
PWS	Port-wine stain
VM	Venous malformation

Vascular malformations are classified by the type of vessel involved (capillary, vein, lymphatic channel, or artery) and the flow characteristics [1]. Slow-flow malformations are comprised of the capillary, venous, and lymphatic vessels, whereas fast-flow malformations demonstrate an arterial component (Fig. 9.1). It is important to differentiate vascular malformations from vascular tumors, such as hemangiomas, which unlike malformations, exhibit endothelial hyperplasia and active proliferation.

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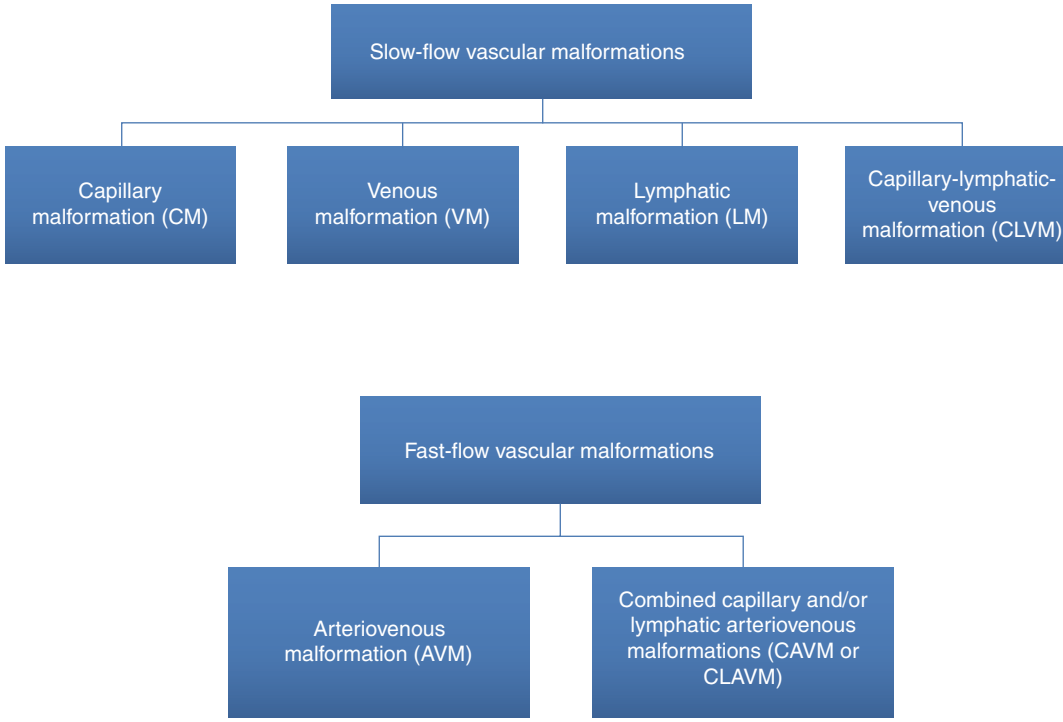

Fig. 9.1 Categorization of vascular malformations

Vascular malformations are believed to be the result of errors in vascular development; however, the exact pathogenesis remains unclear. Although the vast majority of cases are sporadic, familial vascular malformations with known genetic mutations exist, which have provided insight into potential molecular bases of disease.

Extensive vascular malformations may be complicated by invasion into the underlying muscle or bone, compression of vital structures such as the airway, hematologic abnormalities, and functional compromise depending on the size and location. Entire books can be dedicated to the subject of vascular malformations; in this chapter, we will focus on those malformations that represent particular management dilemmas with increased risk of morbidities. Imaging and hematologic evaluation will be discussed in some detail as these are crucial to the accurate diagnosis and management of patients with complex vascular malformations.

9.1 Special Considerations in Evaluation and Management of Patients with Vascular Malformations

9.1.1 Multidisciplinary Approach

A multidisciplinary approach to children with extensive or complex vascular malformations provides the best approach to management. Many large academic centers now have vascular anomaly clinics where specialists including dermatologists, radiologists, interventional radiologists, general and plastic surgeons, otolaryngologists, orthopedic surgeons, hematologists, and other specialists meet to evaluate and help manage difficult or uncertain cases. Vascular anomaly nomenclature in the literature can be confusing, and patients are often misdiagnosed [2]. Because complications of vascular malformations span the expertise of many different specialties, suboptimal management can easily occur in the hands of any one provider. A team of

specialists familiar with the diagnosis and treatment of these rare vascular anomalies can play a vital role in establishing a correct diagnosis and offering a comprehensive approach to care of patients with complex vascular malformations. Patients benefit greatly from having various subspecialty physicians convene to perform a thorough physical exam, review imaging, and discuss treatment options in a group setting. They also benefit because over time, physicians involved in multidisciplinary clinics increase their knowledge and expertise in managing vascular anomalies.

9.1.2 Imaging

Although the diagnosis of a vascular malformation is usually possible on the basis of history and physical exam by a trained clinician, imaging is helpful and sometimes necessary to confirm diagnosis, evaluate for complications, and to assess the true extent of disease in patients with large lesions. It is imperative for dermatologists, who are often the first specialty providers to evaluate such patients, to understand the utility of the various imaging studies in order to select appropriate studies and interpret findings. Table 9.1 briefly summarizes some of the most important advantages and disadvantages that are inherent to various imaging modalities. For most patients with vascular malformations, magnetic resonance imaging (MRI) with contrast is the imaging study of choice. Magnetic resonance angiography (MRA) or venography (MRV) is generally unhelpful without conventional MR imaging sequences; the usual MRI sequences are far more important for diagnosis of lesion type and to define the anatomic structures involved. MRA

Table 9.1 Imaging modality characteristics, advantages, and disadvantages

Modality	Advantages and disadvantages	Characteristic imaging features		
		Venous malformation	Lymphatic malformation	Arteriovenous malformation
Ultrasound	Lower cost	Phlebectatic or spongiform hypoechoic mass, comprised of compressible vascular structures	Cystic and compressible hypoechoic mass	Serpiginous vascular structures, may or may not be compressible
	Real-time imaging capability, allows targeted imaging based on palpation and cutaneous lesion	Phleboliths, if seen, exhibit acoustic shadowing	May contain internal echoes, layering intracystic debris related to intralesional hemorrhage or infection	No phleboliths
	No sedation or anesthesia requirement	Demonstrates venous flow on Doppler imaging	No phleboliths	Demonstrates arterial flow on Doppler imaging
	Excellent for detection of venous thrombosis within known vascular abnormalities		No flow on Doppler imaging	
	Requires significant expertise for optimal diagnosis			
	Incomplete lesion visualization due to inability to visualize areas around vascular lesions due to poor acoustic window			

(continued)

Table 9.1 (continued)

Modality	Advantages and disadvantages	Characteristic imaging features		
		Venous malformation	Lymphatic malformation	Arteriovenous malformation
Computed tomography (CT)	Intermediate cost	Serpiginous low-density vascular structures enhance with contrast	Fluid density lesion with only thin peripheral or septal enhancement	Serpiginous low-density vascular structures enhance with contrast
	Fastest examination – no requirement for sedation	Exhibit local mass effect	Fluid levels inconsistently present with intralesional hemorrhage or infection	Minimal local mass effect
	Ionizing radiation	Excellent for detection of phleboliths	No phleboliths	No phleboliths
	Depicts entire lesion but low soft-tissue contrast leads to lower accuracy	Excellent visualization of bony involvement		Vascular calcifications rarely seen in long-standing lesions
Magnetic resonance imaging (MRI)	High cost	Spongiform or phlebectatic vascular mass with low-flow properties	Fluid-filled lesion comprised of large (macrocystic) or small (microcystic) internal cysts with high T2 signal	Serpiginous vascular lesion with multiple flow voids
	May require sedation or anesthesia	Often significant mass effect	Often significant mass effect	Little or no mass effect
	Depicts entire lesion and effects on surrounding structures	Uniform enhancement with contrast	Thin peripheral mural or septal enhancement	No enhancement with contrast
	High soft-tissue contrast	Enlarged draining veins often present	No enlarged draining veins	Variable enlarged feeding arteries and draining veins
	Highest diagnostic accuracy and most effective for treatment planning	Phleboliths, when present, seen as signal voids	No phleboliths	No phleboliths Lesion angioarchitecture visualized using MR angiography
Catheter angiography or percutaneous puncture under fluoroscopy	Highest cost	Venous vascular structures enhance in the venous angiographic phase	Visualized with direct intralesional injection of radiographic contrast	Vascular structures enhance in the arterial phase
	Usually requires sedation or anesthesia	Enlarged draining veins	Communicating cysts fill with injectate	Enlarged feeding arteries and draining veins
	Invasive Allows endovascular or intralesional treatment	No arteriovenous shunting		Arteriovenous shunting present

and MRV show the vessels well, but do a poorer job of delineating the relationship of these vessels with respect to local anatomy. Additionally, MRA is only adequate for high-flow lesions, so unless a diagnosis of arteriovenous malformation (AVM) is certain, it cannot help in the diagnosis of venous (VM), lymphatic (LM), or mixed malformations. MRA and MRV are useful mainly for specific clinical scenarios. One example is the use of MRV to look for large aberrant venous vasculature to help define risk of pulmonary emboli in Klippel-Trenaunay syndrome (see below). Another is to determine the architecture of feeding arteries in AVMs for planning of therapeutic interventions.

9.1.3 Hematologic Considerations: Diagnosis and Management

Localized intravascular coagulopathy (LIC) may complicate low-flow vascular malformations, particularly extensive venous and combined venous and lymphatic malformations. LIC is thought to result from pooling and stasis within the malformed vessels leading to local consumption of coagulation factors. Baseline hematologic evaluation including complete blood cell count (CBC), prothrombin time (PT), partial prothrombin time (PTT), D-dimer, and fibrinogen should be performed in patients with large or multifocal slow-flow vascular malformations. Thrombocytopenia is rare in vascular malformations. When present, it is typically mild in comparison to the Kasabach-Merritt phenomenon, which occurs in infants with vascular tumors (kaposiform hemangioendothelioma or tufted angioma, see Chap. 10). Patients with markedly elevated D-dimers (five to ten times normal) or low fibrinogen should be seen by a hematologist to help in managing their coagulopathy.

Ongoing clotting is not desirable, and strategies are needed to try to minimize it. It can lead to the ongoing formation of thrombi, causing painful lumps or swelling. Thrombi can subsequently calcify and form phleboliths which can also cause pain. Local trauma can also precipitate LIC by damage to endothelial cells which, in response, promotes coagulation. When superficial, phleboliths can be palpated as hard subcutaneous papules or nodules within the malformation. We hypothesize that chronic LIC with thrombosis and phlebolith formation may contribute to the expansion over time of vascular malformations with a venous component due to compensatory angiogenesis and progressive vascular dilatation.

Elevated D-dimers can result if significant LIC is present, reflecting a chronic low-grade consumptive process. If LIC is severe, fibrinogen can be decreased in addition to elevated D-dimers. One study found that large and/or deep venous malformations and palpable phleboliths were strong predictors for elevated D-dimers [3]. Such patients are particularly at risk for procedural bleeding, bruising, and chronic pain. LIC may evolve to a more severe coagulopathy with systemic effects, particularly in patients undergoing resection, sclerotherapy, embolization, or prolonged immobilization. It is thus important to recheck the aforementioned labs prior to performing invasive procedures, as well as during pregnancy.

Unfortunately studies to guide anticoagulation in the setting of vascular malformations are generally lacking. In patients with evidence of LIC either by laboratory findings (elevated D-dimers) or clinically (presence of phleboliths), treatment with low-dose aspirin (5–10 mg/kg) should definitely be considered. This is a relatively low-risk intervention and may benefit patients – in some cases substantially by decreasing pain and phlebolith formation. A common concern with aspirin therapy is the potential risk of children developing Reye syndrome. Because much higher antipyretic doses of aspirin are typically implicated in Reye syndrome (five to ten times the dosage used for vascular malformations), and there have been no reports with low-dose aspirin, the risk of use in young children is extremely small. A consensus statement from the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young has endorsed the safety of low-dose aspirin in young children with stroke or risk of stroke. They recommended annual influenza immunization, verification of varicella vaccination, and discontinuation of aspirin during suspected varicella or influenza infection [4]. Some experts recommend temporarily discontinuing aspirin in the setting of viral illness as a precautionary measure, but this must be weighed against the tendency for clotting to occur with increased frequency in the setting of viral illnesses and dehydration.

For patients with large VMs found to have low fibrinogen indicative of more severe LIC, we recommend involving hematology consultants regarding the use of more aggressive anticoagulation such as low-molecular-weight heparin (LMWH) or warfarin. LMWH can be effective in preventing the progression from LIC to disseminated intravascular coagulopathy (DIC) and in improving pain [3]. Some experts also advocate for short-term treatment with LMWH perioperatively in high-risk patients, but again, evidence is lacking to support this [5].

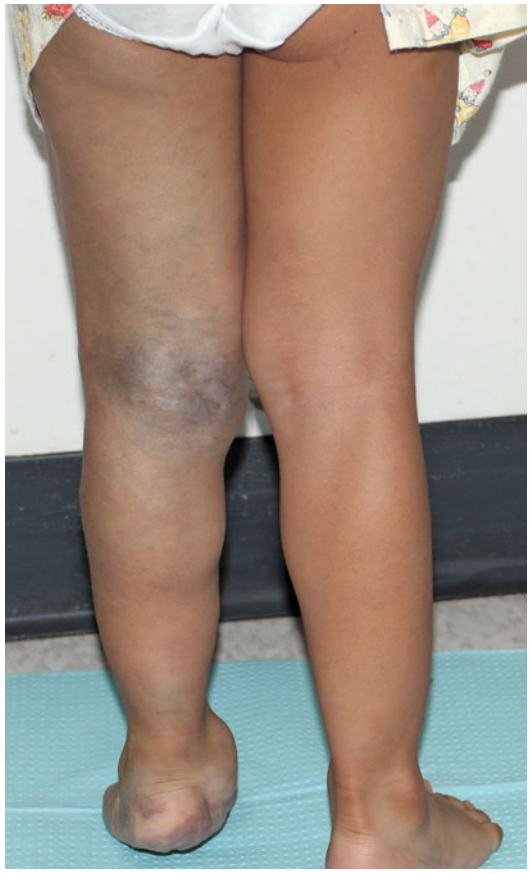

Fig. 9.2 Extensive venous malformation of the leg

9.2 Specific Clinical Settings

9.2.1 Venous Malformation

9.2.1.1 Clinical Presentation

Venous malformations (VMs) are slow-flow lesions composed of a collection of abnormally formed and dilated veins. VMs are the most common vascular malformation presenting to vascular anomaly clinics. Although they are congenital structural anomalies, some may not present until later in life. Typically they present as subcutaneous blue masses which are soft and compressible upon palpation. Over time, they may become more prominent and increase in anatomic extent (Fig. 9.2). Swelling of VMs is particularly common when the affected area is placed in a dependent position.

While small, more localized VMs are often amenable to surgery or long-wavelength lasers such as long-pulsed neodymium YAG (Nd:YAG), larger VMs can cause severe morbidity and require more complex interventions. VMs, especially those of the lower extremities, have the potential to extend into the muscle, joints, or bone, causing significant pain and even joint destruction if recurrent hemarthrosis occurs. Those involving the muscle tend to have more severe pain and increased risk of developing coagulopathy [6]. Decreased bone density and fractures may occur. Head and neck VMs can also be particular problematic, especially those that involve the oral mucosa which may affect dentition or speech or those that encroach on the airway with potential to cause obstructive sleep apnea or even respiratory compromise. Facial VMs are often disfiguring as well. VMs affecting the gastrointestinal mucosa may cause gastrointestinal bleeding.

Unlike lymphatic malformations, infection is rare in the setting of pure venous malformations. However, it is important to note that thrombosis can mimic infection with symptoms of pain and signs of erythema and swelling. Phlebolith formation can be evident both clinically and radiographically and can cause persistent pain. In addition to phleboliths, patients with large VMs may develop deep venous thrombosis (DVT) and in rare instances, acute pulmonary embolism (PE) [7]. Chronic thrombi formation can also result in chronic thromboembolic pulmonary arterial hypertension in patients with large VMs. Levels of D-dimers were found to correlate with pulmonary artery systolic pressure in one study [8], and some authors have recommended routine echocardiograms in patients with large VMs to look for pulmonary hypertension. While this one study is concerning, it is not known whether such screening should be performed in all patients with large VMs, and if so, at what intervals. Certainly, screening for symptoms of exercise intolerance, shortness of breath, and chest pain should be performed in all patients with extensive disease; symptomatic patients should be referred to cardiology.

9.2.1.2 Pathogenesis

The exact pathogenesis of venous malformations remains to be elucidated. Familial forms with autosomal dominant inheritance have been

described. Mutations involving the *Tie2* gene which encodes an endothelial receptor have been described in three families [9, 10]. It is believed that VMs in these familial cases develop from constitutive activation of the Tie2 pathway which is involved in vascular development, causing defective smooth muscle assembly around the veins.

9.2.1.3 Diagnosis

The diagnosis of VM is typically suspected clinically, but MRI is the modality of choice to confirm the diagnosis and define extent of involvement and tissues involved. Intravenous gadolinium chelate should be administered to assess for the presence of enhancement, an important feature in distinguishing between VM and LM. Diagnosis may be possible with CT, although this modality should be avoided due to its higher radiation dose and low soft tissue contrast, which limit its ability to assess the precise boundaries of a venous malformation. Frequently, VMs that appear to be superficial clinically reveal extensive subcutaneous, muscular, osseous, or even visceral involvement on imaging (Fig. 9.3). Doppler ultrasound is attractive because of its lower cost, but has high inter-operator variability and low soft tissue contrast, and permits full lesion characterization only for small subcutaneous lesions. All patients diagnosed with VMs, with the exception of those that are small and localized, should undergo hematologic evaluation that includes CBC, PT, PTT, D-dimer, and fibrinogen levels to evaluate for the presence of LIC, assess the risk of bleeding, and determine whether the patient might benefit from anticoagulation (see Sect. 9.1.3).

9.2.1.4 Management

Treatment options depend on the location and size of the VM and symptoms experienced by the patient. Not all VMs require treatment. The mainstays of treatment include percutaneous sclerotherapy, surgical resection, or a combination of the two. Surgical excision is particularly effective in smaller well-circumscribed lesions. Sclerotherapy involves the direct intralesional injection of sclerosing agents such as sodium tetradecyl or ethanol by interventional radiologists under the visual guidance of ultrasound and/or fluoroscopy. Sclerotherapy is particularly effective in lesions with relatively well-defined collection of veins; VMs with multiple individual veins permeating throughout an affected area are frequently poor sclerotherapy candidates [11]. VMs may recanalize and recur after sclerotherapy. Large VMs often require multimodal therapy with initial sclerotherapy to decrease the size of the VM followed by resection. VMs involving the airway can cause respiratory compromise and require aggressive multimodal management, usually involving a combination of sclerotherapy, laser, and surgical resection [12].

9.2.1.5 Supportive Care

In theory all patients would benefit from compressive therapy. However, compression therapy is impractical in sites such as the head and neck. Extremity VMs are most suitable to compression, though many limitations to achieving compliance exist, including high cost and variable insurance coverage. In addition, young children often do not tolerate compressive garments and may quickly outgrow them. Some patients dislike compression therapy because it worsens pain, is too hot to tolerate, or they dislike the appearance. Despite these limitations, in the highly motivated patient or in those with extensive or symptomatic disease, compression therapy can significantly improve discomfort and may even prevent phlebolith formation.

9.2.2 Lymphatic Malformation

9.2.2.1 Clinical Presentation

Lymphatic malformations (LMs) are slow-flow vascular malformations composed of anomalous lymphatic channels. They are subdivided into macrocystic, microcystic, or combined lesions. Macrocystic LMs of the neck are commonly referred to as cystic hygromas. Lymphangioma circumscriptum is a term used to describe microcystic LMs with superficial blebs, but is a poor descriptor of such lesions as they are often poorly circumscribed and may even extend into the subcutis.

Signs and symptoms of LMs depend on location and extent of involvement. Pure macrocystic LMs often present as large subcutaneous masses,

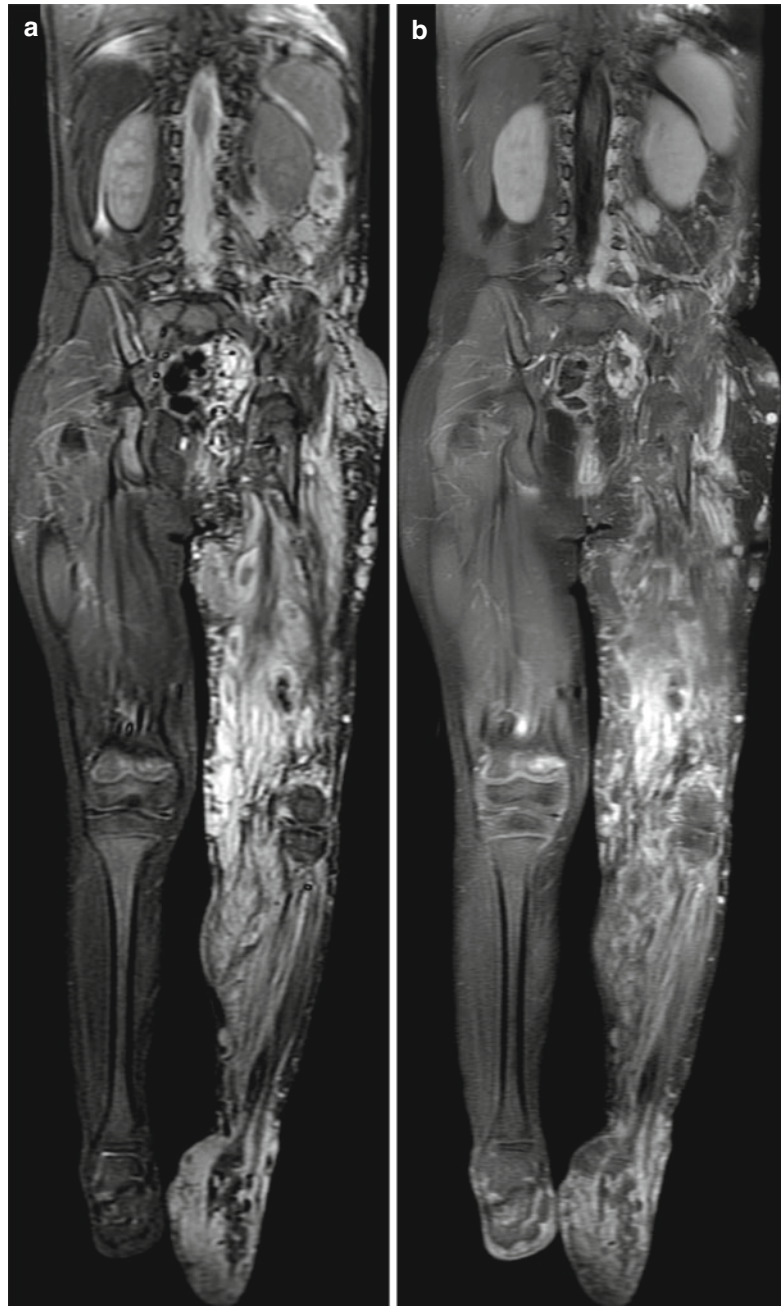

Fig. 9.3 Corresponding MRI of extensive venous malformation of the leg (see Fig. 9.2). (**a**) Fat-suppressed coronal T2-weighted and (**b**) gadolinium-enhanced T1-weighted MR images including the abdomen, pelvis, and lower extremities in a patient with an extensive unilateral (*left*) venous malformation involving the muscles, the peritoneal cavity, and the paraspinal region. The images have an overall similar appearance, but show different imaging features. Slow venous flow, like the contents of lymphatic malformations, appears bright on the T2-weighted image in (**a**), which shows CSF around the spinal cord as bright. Unlike LMs, VMs concentrate gadolinium and thus enhance, as shown in the T1-weighted image in (**b**), which in contrast to (**a**) shows CSF around the spinal cord as dark

whereas microcystic disease may cause mass effect but also more diffuse infiltrative swelling. LMs of the head and neck can cause significant disfigurement, problems with speech, feeding, and dentition, and even obstruct the airway (Figs. 9.4 and 9.5). Swelling of head and neck LMs may occur in the setting of upper respiratory infections. Orbital LMs can present with proptosis and cause visual impairment [13]. Significant bony overgrowth may also occur with macrocystic LMs of the head and neck. Mandibular hypertrophy can be seen in the setting of LMs of the upper neck or inferior mouth. LMs of the extremity may present with diffuse or localized

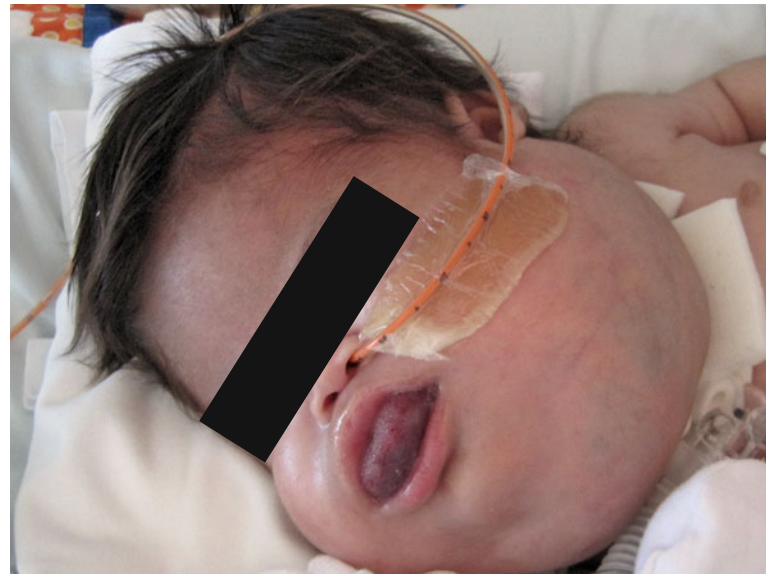

Fig. 9.4 Large macrocystic lymphatic malformation causing airway obstruction

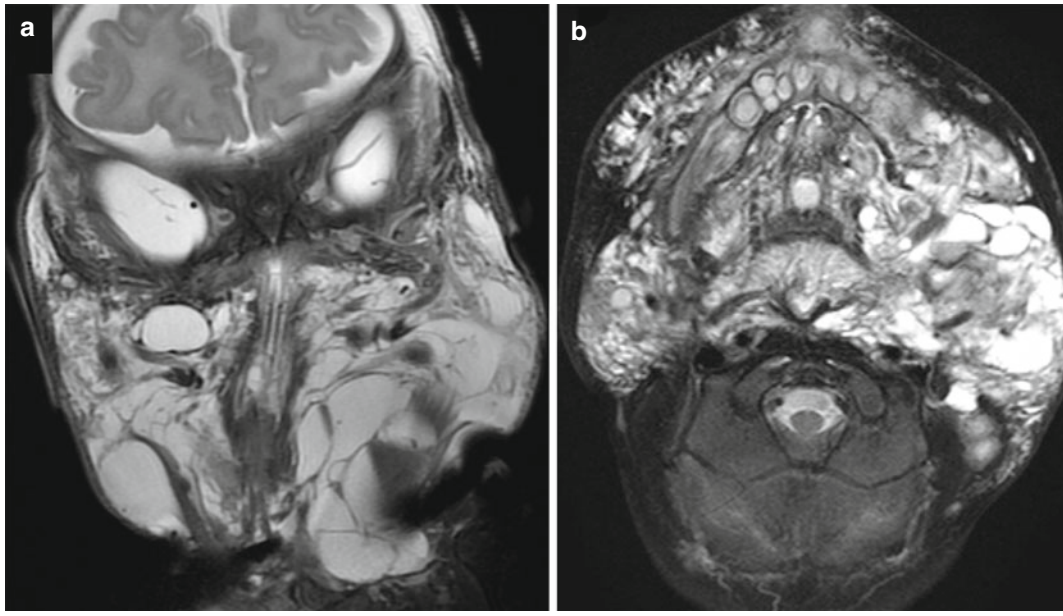

Fig. 9.5 Corresponding MRI of cervicofacial macrocystic lymphatic malformation (see Fig. 9.4). Coronal (**a**) and axial (**b**) T2-weighted sequences of the face in a patient with a large lymphatic malformation of the facial soft tissues. Acquired using fat-suppression techniques, areas with the highest signal intensity correspond to the presence of fluid, making the cystic components of the LM stand out against the normal muscles and fat of the face. Note that the malformation has nearly the same signal as CSF surrounding the brain in (**a**) and the spinal cord in (**b**). By definition, the presence of discrete cystic components within the lesion establishes its diagnosis of a macrocystic LM. Intracystic fluid in lymphatic malformations does not enhance

swelling and induration (Fig. 9.6). Unlike VMs, bacterial superinfection of LMs is relatively common and in rare cases, can even be life-threatening. In addition to classic signs of infection, sudden swelling of LMs can be an important clue to the presence of infection.

Microcystic LMs can occur at any site, but pure microcystic LMs are somewhat more commonly

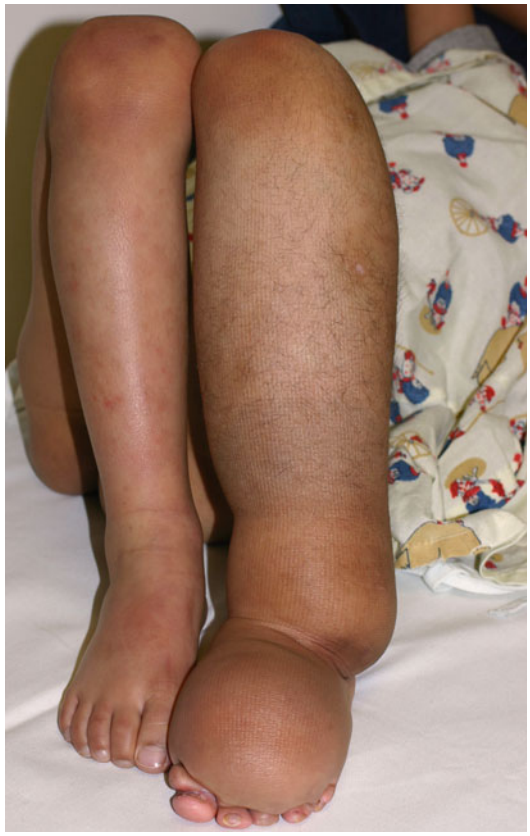

Fig. 9.6 Lymphatic-venous malformation of the leg with prominent lymphedema

found on the extremities and trunk. Those with superficial skin involvement may present with clustered vesicles, often with an admixture of some with clear fluid and others which are blood filled. Superficial LMs have a tendency to develop hyperkeratotic verrucous papules. Patients with microcystic LMs often have chronic leakage from superficial blebs.

9.2.2.2 Diagnosis

As with VMs, contrast-enhanced MRI is the gold standard for diagnosis and characterization of LMs (Table 9.1). Because lymph does not accumulate gadolinium, these lesions enhance to a much lesser extent than VMs, which enhance avidly due to gadolinium-containing venous blood with the lesion itself. Ultrasound can also be useful to differentiate between macrocystic from microcystic LMs, an important distinction that may dictate the modality used for therapy. Extensive macrocystic LMs are sometimes diagnosed in utero on prenatal ultrasound and may be accompanied by polyhydramnios. It is important to detect large macrocystic LMs of the head and neck early as these LMs may obstruct the airway and require early aggressive treatment including tracheostomy in the neonatal period.

9.2.2.3 Management

In general, macrocystic LMs are more amenable to definitive treatment than microcystic LMs. It should also be noted that spontaneous resolution or partial regression, while uncommon, can occur mainly in localized macrocystic cervicofacial LMs [14]. Sclerotherapy and surgical excision are mainstays of treatment. Percutaneous sclerotherapy is generally first-line therapy for macrocystic LMs. Among several agents that may be used as sclerosants, doxycycline is emerging as an agent of choice due to its favorable safety profile, low cost, and documented efficacy [15, 16]. Small, localized LMs are most amenable to surgical excision, which is the only potentially curative option, although the risk of recurrence remains. Radiofrequency ablation appears to be an alternative moderately effective therapy for patients with superficial microcystic LMs of the oral cavity complicated by recurrent bleeding or infection [17]. LMs affecting the airway require a multidisciplinary approach, and in severe cases, tracheostomy may be indicated.

LMs are prone to recurrent bacterial superinfection, and clinicians must have a low index of suspicion for infection as symptoms of pain and swelling may be the only presenting signs, and patients often lack fever or systemic symptoms. While no large-scale studies have been performed to guide antibiotic choices, it is our experience that first-generation cephalosporins, such as cephalexin, generally provide adequate gram-positive coverage in this setting. Prophylactic antibiotics with low-dose amoxicillin or cephalexin may be indicated in patients with recurrent infections (i.e., more than 3–4 infections per year). Ablative lasers such as erbium YAG and CO2 are sometimes used for treating superficial blebs, particularly if they are recurrently bleeding or leaking lymphatic fluid. Repeat treatments may be needed to address these local complications.

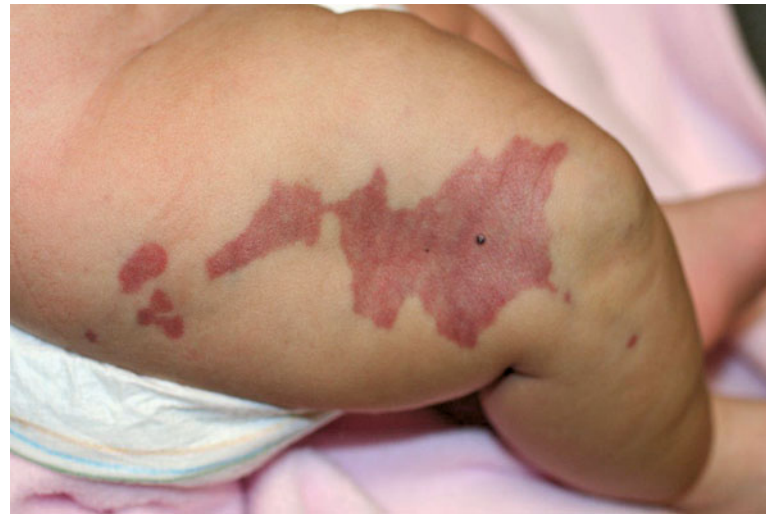

Fig. 9.7 Typical "geographic" capillary malformation of the limb with small blebs in a patient with capillary-lymphatic-venous malformation (Klippel-Trenaunay syndrome)

9.2.3 Klippel-Trenaunay Syndrome

Classically, Klippel-Trenaunay syndrome (KTS) is defined as a triad of varicosities, overlying capillary stain, and limb overgrowth, but may also involve the trunk or pelvis. It is characterized by the presence of a combined capillary-lymphatic-venous malformation (CLVM) and concomitant overgrowth. The majority of KTS patients have this triad without lymphatic disease and fall in the more mild spectrum of disease with stable, nonprogressive overgrowth and mild varicosities. Such patients should be seen at regular intervals to ensure limb overgrowth is indeed stable, but these patients are generally straightforward to manage and often only require compression stockings and supportive treatment of leg length discrepancy. Of greater concern are those patients of a more severe phenotype with extensive CLVM and progressive overgrowth. Such patients tend to have geographic overlying vascular stains and progressive overgrowth that may continue beyond puberty (Fig. 9.7) [18]. For the purposes of this section, discussion will be limited to those more severe cases that pose significant management challenges. Major causes of morbidity include coagulopathy, recurrent infection, lymphangiectasias with recurrent bleeding and drainage, and orthopedic-related complications.

Thrombosis is of major concern in patients with KTS given the underlying venous and lymphatic components. Superficial thrombosis, deep venous thrombosis, and PE have all been reported. PE is of greatest concern given its potential fatal outcome. In one case series, 4 % of KTS patients had radiographic evidence of chronic pulmonary embolism [19]. Those patients with dilated pelvic veins are at highest risk for venous thrombosis resulting in PE. Therefore, it is important to obtain an MRI of the pelvis, including MR venography (MRV), in patients with significant lower extremity, buttock, or perineum involvement. Specifically, the presence of enlarged pelvic veins suggests the propensity to stasis and thrombosis and may place the patient at higher risk of acute or chronic PE. In addition to thrombosis, KTS may be complicated by bleeding. Patients with KTS and LIC are even at risk for progression to DIC after invasive procedures such as sclerotherapy or surgery. Such patients are at high risk for hemorrhagic complications and require support with replacement of coagulation factors and anticoagulation or antifibrinolytic therapy.

A hematologic evaluation should be performed in all patients with KTS, including CBC, D-dimers, fibrinogen, PT, and PTT, as described previously in the Sect. 9.1.3. In patients with a known history of major thrombotic events, long-term anticoagulation is usually recommended. In general, approach to management is similar to

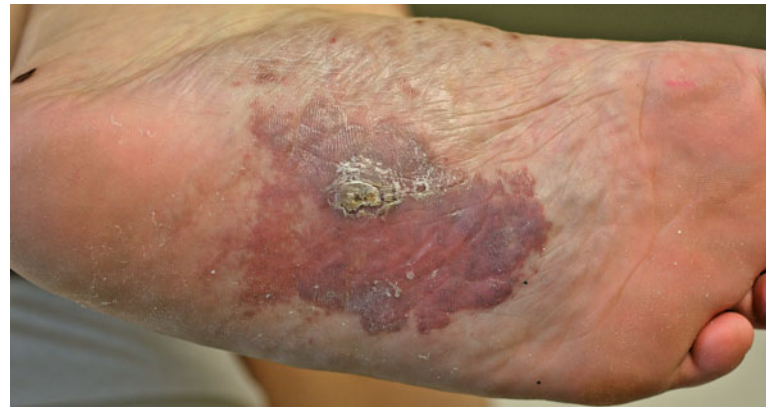

Fig. 9.8 Arteriovenous malformation with overlying crusting on the foot

that of extensive VMs with a few key exceptions. Aggressive surgical resection should be considered cautiously as postoperative complications including lymphedema and poor wound healing are not uncommon. Considerations regarding infection and localized management of superficial blebs are virtually the same as for LM (see discussion above). A multidisciplinary approach is crucial in patients with severe KTS. Orthopedic surgeons are essential in the management of musculoskeletal complications, including limb length discrepancy and articular involvement.

9.2.4 Proteus Syndrome and CLOVES Syndrome

Proteus syndrome is a rare sporadic disorder characterized by the pathognomonic cerebriform connective tissue nevi (often of the soles), epidermal nevi, disproportionate and progressive overgrowth (typically of a limb), lipomas, and vascular malformations. Other manifestations include macrocephaly, various neurologic abnormalities, tumors including ovarian cystadenomas, and pulmonary cysts. Proteus syndrome has recently been found to be due to somatic mosaicism for a mutation in the AKT1 oncogene which is involved in cell proliferation and apoptosis [20]. The vascular anomalies reported in Proteus syndrome include capillary, venous, lymphatic, and mixed capillary-lymphatic-venous malformations similar to those seen in KTS. A more common, but still rare overgrowth syndrome, CLOVES syndrome (*c*ongenital *l*ipomatous *o*vergrowth, *v*ascular malformations, *e*pidermal nevus, and *s*keletal anomalies) closely mimics Proteus syndrome and was recently discovered to be caused by a somatic mosaic activating mutation in PIK3CA which functions upstream of AKT1 [21]. The main differentiating feature in CLOVES syndrome is the presence of overgrowth at birth that is relatively stable rather than being relentlessly progressive. Extensive truncal vascular malformations and symmetrically overgrown feet are also described as being more characteristic findings in CLOVES syndrome [22]. The management of both Proteus and CLOVES syndrome is complex and requires multidisciplinary coordination of care with particular attention to orthopedic and spinal anomalies.

9.2.5 Arteriovenous Malformations

Arteriovenous malformations (AVMs) are composed of anomalous arteries connecting directly to draining veins without intervening capillaries. AVMs can be categorized into four clinical stages with increasing progression: quiescence, expansion, destruction, and decompensation [23]. Stage I AVMs mimic port-wine stains, but have associated warmth. Stage II is associated with enlargement where bruits, thrills, and pulsations can be detected on physical exam. During childhood most AVMs tend not to move beyond stage II. Stage III is complicated by ulceration, bleeding, or tissue necrosis (Fig. 9.8). Finally, stage IV is characterized by cardiac compromise due to a high-output state.

9.2.5.1 Clinical Presentation

It is important for dermatologists to suspect AVM in patients with apparent port-wine stains in which soft tissue swelling (often subtle), excessive warmth, thrills, bruits, or visible pulsations are detected. Excessive pain and/or recurrent bleeding are historical features that can tip off clinicians to the presence of an AVM rather than an ordinary port-wine stain (PWS). PWS with peripheral blanching or those that are unusually recalcitrant to laser therapy are other possible clues to the diagnosis.

9.2.5.2 Diagnosis

Conventional MRI with contrast is the single most effective imaging technique for the diagnosis of AVM. High-flow vascular channels are visualized as signal voids on MRI, sometimes accompanied by reactive changes in surrounding tissues. Because of the rapid rate of blood flow, enhancement is not seen within the AVM itself. Although typically unnecessary, MR angiography (MRA) may be useful in some cases as an adjunct to MRI to characterize the caliber and extent of permeation of vascular structures. Catheter-directed angiography demonstrating arteriovenous shunting can be used both for definitive diagnosis and treatment guidance.

9.2.5.3 Management

Injury or trauma is a well-documented, albeit inconsistent, trigger for more aggressive biologic behavior. Therefore, it is important to consider restricting activity to prevent injury to the affected area. Treatment is generally supportive for stage I and II AVMs. Therapeutic intervention is generally considered in patients with severe pain, bleeding, or extensive disease. Palliative embolization may be the only option in patients with AVMs that are poorly circumcised with extensive permeating vessels that are not amenable to excision. There is some evidence to suggest that preoperative embolization followed by complete resection offers the highest cure rates [24, 25]. Excision should only be attempted if complete resection seems feasible, as partial resection may result in even more symptomatic and aggressive AVMs.

9.2.6 CM-AVM and Parkes Weber Syndrome

Capillary malformation-arteriovenous malformation (CM-AVM) syndrome is an autosomal dominant disorder due to a mutation in the *RASA1* gene in which capillary malformations occur in association with cutaneous or cerebral arteriovenous malformations or fistulas. The *RASA1* gene encodes p120-RasGAP which is involved in signaling for growth factor receptors that control vascular endothelial cell proliferation and migration [26]. The phenotype is variable, but most patients present with small multifocal capillary malformations. A significant minority – perhaps as many as 10–15 % – of patients with CM-AVM have central nervous system or spinal AVMs. Consensus recommendations regarding monitoring of affected patients are lacking, but certainly consideration should be given to imaging studies of the central nervous system, and any patients with neurologic symptoms should be evaluated by appropriate specialists.

Some patients have both multifocal vascular stains and an affected limb with vascular stain, overgrowth, venous varicosities, and small arteriovenous shunts which fulfill diagnostic criteria for Parkes Weber syndrome. Parkes Weber syndrome was previously lumped with KTS because it shares many commonalities with KTS, but it is differentiated by the presences of AV fistulas and AVMs. The realization that at least some patients with Parkes Weber have RASA1 mutations suggests a cause for this condition; however, not all patients with Parkes Weber – particularly if only one limb is affected – have germ-line RASA1 mutations. Patients present similarly to those with KTS, but have additional findings of warmth of the cutaneous vascular malformation and tend to have increased pain relative to KTS. It is important to differentiate the two syndromes, as patients with Parkes Weber syndrome are at risk for high-output complications, including cardiac hypertrophy and congestive heart failure due to the presence of extensive fast-flow vascular malformations. When cutaneous lesions are multifocal, an underlying *RASA1* gene mutation should

be suspected [26]. When Parkes Weber is suspected, a careful inspection for other cutaneous capillary malformations should be performed.

Conclusion

Vascular malformations represent errors in vascular development. They are comprised of localized abnormal vessels and are classified by the vessel type and flow characteristics. Local invasion may cause significant pain and even functional compromise. Clinicians should be aware of associated syndromes and potential systemic complications, such as hematologic abnormalities and pulmonary hypertension. Imaging is often necessary to confirm diagnosis and guide appropriate treatment. A multidisciplinary approach is often best for management of patients with extensive or complex disease.

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Other Vascular Tumors

10

Tina S. Chen and Wynnis L. Tom

Key Points

- Kaposiform hemangioendothelioma and tufted angioma may be complicated by Kasabach-Merritt phenomenon, a usually emergent situation consisting of consumptive coagulopathy and thrombocytopenia.
- Aggressive therapy is needed for cases with KMP, while the management approach for tumors without KMP is less clear.
- Infantile hemangiopericytoma and infantile myofibroma are thought to be related entities, with solitary lesions often having good prognosis including spontaneous regression; multifocal lesions may have more poor outcomes depending on type and location of involvement.
- Multifocal lymphangioendotheliomatosis with thrombocytopenia is a newer entity characterized by multifocal cutaneous and gastrointestinal (GI) vascular lesions, thrombocytopenia, and GI bleeding, still needing determination of optimal therapy.

Abbreviations

KHE	Kaposiform hemangioendothelioma
TA	tufted angioma
KMP	Kasabach-Merritt syndrome
IFN	interferon
HPC	hemangiopericytoma
MLE-T or MLT	multifocal lymphangioendotheliomatosis with thrombocytopenia

Vascular lesions that arise in infants and children are classified into two groups: neoplasms and malformations. The distinction between the two is the cellular proliferation of vessels that occur in neoplasms, but not in malformations. In this chapter, we will discuss the following neoplasms and focus on their systemic treatment options: kaposiform hemangioendotheliomas and tufted angiomas, including the Kasabach-Merritt phenomenon, hemangiopericytomas, infantile myofibromas, and multifocal lymphangioendotheliomatosis with thrombocytopenia.

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10.1 Kaposiform Hemangioendothelioma and Tufted Angioma

Kaposiform hemangioendothelioma (KHE) and tufted angioma (TA) are rare vascular tumors that usually present within the first 5 years of life, with the majority arising in infancy, although a few TA have been reported to be congenital [1, 2]. The two entities are thought to be related as tumors on different ends of the same spectrum [1, 3]. Histologically, they are composed of infiltrative lobules of proliferative capillaries located in the middle and lower dermis, sometimes associated with pericytes or eccrine sweat glands [1, 3, 4]. More specifically, KHE is an endothelial-derived spindle cell neoplasm with slit-like vessels and likely lymphatic differentiation [3], and it rarely has been reported to arise in preexisting lymphatic malformations [5]. Tufted angioma consists of smooth muscle actin-positive, well-circumscribed capillary proliferations in a "cannonball" distribution, without cytological atypia or mitoses [6, 7].

Clinically, KHE and TA usually present as solitary, firm, blue-red tumors or as pink-to-red mottled patches on the head, neck, trunk, shoulder girdle, thigh, perineum, or retroperitoneum [8] (Fig. 10.1). The lesions may be slightly warm, have lanugo hairs, or exhibit hyperhidrosis [4], and can sometimes be tender [9]. They may have an initial growth phase followed by lateral extension for several months to several years, with growth reported even up to 10 years [10]. The differential diagnosis for KHE and TA includes infantile hemangioma, angiosarcoma, leukemia, neuroblastoma, and hemangiopericytoma [11].

The two lesions do have some differences. KHE is often more locally aggressive and can be infiltrative into surrounding tissues [5, 12], resembling rhabdomyosarcoma or aggressive fibromatosis radiographically when it invades bone [13]. Mortality in patients with KHE is much higher as a result (10–24 % vs. no reports for isolated TA) and is related to the location, size, depth, and degree of hemorrhage of the tumor, along with secondary organ failure [11]. TA lesions usually remain localized tumors, though they can grow in size. While KHE is not known to spontaneously regress, TA rarely spontaneously resolves over years [14, 15]. Some feel KHE should be categorized as an intermediate malignancy because of the occurrence of invasion into adjacent lymph nodes or organs. However, neither lesion metastasizes to distant sites [16], and malignant transformation of TA has never been reported [17].

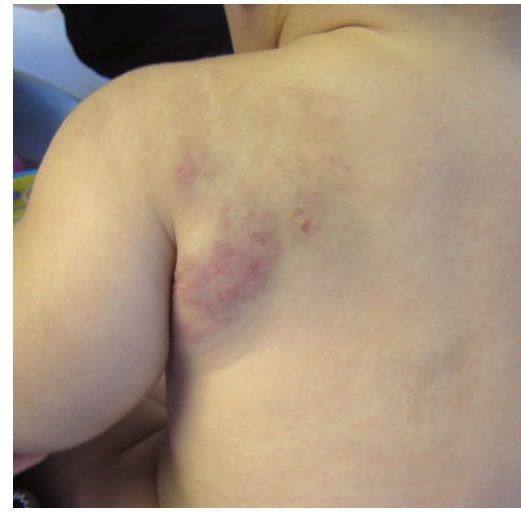

Fig. 10.1 Tufted angioma in a 4-month-old with overlying lanugo hairs

KHE and TA are the most common tumors to be associated with the Kasabach-Merritt phenomenon (KMP) or Kasabach-Merritt syndrome. First described in 1930 [18], KMP is a rare, aggressive clinical syndrome consisting of a consumptive coagulopathy with decreased fibrinogen levels and D-dimer elevation, thrombocytopenia, prolonged prothrombin (PT) and activated partial thromboplastin time (APTT) levels, and microangiopathic hemolytic anemia in association with a rapidly enlarging vascular tumor [19]. Because of the resulting thrombocytopenia, it has also been referred to as a "platelet trapping syndrome." Tumors larger than 8 cm correlate with the occurrence of KMP [20]. Clinical findings may include bruising and bleeding, both internally and externally (Fig. 10.2). Any rapidly enlarging vascular lesion with or without bruising or darkening should raise consideration of KMP and laboratory studies performed. In the

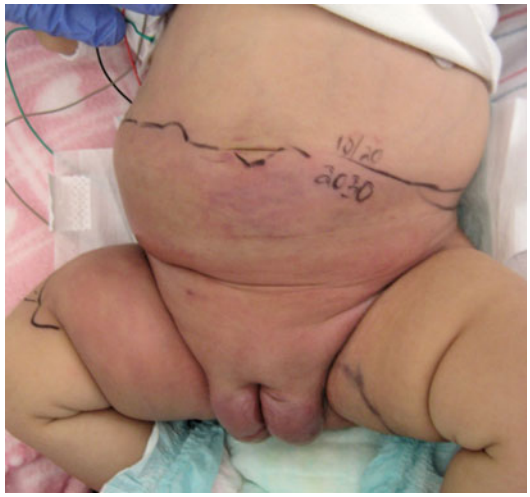

Fig. 10.2 Kasabach-Merritt phenomenon in a 3-month-old with a large kaposiform hemangioendothelioma of the abdomen and pelvis – the child did stabilize with systemic steroids and vincristine therapy

setting of KMP, the mortality of KHE and TA has been reported to be as high as 20–30 %, due to shock and uncontrolled hemorrhage, particularly with mediastinal and retroperitoneal tumors [21–23]. TA lesions without thrombocytopenia but with chronic low-grade coagulopathy causing intermittent pain have been described [24].

10.1.1 Surgical Excision

When the tumor is amenable to surgical excision, this should be pursued as it has the highest chance for permanent resolution of the lesions, although recurrence has been reported [25, 26]. However, risks and benefits need to be critically assessed, as intraoperative bleeding is of great concern, and deaths have been reported with attempted resection of internal/deep lesions [2].

10.1.2 Treatments Used and Side Effect Considerations: In the Setting of KMP

The goals of treatment of KMP are to halt the consumptive process and induce tumor regression.

Most immediate is management of the coagulopathy and thrombocytopenia. It is actually important to limit transfusions of platelets and cryoprecipitate/fresh frozen plasma. Tumors with KMP can consume platelets with a half-life of 1–24 hours and promote their own growth via intralesional clotting. Replacement products may actually provide further substance for consumption, thus exacerbating the KMP [27, 28]. Products should mainly be administered if there is actual clinical bleeding, prior to a procedure, or when laboratory parameters are near a level that would put the patient at significant risk of bleeding (i.e., platelets <10,000–15,000/μL). The patient should be monitored for fluid overload and heart failure with transfusions.

Complete surgical excision is the treatment of choice for small tumors with KMP, but many are not completely resectable given their location, large size, or invasion of surrounding tissues [29]. Embolization by interventional radiology can limit the tumor's blood supply, but is also frequently not a feasible option. As a result, most KHE and TA will require systemic therapy, and even still, complete resolution of these tumors with systemic therapy is rare [30]. The development of KMP is a life-threatening emergency and aggressive therapy is necessary [31]. Oftentimes, a multispecialty approach is best, given the high mortality and the lack of agreed-upon treatment guidelines. Table 10.1 summarizes therapies used and Fig. 10.3 is a suggested treatment algorithm. We will discuss several of the major treatment modalities below.

10.1.2.1 Systemic Corticosteroids

Therapy with systemic corticosteroid monotherapy is only successful approximately 10 % of the time for the tumors themselves [34, 47]. However, it may be beneficial for KMP 33–40 % of the time and has been considered first-line medical therapy for KHE and TA with KMP, partly due to its cost-effectiveness, ease of administration, and rapid response in those who are responders [6, 35, 46, 48, 49]. Increasingly, however, corticosteroids in conjunction with a cytotoxic agent such as vincristine or IFNα are being considered first-line therapy, with some proposing that vincristine

Table 10.1 More commonly reported treatment options for kaposiform hemangioendothelioma and tufted angioma, with or without Kasabach-Merritt phenomenon (KMP)

Management	Dosing	Side effects[a]	Special considerations
Surgical excision	N/A	May have serious complications of surgery, including some reported deaths from excessive bleeding	Highest chance for permanent cure, but risks and benefits need to be very carefully considered
Systemic corticosteroids	Prednisolone 1–5 mg/kg/day (most often 2–4 mg/kg/day)	Hypertension, Cushingoid appearance, diabetes, increased appetite, opportunistic infections, gastrointestinal irritation, growth suppression, and bone demineralization	Other forms of corticosteroid therapy that have been beneficial to some patients include: Intravenous dexamethasone (0.32 mg/kg/day) Oral methylprednisolone (30 mg/kg/day with rapid taper, see text) Intralesional injection of compound betamethasone (1 mL = 7 mg)
Vincristine	In infants less than 10 kg: 0.05 mg/kg/week IV In children greater than 10 kg: 1–2 mg/m^2/week IV	Neurotoxicity (dose limiting) manifesting as peripheral mixed sensory and motor neuropathy or autonomic neuropathy leading to abdominal pain, hematologic abnormalities, syndrome of inappropriate hormone secretion (SIADH) – all adverse effects are often reversible	Two chemotherapy combinations that have been successful in achieving remission: Actinomycin D (500 microgram/m^2), cyclophosphamide (300 mg/m^2), and vincristine Vincristine (1.5 mg/m^2), cyclophosphamide (500 mg/m^2), actinomycin D (1.5 mg/m^2), and methotrexate (10 mg/m^2)
Interferon-α	0.5–10 (most often 0.5–3) million units SQ per day or three to four times a week for 2–7 months	Flu-like symptoms, neutropenia, mild anemia, mild elevation of liver enzymes, and spastic diplegia in infancy (most worrisome, and often requires long-term rehabilitation and may lead to permanent disabilities)	IFNα 2a and INFα 2b are likely equally efficacious, with similar dosing [32]. As a note of caution, IFNα has also been reported to worsen KMP [33]
Antiplatelet/antifibrinolytic	Variable	Bleeding may be a potential adverse effect, though the use of these medications may slow the consumptive coagulopathy associated with KMP (which may lead to hemorrhage as well)	Treatment options that have been of at least partial benefit to patients with KMP include: Cryoprecipitate Ticlopidine (10 mg/kg/day) Aspirin (10 mg/kg/day)[b] Danaparoid (1,250 U × 2/day, IV) Tranexamic acid (0.5 g × 3/day PO) Epsilon-aminocaproic acid Dipyridamole Pentoxifylline Heparin and LMW heparin Intra-arterial thrombin
Propranolol	1–3 mg/kg/day (usually in divided doses)	Hypotension, symptomatic hypoglycemia, bronchial hyperreactivity, restless sleep, constipation, cold extremities	Has not been effective in the majority of patients, but can be tried in combination with prednisolone or vincristine, or considered in nonemergent cases given a lower-risk profile

Table 10.1 (continued)

Management	Dosing	Side effects[a]	Special considerations
Sirolimus	0.1 mg/kg/day	Effects on liver and renal function, bone marrow, cholesterol metabolism, gastrointestinal symptoms, progressive multifocal leukoencephalopathy	Considered experimental at present time though some recent reports are promising
Radiotherapy	Variable	Secondary malignancy (most feared), bone growth abnormalities, muscle atrophy	

Table based on Refs. [1, 6, 7, 10, 11, 13, 25–28, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45]
[a]Not an all-inclusive list of side effects
[b]Reye syndrome is an acute encephalopathy that has been linked to aspirin administration in children with a viral illness, though the cause-effect relationship between aspirin and Reye syndrome remains unproven [46]

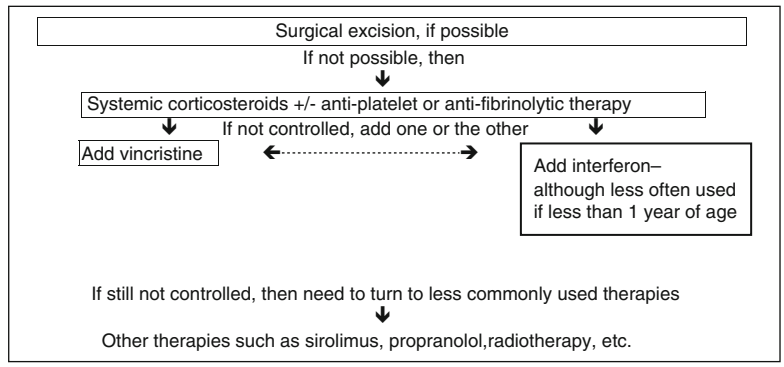

Fig. 10.3 A suggested treatment algorithm for lesions with Kasabach-Merritt phenomenon. Note that treatment order is debatable and controversial given the lack of adequate studies documented in the medical literature

become the adjuvant treatment of choice given the severity of potential neurotoxicity associated with IFNα [50].

Prednisolone, intravenous dexamethasone, oral methylprednisolone, and intralesional injection of compound betamethasone have been used with benefit [36, 37, 46, 51]. Higher doses of corticosteroids (3–5 mg/kg/day) may have better clinical response than 1–2 mg/kg/day for treatment of KMP. One group's recommended dosing regimen even uses oral megadose methylprednisolone: 30 mg/kg daily for 3 days, then 20 mg/kg daily for 4 days, then 10, 5, and 2 mg/kg for 1 week each, followed by a gradual taper to 1 mg/kg [37].

10.1.2.2 Vincristine and Other Chemotherapeutic Agents

Vincristine has been reported to have an excellent survival rate in patients with KMP [52]. It is a chemotherapy agent that inhibits mitosis by arresting metaphase. It also appears to inhibit endothelial proliferation but does carry a 2–4 week latency period to response and can have major side effects (loss of appetite, bronchospasm, and especially neuromuscular/sensorimotor dysfunction), though it is usually well tolerated [11, 52–54]. KMP appears to respond well with stabilization in nearly all cases, although relapse may occur, while only up to 85 % of the tumors themselves decrease in size with treatment [52, 53]. It has been found to be beneficial in tumors with KMP even after a patient fails a systemic steroid and IFN-α-2a [55]. However, it is not uniformly effective and several cases of nonresponse have been noted as well [38]. Many authors recommend vincristine as first-line therapy in combination with systemic corticosteroids or second-line therapy following systemic corticosteroids [39]. Vincristine combined with ticlopidine (10 mg/kg/day), with or without aspirin (10 mg/kg/day) [56, 57], has been beneficial for select patients.

Other chemotherapeutic agents may also be beneficial in treating KMP. Two such regimens that successfully achieved remission were actino-

mycin D, cyclophosphamide, and vincristine combination therapy [58] or vincristine (1.5 mg/m^2), cyclophosphamide (500 mg/m^2), actinomycin D (1.5 mg/m^2), and methotrexate (10 mg/m^2) administered every 3 weeks for eight cycles [27].

10.1.2.3 Interferon-Alpha (IFNα)

Similar to vincristine, IFNα is generally considered a second-line therapy. The potential adverse effect of development of spastic diplegia is of significant concern, however, and has limited the use of IFNα, especially in those less than 1 year of age. Like vincristine, IFNα has a slower onset of action (average 2–4 weeks) compared to corticosteroids, is more costly, and has had conflicting results, having an overall response rate of 50–60 % [10, 11, 23, 27, 47, 51, 59–62]. Nevertheless, it has led to improvement in patients, even as monotherapy and in those who may have failed systemic steroids or vincristine previously [2, 4, 63–66].

IFNα limits angiogenesis by inhibiting endothelial cell migration via suppression of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) transcription. The bFGF is found to be elevated in many tumors involving capillary proliferation, though it is usually normal in patients with TA and response of TA to IFNα has been reported despite low urinary bFGF [10, 67]. Further study is needed to determine mechanisms of KHE and TA response to therapy.

10.1.2.4 Antiplatelet and Antifibrinolytic Agents

Treatment with antiplatelet and antifibrinolytic agents has been helpful in multiple cases of KMP. Agents that have been found to at least be partially beneficial in halting the consumptive coagulopathy include cryoprecipitate, ticlopidine (10 mg/kg/day), aspirin (10 mg/kg/day), danaparoid (1,250 U × 2/day, IV), tranexamic acid (0.5 g × 3/day PO), epsilon-aminocaproic acid, dipyridamole, pentoxifylline, heparin, low-molecular-weight (LMW) heparin, and intra-arterial thrombin [4, 22, 40–42, 68–75]. Notably, therapy with heparin for KMP was previously contraindicated since tumoral growth was noted in a murine model with KMP [76], though the combination of heparin and cryoprecipitate has since been documented to successfully manage KMP in the clinical setting [43].

10.1.2.5 Propranolol

Propranolol is a beta-blocker that has been found to be very effective in the treatment of infantile hemangiomas (see Chap. 8). There is conflicting evidence for the efficacy of propranolol in KHE-associated KMP. One case had marked clinical improvement with propranolol 2 mg/kg/day and vincristine 1.0 mg/m^2/dose for 4 weeks, followed by oral propranolol alone for an additional 13 months and no relapse 2 months after discontinuation [77]. But in a small case series, propranolol was found to be ineffective in the majority of patients, with only one of seven having complete response of the tumor and KMP (dosed 2 mg/kg/day and prednisolone was used concurrently initially) and no response in the remainder [78]. The nonresponders included difficult tumors previously managed with other therapies, as well as newly diagnosed lesions that then tended to have better response to prednisolone and vincristine combination therapy after the short trial of propranolol. Two additional children without KMP at the time of starting propranolol monotherapy did have partial response with lesion stabilization and softening with fewer symptoms, respectively. In the case of TA, propranolol led to resolution of one lesion with associated KMP (given 3 mg/kg/day), but there was nonresponse in the other without KMP (given 2 mg/kg/day) [78].

10.1.2.6 Sirolimus

Sirolimus is a relatively new drug that has been shown to have antiangiogenic activity in preclinical models [79]. Blatt et al. reported a case of a 1-year-old girl with KHE and KMP who had a rapid and dramatic response to sirolimus (0.1 mg/kg/day) without any toxicity, after only having had transient response to prednisone, dexamethasone, IV methylprednisolone, vincristine, serial embolization, sclerotherapy, and no response to propranolol and bevacizumab [79]. A few additional subjects with response have since been reported and a clinical trial is now underway [80]. The placement of sirolimus may

therefore change with increased data on response and safety.

10.1.2.7 Radiotherapy

Radiotherapy is considered third line in the management of KMP [44, 45]. While unsuccessful in some [9], it has benefited several others with KMP and can have a dramatic response when used in conjunction with corticosteroids [45, 81, 82]. Treatment doses of radiation can vary from a total of 6 Gy divided into six fractions to megavoltage irradiation delivered through a 6-MV linear accelerator [total dose of 900 cGy in six fractions (150 cGy/fraction) administered daily for 3 days].

10.1.2.8 Miscellaneous (Cryotherapy, Laser Therapy, Other Agents)

Some less commonly tried treatment modalities include cryotherapy, pneumatic compression, embolization, and laser therapy.

Cryotherapy has not proved to be very successful [9]. Pneumatic compression led to resolution of KMP and a partial resolution of a giant angiomatous nevus on the leg; chronic edema resulted from pneumatic compression but improved after discontinuation of use [83]. Therapeutic embolization with polyvinyl alcohol has also successfully treated KMP in one infant [84].

Some new experimental agents are also being evaluated. Human angiostatin, an inhibitor of angiogenesis generated by the proteolytic cleavage of plasminogen, was found to inhibit KHE growth in a murine model [85]. In another murine model with KMP, pegylated human megakaryocyte growth and development factor (Peg-rHuMGDF), known to stimulate platelet production, prolonged survival, elevated platelet counts, and inhibited tumor growth [86]. Angiostatin also increased survival and prevented the development of profound thrombocytopenia and anemia associated with KMP [85].

10.1.3 Treatments Used and Side Effect Considerations: In the Setting Without KMP

The approach to unresectable KHE and TA lesions without KMP is less clear, particularly if there are no local symptoms or infiltration. Tufted angiomas in particular could be monitored if not growing rapidly, given the occasional self-resolution. In a recent study surveying the practices at 27 vascular anomalies centers in the United States and Canada, first-line approaches were active nonintervention/close monitoring and systemic corticosteroids (each approach chosen by ~33 % of responders) [87]. A small percentage would institute vincristine alone (8 %), and a few would use systemic steroids with vincristine, aspirin, or rapamycin. The most common second-line treatments reported by the centers were vincristine (29 %), systemic steroids (13 %), rapamycin (8 %), and propranolol (8 %). The authors did not find a clear trend identified in the management of KHE and TA not causing KMP.

The utility of pulsed dye laser (PDL) therapy for treatment is controversial, as it has not been very effective in some [4], though use in one case of TA (585 nm, 6.0–7.5 J/cm^2, 0.45 ms, 5 mm spot size × 5 treatments; 585 nm, 6.5–8.0 J/cm^2, 0.45 ms, 7 mm spot size) did lead to a significant reduction in pain and discomfort from the tumor, without recurrence of symptoms 2 years later [88].

10.2 Hemangiopericytoma

Stout and Murray first described hemangiopericytoma (HPC) as a distinct entity in 1942 [89], as a rare, slow-growing vascular tumor derived from the contractile pericytes of Zimmermann that surround blood vessels. The tumor can arise in patients of all ages and was thought to affect any part of the body that contains pericytes, which would include all major organ systems. But in more recent years, this concept has been abandoned in favor of a fibroblastic cell of origin, at least for the childhood-adult type of HPC (see below) [90]. A new term, solitary fibrous tumor, has been advocated for these lesions by the World Health Organization.

HPC constitutes less than 1 % of all neoplasms and typically affects adults during the fifth or sixth decade with equal gender distribution [91]. Only about 5–10 % of cases are found in children, in whom the tumors have a predilection for the head and neck region, pelvis, and the lower extremities and with a slight male predominance (male-to-female = 1.8:1.0) [92]. The majority of

HPC tumors are benign, but aggressive behavior and distant spread have been reported, and often are determined clinically rather than histologically [33, 93]. Cutaneous HPC lesions classically present as a single, firm, or rubbery painless nodule and, rarely, may be multicentric [94, 95]. The development of pain tends to be a late symptom [94]. Lesions can have rapid growth, but there is no known correlation between growth rate and risk of complications or death [96]. Noncutaneous HPC have poorer prognosis with a mean survival of 19 months, and those that have presented with operable tumors have had a significantly longer median survival compared to those with advanced or diffuse disease [97].

There are two subtypes of HPC: an infantile type (presenting before 12 months of age) and a childhood-adult type [93]. Forty percent of HPC in children are in the infantile subtype, which has an excellent prognosis since most present as dermal or subcutaneous masses rather than as deeper lesions [92, 94, 98]. The childhood form is akin to adult disease, having more aggressive behavior with a significantly worse prognosis [32]. Lymph node and lung metastases may be present at the time of diagnosis, and the tumor often develops pulmonary and bone metastases as well [93]. Histologically, there are no differentiating characteristics between the two subtypes of HPC [32]. HPC is characterized by a "staghorn" pattern of sinusoidal vessels, tightly packed cells around thin-walled, endothelium-lined vascular channels [94].

Because of the rarity of the lesions, it is difficult to propose a protocol-based treatment plan for these tumors. More conservative treatment approaches are appropriate for infantile tumors, including infants with multicentric tumors, as chemoresponsiveness [99] and spontaneous regression have been documented [95, 100, 101]. As a result, recent literature advocates careful monitoring of uncomplicated disease in infants. When needed, it is recommended that infantile HPC be preoperatively treated with chemotherapy given the high degree of response [101–103]. Treatment options do need to be carefully considered, as death from overaggressive therapy has also been documented [94, 104].

Childhood and adult tumors require a more aggressive multimodality treatment approach. In these patients, optimal therapy for HPC is complete surgical excision, when possible [92, 104]. Adjuvant chemotherapy and radiotherapy may be beneficial but only in about 70 % of cases [102–105].

Chemotherapies used to treat HPC have included combinations of vincristine, cyclophosphamide, dacarbazine, doxorubicin, actinomycin D, etoposide, cisplatin, ifosfamide, methotrexate, mitoxantrone, and other alkylating agents [32, 106–108] though complete response from chemotherapy alone may be uncommon [109]. Two patients with unresectable tumors did have very good clinical responses with a 3-drug regimen consisting of vincristine, actinomycin D, and cyclophosphamide [32]. IFN has also been used in the treatment of HPC with clinical improvement [110, 111]. More recently, antiangiogenic therapy with sorafenib [400 mg BID, in combination with dacarbazine (1,000 mg/m^2 every 3 weeks)] and sunitinib (50 mg) have achieved partial responses in patients with HPC [112–114]. CyberKnife stereotactic radiosurgery can also be an effective therapy for recurrent, metastatic, and residual HPC [115]. Radiation doses >50 Gy are considered necessary for treating local disease [109]. Recurrence as late as 15 years after excision has been documented, and thus, long-term follow-up is necessary [116].

10.3 Infantile Myofibroma

In 1954, Stout classified a distinct entity within juvenile fibromatoses [117], which was later named infantile myofibromatosis by Chung and Enzinger [118]. These mesenchymal tumors are the most common fibrous tumors of infancy [119], although still relatively rare. They mainly present prior to 2 years of age and are often congenital. The etiology is unknown, although a genetic component has been theorized [120–123]. The tumors are divided into two groups: solitary and multicentric. Some subdivide multicentric into those with and those without visceral involvement. Solitary tumors are the most

common and have a good prognosis. They are most often found in the soft tissues of the head and neck, followed by the trunk and upper extremities [118]. Solitary lesions involving the orbit, gingiva, or in association with self-limited thrombocytopenia have also been reported [110, 111, 124, 125]. Multicentric disease may involve bone and viscera; solitary bone involvement only accounts for 10 % of multicentric cases [118]. Solitary forms are more common in boys (69 %) while multicentric forms have a female predominance (63 %) [118].

Infantile myofibromas without visceral involvement have a relatively good prognosis with or without excision. Some lesions may spontaneously regress [119, 124], though rapid growth in the perinatal period has been reported [126]. In lesions that do not spontaneously regress, surgical excision is the treatment of choice when possible, and complete surgical excision has approximately a 10 % recurrence rate [127]. Multicentric disease carries a poor prognosis [118], and patients with involvement of viscera generally die within 3–4 months, most commonly due to cardiopulmonary or gastrointestinal complications [119]. Dissemination and malignant transformation have not been reported in this entity [118]. Long-term follow-up is necessary in these patients because new nodules may appear in later childhood [118] or even adulthood [122].

Given overlapping clinical behavior and pathological features with infantile HPC and infantile myofibromatosis, it has been suggested that these two entities are related variants along a continuous spectrum and their histologic characteristics may correspond to different maturation stages [95].

10.4 Multifocal Lymphangioendotheliomatosis with Thrombocytopenia

Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLE-T or MLT) was first described by North et al. in 2004 as a new entity characterized by multifocal cutaneous and gastrointestinal (GI) vascular lesions, thrombocytopenia, and GI bleeding [128]. It has also been referred to as cutaneovisceral angiomatosis with thrombocytopenia (CAT syndrome), but the two are synonymous [129]. In total, at least 17 cases have been reported in the English medical literature [128, 129], and it is likely that cases have previously been misdiagnosed as hemangiomatosis, blue rubber bleb syndrome, multifocal kaposiform hemangioendothelioma, hemangiopericytoma, and tufted angioma [130, 131]. The red-brown vascular macules, papules, and nodules are typically present at birth, may have a proliferative phase, and do not tend to spontaneously involute. GI bleeding is reported as an inevitable sequela, though there exists a rare report of MLE-T where the infant had clinical and histochemical features consistent with MLE-T without thrombocytopenia or GI tract bleeding [132]. Vascular lesions in MLE-T may also affect other organ systems, such as the lungs (most commonly reported), thyroid, liver, omentum, kidneys, muscle, bone, and brain [130]. Histologically, the vessels are lined with a single layer of slightly hobnailed endothelial cells that stain positive for D2-40 and LYVE-1, two lymphatic markers [128, 129].

Optimal management for MLE-T has not yet been established. Most patients have been treated with systemic corticosteroids (2 mg/kg/day) with minimal, if any, response [128]. Vincristine (0.025 mg/kg/dose every 1–2 weeks), IFNα-2a, and IVIG have also not demonstrated much clinical efficacy. Thalidomide led to decreased frequency of transfusions in two patients [130], but was thought to be the cause of sepsis in a third patient 2 months after initiation of therapy [133]. More recently, a vascular endothelial growth factor inhibitor, bevacizumab (5 mg/kg/dose every 2 weeks), was used to treat two children with MLE-T with a significant decrease in need for transfusions [133, 134]. Similar to KMP, platelet transfusions should only be given to control active bleeding, as they may worsen consumptive coagulopathy without alteration in frequency or severity of bleeding [130]. Comanagement with a pediatric gastroenterologist is recommended for control of potentially life-threatening GI bleeding.

Deaths from the disease are usually secondary to hemorrhage, though the severity of thrombocytopenia and bleeding tends to decrease after the first 3 years of life [128], if the initial hematologic complications can be managed.

Conclusion

The vascular neoplasms kaposiform hemangioendotheliomas, tufted angiomas, hemangiopericytomas, infantile myofibromas, and multifocal lymphangioendotheliomatosis with thrombocytopenia are generally benign but often complicated tumors. As a result of their rarity, they lack the more definitive management approaches of their counterparts, infantile hemangiomas. Guidelines of therapy and clinical drug trials are still needed for most of these entities, some of which are underway.

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Part IV

Genodermatoses

Current and Novel Approaches for Genetic Skin Disorders

11

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Key Points

- Genetic skin disorders are associated with significant morbidity and some cause early mortality.
- Disease-modifying therapies have been lacking, but our rapidly growing understanding of the pathomechanisms of many genodermatoses gives tremendous translational therapeutic potential.
- Pathogenesis-based therapy with specific targeting of pathways using existing and/or novel drugs and molecules is an approach being applied to disorders such as the ichthyoses and tumor syndromes. Other areas of active investigation include new methods for gene suppression and revertant cell therapy.
- These and other novel concepts will hopefully soon expand the armamentarium of management options available for severe genetic skin disorders.

Abbreviations

CHILD	Congenital hemidysplasia with ichthyosiform erythroderma and limb defects
RAR	Retinoid Acid Receptor
RXR	Retinoid X receptor
KID syndrome	Keratosis-Ichthyosis-Deafness syndrome
OMIM	Online Mendelian Inheritance in Man
NSDHL	NAD(P)H steroid dehydrogenase-like syndrome
NS	Netherton syndrome
KLK5-PAR2-TSLP	Kallikrein 5-proteinase-activated receptor2-thymic stromal lymphopoietin
SPINK5	serine protease inhibitor Kazal-type 5
LEKTI	lymphoepithelial Kazal-type-related inhibitor
TSLP	thymic stromal lymphopoietin

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TNF	tumor necrosis factor
NBCCS	nevoid basal cell carcinoma syndrome
BCC	basal cell carcinoma
SMO	smoothened
Gli	glioma-associated transcription
TS	tuberous sclerosis
mTOR	mammalian target of rapamycin
NF1	neurofibromatosis type 1
MFS	Marfan syndrome
FBN1	fibrillin-1
TGF	transforming growth factor
PC	pachyonychia congenita
K6A	keratin 6a
K6B	keratin 6b
K17	keratin 17
RNA	ribonucleic acid
siRNA	small interfering RNA
HED	hypohidrotic ectodermal dysplasia
EDA	ectodysplasin A
EDAR	EDA receptor
EDARRADD	EDAR-associated death domain
SNA	spherical nucleic acid
SMART	spliceosome-mediated RNA trans-splicing therapy

During the past 20 years, tremendous progress has been made in our understanding of the molecular basis of many genetic skin conditions. Despite these great strides, the translation of these laboratory findings into effective therapies for affected individuals has been slow. In large part, the slow translation results from the risk of carcinogenesis from random viral genomic integration, the lack of efficacy of topically applied genetic material and most proteins due to the epidermal barrier, and ethical and governmental regulatory hurdles [1]. The greatest progress to date involves gene replacement for epidermolysis bullosa (see Chap. 12). Although intervention at the gene, protein, or cellular level appears remote for most other genetic disorders, our increased knowledge about the pathogenesis of disease also allows specific targeting of pathways with existing and/or novel drugs and molecules. In contrast to the requirement for personalization of most gene-based therapy, pathogenesis-based therapy is pathway-specific and has broader applicability. In this chapter, we provide an overview of novel and emerging treatments for several genetic skin disorders, among them the ichthyoses (lamellar ichthyosis, CHILD syndrome, and Netherton syndrome), tumor syndromes (nevoid basal cell carcinoma syndrome, neurofibromatosis, and tuberous sclerosis), keratin gene disorders (pachyonychia congenita), and hypohidrotic ectodermal dysplasia.

11.1 Syndromic and Non-syndromic Ichthyoses

The ichthyoses consist of a genetically heterogeneous group of conditions in which there is a deregulation of cornification [2]. The skin is characterized by widespread scaling associated with inflammation and blistering in some subtypes. The management of ichthyosis is largely directed towards scale reduction using topical treatments, emollients, and keratolytics, particularly urea, α-hydroxy acids, and retinoids [1]. In severe cases, oral retinoids such as acitretin, isotretinoin, and alitretinoin can be used [3, 4]. Retinoids are vitamin A derivatives that are either naturally or synthetically derived. They have pleiotropic effects and are able to regulate cell differentiation, apoptosis, and proliferation [5]. In the target cell, they exert their effects by binding to specific nuclear receptors, namely, retinoid acid receptors (RAR) and retinoid X receptors (RXR) [6]. RAR and RXR each consist of three subgroups, namely, RAR-α, RAR-β, and RAR-γ and RXR-α, RXR-β, and RXR-γ, respectively. In the human skin, the predominant retinoid receptors are RAR-γ and RXR-α. Retinoids promote epidermal shedding and reduce epidermal hyperkeratosis in a nonspecific manner [3, 7]. While this therapeutic approach might confer benefit to the patient, it may be intuitively counterproductive since the hyperkeratosis likely reflects a compensatory mechanism to reestablish a functioning epidermal barrier [1]. Despite the molecular diversity of the ichthyoses, it is noteworthy that the same oral

retinoid can be beneficial for most subtypes of ichthyoses. An important consideration when using oral retinoids is the risk of teratogenicity in females of childbearing age, who must be appropriately counseled [8]. In this group of patients, isotretinoin may be preferred given its shorter half-life of elimination compared to acitretin. Furthermore, the risk of skin fragility must be considered in patients with severe ichthyosis in whom oral retinoids are started. This is particularly important in cases of epidermolytic hyperkeratosis in whom acitretin is generally maintained at a low dose, or given intermittently, as these patients are prone to skin blistering [9]. In addition, the rare side effects of systemic retinoid-induced soft tissue ossification, benign intracranial hypertension, and spinal hyperostosis should not be underestimated [10–13]. Another retinoid that has been used in ichthyosis is alitretinoin (not available in the USA). To date, there has been a single case report of its use in ichthyosis, namely, keratitis–ichthyosis–deafness (KID) syndrome, an autosomal dominant condition caused by mutation in the connexin 26 (*GJB2*) gene [4]. Alitretinoin, also known as 9-cis-retinoic acid and obtained through isomerization of tretinoin, is able to bind to all 6 known retinoid receptors with greater affinity for RAR compared to RXR [14]. In this patient with KID syndrome, alitretinoin was used for 5.5 months at an initial dose of 10 mg/day for 2 weeks followed by a maintenance dose of 30 mg/day for 5 months, resulting in excellent resolution of her hyperkeratosis [4]. While data on the use of alitretinoin in ichthyosis is limited, it may be another option for the treatment of difficult cases. Similar to isotretinoin, it has a shorter half-life of elimination compared to acitretin and therefore may be an attractive treatment consideration in females of childbearing age.

Our greater understanding of the pathomechanisms of the ichthyoses has paved the way for innovative therapeutic approaches in ichthyosis management. Novel treatments involving gene or protein therapy still remain remote given the widespread nature of the disease, difficulties in transcutaneous drug delivery, and the long-term risk of viral transduction involved in gene correction [1], notwithstanding ethical and governmental hurdles [15]. An alternative approach would be to use a pathway- or mechanism-based strategy for these disorders. For instance, in syndromic lipid metabolic disorders, the cutaneous and extracutaneous features result from both a deficiency of the pathway product and an accumulation of upstream toxic metabolites [16, 17]. In inherited disorders of distal cholesterol metabolism, a therapeutic strategy would be to treat the extracutaneous features with the oral coadministration of cholesterol and statins [18, 19]. This approach may, however, be hampered by first-pass metabolism of statins and intrahepatic incorporation of cholesterol into lipoparticles. To circumvent this problem, a topical strategy could be used, allowing direct access to the skin and perhaps to the extracutaneous tissues as well. In 2011, Paller and coworkers reported the success of this topical approach in two unrelated patients with CHILD syndrome (congenital hemidysplasia with ichthyosiform erythroderma and limb defect; OMIM 308050), a syndromic disorder of distal cholesterol metabolism [1]. CHILD syndrome is an X-linked dominant disorder resulting from mutations in the *NAD(P)H steroid dehydrogenase-like* (*NSDHL*) gene [20]. This gene encodes a member of the enzyme complex that removes the C-4 methyl group from lanosterol. Mutations in the *NSDHL* gene prevent the post-lanosterol generation of cholesterol but concurrently lead to accumulation of upstream, potentially toxic metabolites. Histologically, skin biopsies from individuals with CHILD syndrome show marked hyperkeratosis and acanthosis with absent granular layer and dermal foam cells [1]. Ultrastructurally, severe alterations in the epidermal lipid secretory system are present. These include premature fusion of individual organelles into intracellular multivesicular bodies that are incompletely secreted [1]. Furthermore, the stratum corneum extracellular matrix displays a reduced amount of secreted lamellar material interspersed with abundant non-lamellar vesicles. Topical application of 2 % cholesterol and 2 %

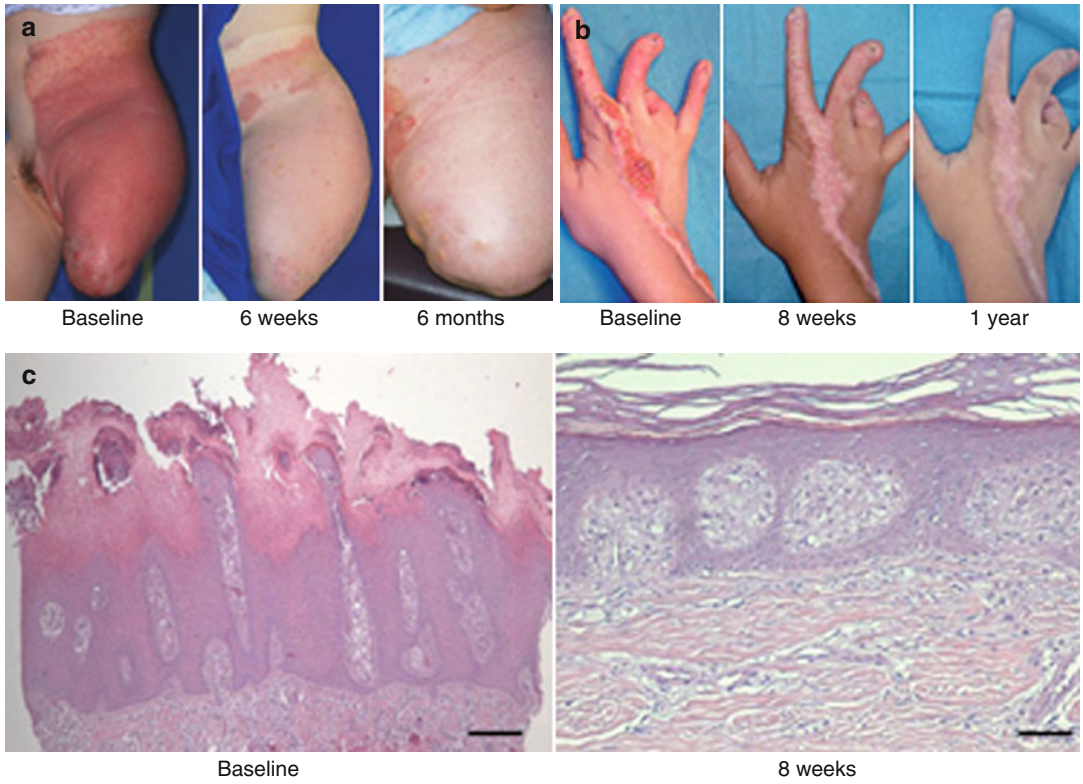

Fig. 11.1 Clinical and histological improvement of two patients with CHILD syndrome with topical applications of lovastatin/cholesterol. (**a**) Treated skin of patient #1. (**b**) Treated skin of patient #2. (**c**) Histopathological evaluation of lesional skin of patient #2 at baseline (*left*) showed marked epidermal acanthosis with psoriasiform hyperplasia. The granular layer was absent, and the stratum corneum showed parakeratosis and retention hyperkeratosis. *Bar* = 25 μm. By ~3 months after treatment initiation (*right*), the epidermis was of normal thickness with regular orthokeratinization and a normal granular layer. *Bar* = 7 μm (Reproduced with permission from Paller et al. [1])

lovastatin (but not cholesterol alone) resulted in reduced inflammation, skin thickening, and scaling in the two patients with CHILD syndrome as early as 4–6 weeks following initiation of treatment [1] (Fig. 11.1). By 6 months, the treated skin had largely normalized at a clinical level, as well as histologically and ultrastructurally. Both patients tolerated the treatment with no systemic side effects. Another condition that might benefit from a statin/cholesterol combination is Conradi–Hunermann–Happle syndrome, which presents with bone defects and patterned ichthyosis without lateralization [1]. Furthermore, pathogenesis-based therapy can be applied to many other syndromic and nonsyndromic disorders of fatty acid and ceramide metabolism, such as recessive X-linked ichthyosis, Sjogren–Larsson syndrome, Chanarin–Dorfman syndrome, type II Gaucher disease, and Refsum disease [1, 16].

11.1.1 Pathogenesis-Based Therapy in Netherton Syndrome

Along the lines of pathogenesis-based therapy, Fontao and coworkers reported clinical improvement in Netherton syndrome (NS) (OMIM 256500) by targeting the kallikrein 5-proteinase-activated receptor 2-thymic stromal lymphopoietin (KLK5-PAR2-TSLP) pathway using infliximab [21]. NS is a rare autosomal recessive genodermatosis caused by pathogenic mutations in the *serine protease inhibitor Kazal-type 5* (*SPINK5*) gene that encodes the lymphoepithelial Kazal-type-related

inhibitor (LEKTI) [22]. Affected individuals with NS have severe skin inflammation as well as allergic tendencies, including atopic dermatitis and highly elevated serum IgE levels [21]. Thymic stromal lymphopoietin (TSLP) and tumor necrosis factor alpha (TNFα) have been shown to be overexpressed in LEKTI-deficient skin of NS patients and in *SPINK5*-null mice as a result of unrestricted activity of epidermal proteases, including kallikreins [23, 24]. This leads to activation of PAR2 signaling and subsequent NF-κB activation and TSLP expression [24]. TSLP can induce an atopic response in mice and its expression can also be increased by TNFα and interleukin 1 [25–27]. Infusions of infliximab (5 mg/kg) were administered at weeks 0, 2, and 6 and then monthly to a patient with Netherton syndrome unresponsive to dapsone and topical steroids, tacrolimus, and pimecrolimus [21]. At baseline, the patient's keratinocytes exhibited a 15-fold increase in TNFα expression compared to control keratinocytes. Clinical improvement was noted after the second infusion, and after the 12th infusion, the skin was clear of inflammation, although the ichthyosis, xerosis, and serum IgE levels were unchanged. The treatment was well tolerated during the 2-year follow-up period. At a molecular level, a fourfold reduction in TSLP was noted in both lesional and non-lesional skin 1 year after therapy and remained reduced after 2 years. Of note, however, the level of TNFα was not reduced because infliximab is a neutralizing antibody and does not downregulate TNFα gene expression.

11.2 Tumor Syndromes

11.2.1 Novel Treatments for Nevoid Basal Cell Carcinoma

Nevoid basal cell carcinoma syndrome (NBCCS) (OMIM 109400), also known as basal cell nevus syndrome (BCNS) and Gorlin–Goltz syndrome, is an autosomal dominant condition with high penetrance and variable expressivity [28, 29]. It results from an inactivating germline mutation in the tumor suppressor gene, *PTCH1*. Tumor formation is thought to result from a second-hit mutation in the normal allele, possibly as a result of ultraviolet radiation [30, 31]. The characteristic clinical features include multiple basal cell carcinomas, odontogenic cysts, palmoplantar pits, and facial abnormalities, including frontal bossing and hypertelorism. Other less frequent features include spine and rib abnormalities and calcification of the falx cerebri. NBCCS may also be associated with other malignancies [32]. The treatment of the basal cell carcinomas (BCCs) is mainly surgical (excision, curettage and cautery, and Mohs micrographic surgery). Other therapeutic modalities include oral retinoids, radiotherapy, photodynamic therapy, cryosurgery, ablative laser treatment, and topical agents such as 5-fluorouracil and imiquimod [33–35]. Despite the availability of these options, the treatment of NBCCS remains challenging. A fine balance must be struck between long-term skin preservation and the treatment of tumors that relentlessly develop throughout the patient's life and which require complex surgical and medical management.

The *PTCH1* gene encodes the transmembrane protein PTCH1, which is the primary receptor for ligands of the hedgehog signaling pathway [28, 36]. Under physiological conditions, the hedgehog signaling pathway is suppressed with inhibition of the smoothened (SMO) protein by PTCH1. As a result, glioma-associated transcription factors (Gli1, Gli2, and Gli3), which are the downstream hedgehog effectors and which control the expression of hedgehog target genes, become inactivated. In NBCCS, there is loss of PTCH1 inhibition of SMO, resulting in downstream uncontrolled cellular growth and proliferation (for review, see Tang and Marghoob [37]). Thus, the identification of *PTCH1* mutations in NBCCS and its involvement in the hedgehog signaling pathway offers exciting opportunities for novel molecularly targeted therapies. One therapeutic strategy is to block hedgehog signaling; the steroidal alkaloid cyclopamine was previously shown to be able to block hedgehog signaling by binding to SMO and thus inhibiting downstream hedgehog target genes [38]. Subsequently, a novel SMO inhibitor GDC-0449, now known as vismodegib and discovered by high-throughput drug

screening, was shown in a phase 1 clinical trial to have antitumor activity in locally advanced or metastatic basal cell carcinoma, with substantial tumor shrinkage or healed visible lesions seen in 43 % of patients with locally advanced BCC and in 30 % of patients with metastatic BCC [39]. In 2010, a case report was published demonstrating the efficacy of GDC-0449 in a 53-year-old man with NBCCS [40]. This individual previously had Mohs micrographic surgery and surgical excisions for 282 histologically confirmed BCCs, as well as several treatment courses of imiquimod cream, oral retinoid, and topical 5-fluorouracil. The patient was started on 270 mg/day of GDC-0449. After 8 weeks, considerable reduction in the number and size of his BCCs was noted. After 12 weeks, no additional BCCs were seen on his skin and most of his existing BCCs had regressed [40]. He subsequently continued his oral treatment with GDC-449 [41]. After 2 years into this regimen, there was the unexpected finding of progressive resolution of the patient's odontogenic keratocysts, suggesting that treatment with an SMO inhibitor might confer both cutaneous and extracutaneous benefits [41]. A phase II clinical study is being conducted to determine whether vismodegib is effective in NBCCS [42]. In this study, 41 patients were recruited and randomized in a 2:1 ratio to receive either vismodegib or placebo. The primary endpoint was the number of new surgically eligible BCCs per month after 3 months of treatment, and the secondary endpoints were a change in the size of existing BCCs as well as assessment of safety and tolerability. The preliminary data showed that the 24 subjects who were assigned to receive vismodegib developed 0.07 new BCCs per month while the placebo arm developed 1.74 new BCCs per month. In addition, the aggregate size of existing BCCs decreased by 24 cm in the vismodegib group, while in the placebo arm, the decrease in size was 3 cm. Interestingly, near-complete remission was seen in some patients in the treatment arm, histological clearance was seen in seven out of 11 biopsies, and importantly, no BCCs developed resistance [42]. At the interim analysis at 18 months, however, 54 % of those receiving vismodegib had discontinued drug treatment due to adverse events, which included loss of taste, muscle cramps, hair loss, and weight loss [43]. These side effects reversed on discontinuation, but tumor growth also resumed once again, with cumulative diameter of existing BCCs returning to pretreatment levels several months after vismodegib was stopped.

Additionally, topical treatment with another SMO antagonist, LDE225, has recently been reported to be effective in NBCCS [44]. In this double-blind, randomized, vehicle-controlled, intraindividual study, eight patients with a total of 27 BCCs were treated with 0.75 % LDE225 or vehicle cream twice a day for 4 weeks. Of the 13 BCCs treated with LDE225 cream, 3 showed a complete response, 9 showed a partial response, and 1 had no clinical response. While this data is still preliminary, it offers promise that topical delivery of an SMO inhibitor may be beneficial in patients with NBCCS. However, caution should be exercised because acquired resistance to SMO inhibitors has recently been described in an individual with metastatic medulloblastoma who initially responded to vismodegib but whose disease recurred at ~3 months [45]. Further analysis showed that the nonresponding medulloblastoma tissue has acquired an SMO mutation that was refractory to inhibition by vismodegib [46]. Several other SMO-binding hedgehog signaling pathway antagonists are currently in clinical trials and may provide a number of different treatment options for patients with NBCCS.

11.2.2 Novel Treatments in Tuberous Sclerosis

Tuberous sclerosis (TS) (TS1, OMIM 191100 and TS2, OMIM 191092) is an autosomal dominant multisystemic disorder characterized by widespread hamartomas in several organs such as the skin, brain, kidneys, eyes, liver, and lung [47] It affects about 1 in 6,000 people and results from mutations in either the *TSC1* or *TSC2* genes, which are found in two-thirds of patients [48–51] [47]. These genes encode hamartin and tuberin,

respectively, which together form a complex to inhibit the mammalian target of rapamycin (mTOR) pathway that is crucial for the control of cell growth and proliferation [52–54]. The cutaneous features include (1) hypomelanotic macules, which are the most common dermatological manifestation and present in 90–98 % of patients with TS [55, 56]; (2) facial angiofibromas, seen in 80 % of affected children older than 5 years of age [56]; and (3) shagreen patches, which are connective tissue nevi found in ~54 % of children older than 5 years of age [56]. Renal complications, including multiple bilateral angiomyolipomas, are the most frequent cause of TS-associated deaths [57]. In addition, ~85 % of children with TS have central nervous system abnormalities, including epilepsy, cognitive impairment, behavioral problems, and autism [58]. In the brain, structural abnormalities may be present and include cortical tubers, subependymal nodules, subependymal giant cell astrocytomas, and white matter abnormalities [59, 60]. The discovery of the upregulated mTOR signaling in TS offers molecularly directed therapies for treating this condition. Rapamycin has been shown to regulate cellular proliferation and growth through its inhibitory action on mTOR. Orally administered rapamycin (also called sirolimus) caused at least 50 % regression of angiomyolipomas in patients with TS, after 12 months, but no significant improvement in lung function; upon discontinuation of sirolimus, the angiomyolipomas increased in size [61]. A separate study confirmed both the shrinkage of renal angiomyolipomas and the lack of improvement in pulmonary function [62]. Subsequently, everolimus, another mTOR inhibitor, reduced significantly the volume of subependymal giant cell astrocytomas as well as seizure frequency [63]. In addition, sirolimus given for 52 weeks induced the regression of renal angiomyolipomas, subependymal giant cell astrocytomas, and liver angiomyolipomas [64]. Subjective improvement in the number of facial angiofibromas, shagreen patches, ungula fibromas, and hypomelanotic macules was noted [64]. Using topical rapamycin for the treatment of the facial angiofibromas is appealing, since facial angiofibromas are often associated with significant negative psychological effects in affected individuals [65]. Several groups have now reported the efficacy of using topical rapamycin for facial angiofibromas [65–70]. The response of oral or topical mTOR inhibitors raises the three questions: (1) When should treatment with mTOR inhibitors start? (2) For how long should treatment be continued or stopped? (3) What are the consequences of prolonged mTOR inhibition? Answers to these questions will provide better insight into the mechanism of action of these novel treatment options.

11.2.3 Emerging Treatments in Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1) (OMIM 162200) is a common autosomal dominant condition that affects 1 in 3,000 individuals. It is caused by mutations in the *NF1* gene which encodes neurofibromin [71]. It is characterized by the development of malignant and nonmalignant tumors, such as plexiform neurofibromas, which can affect up to 40 % of individuals with NF1 [72]. The management of NF1 is challenging; patients often present with numerous neurofibromas which lead to significant disfigurement and psychological morbidity. An important breakthrough in management was reported in 2008 with the discovery that imatinib was able to reverse neurofibroma pathology in a mouse model of NF1 [72]. This prompted the use of imatinib in a critically ill 3-year-old child with a life-threatening plexiform neurofibroma causing airway compromise. Following 3 months of treatment with imatinib, the tumor shrunk by approximately 70 %, and after 6 months of therapy, it had stabilized leading to discontinuation of treatment [72]. A cautionary note, however, is that gastrointestinal stromal tumors, which occur more frequently in patients with NF1, do not respond effectively to imatinib, suggesting that c-kit signaling may not be critical in the pathogenesis of tumors other than plexiform neurofibromas [73].

11.2.4 Novel Treatments for Marfan Syndrome

Marfan syndrome (MFS) (OMIM 154700) is an autosomal dominant multisystemic condition affecting approximately 1 in 5,000 individuals [74, 75]. It is caused by mutations in the *FBN1* gene that encodes fibrillin-1, an important component of microfibrils [74]. The main cause of death in patients with MFS is aortic rupture, which was thought to be due to loss of integrity of the vessel wall [75]. The prevention of this complication has therefore largely been directed towards reducing aortic wall stress with β-blockers and prophylactic surgery [76]. Recently, it has been shown that fibrillin-1 participates in elastic fiber maturation and remodeling, even in postnatal life, and is not just confined to embryogenesis. Furthermore, a mouse model of MFS has demonstrated that fibrillin-1 deficiency is associated with increased transforming growth factor-β signaling. This results in abnormal tissue formation and remodeling, factors that promote an intense elastolysis and collapse of an already abnormal aortic wall [77]. This new knowledge has led to a different approach in the management of the aortic complications in MFS. In the same study, it was shown that the prenatal or even the postnatal administration of losartan, an angiotensin II receptor blocker, was able to prevent aortic dilatation and the destruction of the aortic wall [77]. This was subsequently corroborated by a retrospective study in which 18 pediatric patients with severely progressive MFS showed a statistically significant decrease in the rate of aortic root diameter growth after 1 year of treatment with an angiotensin II receptor blocker [76]. Other treatment options may also be on the horizon. For instance, pravastatin, a HMG-CoA reductase inhibitor, has been shown to be able to reduce the cardiac expression of TGF-β in an *in vivo* model of diabetic glucose intolerance [78]. Pravastatin might have a similar effect to losartan in reducing the rate of progression of aortic root dilatation. A recent study in a mouse model of MFS demonstrated that pravastatin has a beneficial effect in reducing aortic root dilatation, but significant pathological changes were still seen within the aortic wall compared to treatment with losartan [79]. It would therefore be valuable to determine whether the combination of these two drugs could confer additional benefits to children with MFS in further reducing the rate of aortic root complications.

11.2.5 Novel Therapeutics for Pachyonychia Congenita

Pachyonychia congenita (PC) is a rare autosomal dominant condition resulting from pathogenic mutations in genes encoding keratin 6a (K6A) (~50 % of cases), keratin 6b (K6B), keratin 16 (K16), or keratin 17 (K17) [80]. These mutations act by a dominant negative mechanism to cause disease [81]. A characteristic feature of PC is the development of painful focal palmoplantar keratoderma, particularly on the weight-bearing areas of the soles of the feet. Currently, the mainstay of medical management is oral retinoids, such as acitretin, leading to variable success [82]. An important consideration is that the reduction in the thickness of the keratoderma does not necessarily benefit the patient. Instead, the skin might become more sensitive and vulnerable to pain and blistering [82]. During the past 4 years, there have been a number of novel therapeutic approaches in PC. One such approach is to use small interfering RNA (siRNA) technology. Small interfering RNAs are short double-stranded RNA that can target complementary DNA resulting in its degradation and thus inhibition of specific gene expression in a process known as RNA interference. Since the discovery of RNA interference, more than 30 clinical trials involving siRNAs have been initiated in a variety of conditions. With regard to PC, a phase 1b clinical trial in a single patient has been reported using TD101, an siRNA that selectively targets the *K6A* mutation, p.Asn171Lys [83]. This left-right comparative study was a 17-week prospective, double-blind, vehicle-controlled trial in a single patient with PC. The siRNA and vehicle were injected intradermally into a small affected area on the foot. It represented the first time in which siRNA has

been used in a clinical setting and also the first time in the skin. The results were promising in that there was a marked reduction in callus formation in the siRNA-treated areas compared to the vehicle-treated areas. There were no adverse side effects, although the injections were painful [83]. This study provided proof of principle that such an approach can work in a dominant negative disorder. Nonetheless, the success of this therapeutic option will depend as much on the delivery system as the efficiency of the siRNA. Indeed, tremendous efforts are being channeled in the development of patient-friendly delivery technologies such as the use of dissolvable microneedle arrays [84].

Another potential therapeutic strategy is the use of pharmacological therapy in PC. In 2009, the macrolide rapamycin was administered to three patients with PC [84, 85]. This stemmed from the observation that rapamycin is able to selectively block translation of mRNAs such as *K6A* that contain a terminal 5′ oligopyrimidine (TOP) tract by altering the activity of mammalian target of rapamycin (mTOR) and therefore inhibiting downstream mTOR signaling. Another study demonstrated inhibition of K6A expression in cultured human keratinocytes, which supported the development of the off-label clinical trial of oral rapamycin in three patients with PC. Rapamycin was administered daily for 15–25 weeks with dosage titration to reach a therapeutic range of 9–12 ng/mL. All three patients reported an improvement in their quality of life and a subjective reduction in their plantar pain. Only one patient reported a reduction in her plantar keratoderma. However, the study had to be discontinued because of side effects including diarrhea, aphthous ulcers, gastrointestinal distress, loss of appetite, and acneiform follicular eruption [85]. Despite this setback, this study provided evidence that pharmacological modulation of K6A expression may be useful as a therapeutic strategy in PC and that the identification of safer but similarly related drugs might be an attractive option for this debilitating disease. The recent discovery that statins are able to downregulate *K6A* promoter activity and protein expression [7] may enable the use of existing and hopefully inexpensive drugs to treat PC. Using small-molecule library screening, nine molecules were identified to be able to inhibit *K6A* promoter activity by more than 50 %. Of these, one molecule called compactin was found to be the precursor to the cholesterol-lowering statin class of drugs, which is in widespread clinical use. This led to the subsequent observation that simvastatin and several other statins, such as pravastatin, fluvastatin, lovastatin, and mevastatin, can inhibit *K6A* promoter activity and protein expression through a mechanism that involves inhibition of the mevalonate/cholesterol biosynthetic pathway rather than an off-target effect [7]. Open-label clinical trials of statins in patients with PC identified through the International Pachyonychia Congenita Research Registry are in progress.

11.2.6 Emerging Therapies for Hypohidrotic Ectodermal Dysplasia

Hypohidrotic ectodermal dysplasia (HED) (OMIM 305100) is the most common form of ectodermal dysplasia. HED is characterized by the abnormal development of ectodermal structures resulting in impaired sweating, hypotrichosis, and abnormal or missing teeth [86]. HED can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner. X-linked HED, the most common type, results from mutations in the *EDA1* gene which encodes ectodysplasin [87, 88]. Mutations in the *EDA receptor* (*EDAR*) and *EDAR-Associated Death Domain* (*EDARADD*) genes result in autosomal recessive and dominant forms of HED, respectively [89–91]. The human X-linked HED has a murine counterpart called the Tabby mouse, which results from mutations in the murine homolog of *EDA1* [92]. The availability of this mouse model has permitted several elegant phenotypic reversal experiments that may prove beneficial in the treatment of the human form of X-linked HED. In 2003, Gaide and co-workers demonstrated that the short-term intravenous

administration to pregnant Tabby mice of a recombinant EDA protein, consisting of an Fc portion of human immunoglobulin that would allow transplacental transfer into the affected fetus, permanently rescued the Tabby phenotype in the offsprings. Interestingly, these mice were also able to develop normal sweat glands postnatally [93]. Since the sequence of developmental events induced by EDA is similar in humans, it is conceivable that recombinant EDA protein therapy might be a feasible option to treat affected fetuses with HED. While this approach has its merits, one counterargument is that it does not reflect the real-life clinical situation, since most affected individuals with HED are diagnosed postnatally. In 2007, dogs with X-linked HED treated postnatally with recombinant EDA showed almost complete improvement in their adult dentition but no improvement in hypotrichosis. Interestingly, there was some improvement in other clinical features such as lacrimation and degree of sweating [94], findings which have implications for affected neonates.

11.3 Future Directions

The past decade has seen numerous advances in our understanding of the pathophysiology of many genetic skin disorders. This has led to the development and application of several novel therapeutic approaches as discussed in the preceding sections, all of which need to be scaled up to render them more accessible to affected individuals. In addition, alternative approaches are being developed for gene suppression, including spherical nucleic acids (SNAs; spherically oriented siRNA or antisense DNA around a central nanoparticle) and spliceosome-mediated RNA trans-splicing (SMART) therapy, both of which may be useful for the treatment of dominant negative disorders [95–97]. Other possible approaches include polymer nanoneedle-mediated intracellular drug delivery to achieve higher cytoplasmic delivery of drugs such as siRNA with low toxicity [98] and readthrough therapy for genetic diseases caused by premature termination codons such as in xeroderma pigmentosum [99]. Furthermore, induced pluripotent stem cells are being experimentally developed for the treatment of several genodermatoses such as lamellar ichthyosis. These novel concepts hopefully will provide us with different treatment options for the management of these currently incurable and debilitating genetic skin disorders.

Conclusions

The translation of molecular discoveries from the bench to the bedside is often fraught with difficulties resulting in slow progress. However, during the past 5 years, there seems to have been a push towards faster translation, resulting in an explosion of novel but still experimental therapies for patients with genetic disorders. Not all of them will make their way into our therapeutic armamentarium, but they promise to provide hope and symptomatic relief for thousands of patients with rare genetic conditions. Therapeutic advances through induced pluripotent stem technology, revertant cell therapy, and small-molecule drug screening will soon bring beneficial treatments.

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Multisystem Management of Epidermolysis Bullosa

12

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Key Points

- While epidermolysis bullosa (EB) is well known for skin and mucosal fragility, severe forms are effectively multisystem disorders, and their management must include a comprehensive, multisystem approach.
- The extracutaneous systems most likely to be affected include nutrition, the gastrointestinal tract, and hematologic (anemia), musculoskeletal, ophthalmologic, and dental/oral health.
- Additionally, addressing pain, itch, and psychosocial health is important in maintaining good quality of life for patients with severe disease.
- Involvement of and coordination of care with other pediatric subspecialists, social workers and counselors, dedicated nursing staff, and support groups are of great benefit in the care of patients with EB.

Abbreviations

BMD	Bone mineral density
BMI	Body mass index
DEB	Dystrophic EB
DXA	Dual energy x-ray absorptiometry
EB	Epidermolysis bullosa
EBS	EB simplex
Hgb	Hemoglobin
JEB	Junctional EB
NG	Nasogastric
RDEB	Recessive dystrophic EB

Epidermolysis bullosa (EB) is a family of rare, inherited skin disorders characterized by fragility of the skin and mucosa. At least 14 genes have been implicated in the etiology of various forms of EB [1, 2]. The most recent classification system for EB includes four major types determined by the ultrastructural level of blistering in the skin: simplex (EBS, blistering within the epidermis), junctional (JEB, blistering between the epidermis and dermis), dystrophic (DEB, blistering within the superficial dermis), and Kindler

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syndrome (mixed pattern of blistering) [1]. Data from the National EB Registry found the incidence to be ~1 per 50,000 live births when all types are included, and the incidence of the less common but more disabling, recessively inherited forms (such as JEB and recessive dystrophic EB [RDEB]) to be ~1 per 500,000, respectively [3]. The skin and mucosal fragility of EB leads to a range of primary disease manifestations that include blisters, erosions, and in some cases, scarring. In addition, secondary complications in non-cutaneous organ systems are frequently seen in forms at the severe end of the spectrum. While much of what is written about EB focuses on cutaneous aspects and wound management, it must be remembered that the more severe forms of EB, particularly JEB and RDEB, are effectively multisystem disorders, and the management of severe EB must include a comprehensive, multisystem approach. Readers interested in learning about wound care for EB are directed to a comprehensive review by Lara-Corrales and colleagues [4] and consensus guidelines published by Pope and colleagues [5]. Of note, the consensus approach to wound care points out that focusing on wounds alone without considering the EB patient's overall health is likely to lead to suboptimal outcomes [5]. This chapter will discuss a multisystem rubric for managing the complex needs of patients with severe forms of EB. While this approach is most suited for patients with JEB and RDEB, it can be modified to fit the needs of those with other forms of EB as well.

12.1 The Multidisciplinary Model Is Ideal

Severe forms of EB can be complicated by a dizzying array of associated morbidities (see Table 12.1) that require differing skill sets for management. The magnitude (both in number and severity) of health problems seen in severe EB can be overwhelming, particularly for a single health-care provider. It is important to keep in mind that although EB is not curable currently, the goal of treatment is to help patients maintain the highest possible quality of life by minimizing the impact of treatable disease complications.

Table 12.1 Extracutaneous complications of severe EB [6, 7]

Organ system	Manifestations
Mucosal complications Mucosal surfaces may show primary lesions of EB (blisters, erosions), secondary changes such as scarring or granulation tissue, or other complications of the disease	
Ophthalmologic	Blisters, erosions, scarring, pannus formation, dryness, keratitis, ectropion
Otolaryngologic	Hoarseness, stridor (primarily in JEB), glottic or supraglottic stenosis, stenosis of external auditory canal
Gastrointestinal	Blisters, erosions, microstomia, ankyloglossia, esophageal strictures/stenosis, malabsorption, nutritional inadequacy, growth retardation, gastrostomy placement, gastroesophageal reflux, constipation, inflammatory bowel disease, pyloric atresia (with deficiencies in alpha-6 or beta-4 integrin)
Genitourinary, renal	Blisters, erosions, scarring, meatal stenosis/strictures, meatal diverticuli, hypospadias, epispadias, bladder edema, cystitis, reduced bladder capacity, thickening of the bladder wall, bladder exstrophy, ureteral stenosis/strictures, ureteral fibrosis, ureteral reflux with posterior urethral valves, hydronephrosis, glomerulonephritis, renal failure
Non-mucosal complications Most of these complications are multifactorial in nature	
Hematologic	Anemia, thrombocytosis
Musculoskeletal	Osteopenia, osteoporosis, fractures, contractures, pseudosyndactyly, muscular dystrophy (with plectin deficiency)
Dental	Enamel hypoplasia (in JEB), caries
Cardiac [8, 9]	Dilated cardiomyopathy, congestive heart failure
Endocrine	Growth retardation, delayed puberty

A multidisciplinary approach to managing EB can be beneficial to patients and health-care providers, and at some children's hospitals in the

USA, Canada, and abroad, EB patients receive ongoing care in multidisciplinary clinics. As an example, the EB clinic at Children's Hospital Colorado is a monthly clinic that includes pediatricians, dermatologists, dermatology/wound care nurses, anesthesiologists, a geneticist, physical therapist, occupational therapist, nutritionist, and social worker. In addition, designated specialists in dentistry, gastroenterology, and pain management are available for evaluation and treatment, and consultants in other specialties are available as well. Patients see several providers in the clinic, and the providers meet after clinic to coordinate care. In this model, each expert is able to focus on his or her particular area of expertise while working with others to create a comprehensive plan for the patient, and patients are able to have many of their needs addressed during a single trip to the hospital. While we feel this model is ideal, it requires significant investments of time and resources to create and maintain, and it may not be feasible or realistic for those who do not see many patients with EB. For those without a multidisciplinary EB clinic, care for patients with EB can be coordinated by utilizing other pediatric subspecialists and following a few key principles: (1) organize patient management by organ systems, giving systems most likely to develop complications the highest priority; (2) screen for complications using a thorough review of systems and surveillance laboratory tests (see Table 12.2); and (3) communicate directly with consultants about the special needs of patients with EB and advocate for their care.

Table 12.2 Surveillance guidelines for severe EB

Organ system	Monitoring
Cardiac	Consider annual echocardiogram in children ≥2 years
Dental	Dental visits every 3–6 months
Dermatologic	Clinic visits every 3–6 months, including complete skin examinations without bandages to examine for squamous cell carcinoma in all older children, adolescents, and adults
Endocrine/ gynecologic	For delayed puberty: basal serum LH, FSH, estradiol (girls) or testosterone (boys), pelvic ultrasound for girls to evaluate uterine and ovarian development
	Bone age if indicated
Gastrointestinal/ nutrition	Evaluate height, weight, BMI every 3–6 months
	Liver function tests and zinc, selenium, carnitine levels every 6–12 months
Hematologic	Complete blood count, iron studies every 6–12 months (more frequently for patients with severe anemia)
Infectious	Wound cultures for evidence of skin infection
Musculoskeletal	DXA scans annually after age 5–6 years, plain films to evaluate pain
	Bone profile (calcium, phosphate, alkaline phosphatase, 25-hydroxy vitamin D level) every 6–12 months
	Regular follow-up with physical and occupational therapy
Ophthalmologic	Semiannual or annual eye exams
Renal/ genitourinary	Serum urea, creatinine, and electrolytes, blood pressure, and urinalysis every 6–12 months

Modified from Martinez [10]
LH luteinizing hormone, *FSH* follicle-stimulating hormone, *BMI* body mass index, *DXA* dual energy x-ray absorptiometry

12.2 Nutrition

The ongoing demands of skin healing and chronic inflammation increase the nutritional requirements of patients with severe EB. Meeting those demands with adequate calories, protein, and micronutrients is important for optimal wound healing, resistance to infection, and growth and development [11]. This challenge is compounded by difficulties in eating and swallowing due to mucosal disease, as well as possible malabsorption in the gut (see below).

For all children with EB, the simple act of using growth charts to follow weight, height, and body mass index (BMI) cannot be forgotten. Declines in the velocity of weight gain (also reflected as decreasing BMI) signify the patient is not getting adequate calories and need to be addressed promptly. Because the nutritional needs of EB patients are chronic and complex, the ongoing involvement of a nutritionist is critical.

Being proactive about good nutrition should begin at birth. If the oral mucosa is not affected, infants may breastfeed on demand. If there is difficulty with breastfeeding due to erosions of the oral mucosa or a weak suck, however, expressing breast milk or giving formula with a specialized feeder, such as the Haberman feeder, can be helpful. Oral pain control should also be optimized. Breast milk or formula may need to be fortified with additional calories to meet the metabolic needs of the infant, especially if wounds are extensive. In fact, we have found that being proactive about adding additional calories, rather than waiting until infants are having signs of trouble gaining weight, is a better strategy for maintaining adequate growth and weight gain. In rare instances, a soft nasogastric (NG) tube feeding may be used as a temporary intervention to aid in feeding. However, NG tubes should be placed with caution as they may cause trauma to the oral mucosa and esophagus and promote the development of strictures.

Introduction of soft solid foods should begin at 4–6 months of age and advanced slowly as tolerated, although crunchy and sharp foods should be avoided. Patients with severe EB may not tolerate solid foods well due to trauma and scarring of the oral mucosa, and the development of feeding coordination can be delayed. In these cases, the input of an experienced feeding therapist can be invaluable. Many patients remain dependent on calorically dense liquid supplements to meet their caloric needs throughout their life. In devising a dietary plan, aiming to increase protein and energy content without increasing volume of feeds may be better tolerated. A gastrostomy tube is a means to ensure the delivery of nutrition and medications and can relieve stress over oral battles for patients and families. Gastrostomy tubes can be used to meet some, most, or all of a patient's nutritional needs, depending on the ability to take foods by mouth. For instance, some patients use gastrostomy tube feeds to supplement oral intake or to bypass taking medication by mouth [11]. Feeds can be given as intermittent boluses or run continuously overnight.

Daily requirements for vitamins and minerals are likely increased in patients with EB, possibly due to increased utilization for metabolism and wound healing, along with inadequate intake and absorption. It is not uncommon to find patients with low levels of iron, zinc, and vitamin D [12], to name just a few. All infants with EB should be started on a daily multivitamin, ideally with iron. Additional supplements may need to be added based on the results of screening laboratory tests (Table 12.2). In addition to multivitamins and iron, the most common supplements used in our clinic include calcium, vitamin D, zinc, selenium, and carnitine. Zinc is important for adequate immune function, wound healing, and growth. Dividing the dose of zinc to twice daily can sometimes minimize side effects such as nausea and vomiting. Also, as zinc may interfere with iron absorption, administering it at a different time is advocated [11]. Selenium and carnitine deficiencies have been postulated to contribute to the development of dilated cardiomyopathy in patients with RDEB [8].

12.3 Oral and Gastrointestinal Abnormalities

The gastrointestinal tract is likely the most frequently affected extracutaneous site in patients with severe EB, particularly RDEB. Blisters and erosions involve the oral mucosa and esophagus, producing pain and difficulty with swallowing, which can disrupt adequate nutritional intake and impair oral hygiene. In RDEB, lesions heal with fibrosis and scarring, leading to microstomia, ankyloglossia, and esophageal strictures. RDEB patients are also at risk for developing squamous cell carcinomas in the oral mucosa [13], and oral changes must be monitored closely.

Esophageal strictures cause progressive dysphagia, leading to malnutrition, impaired growth, and in some cases aspiration pneumonitis. Signs and symptoms of strictures include difficulty swallowing – first with firm solids, then progressing to softer foods and liquids, pain with swallowing, choking, and vomiting after swallowing. Esophagrams can be used to make the initial diagnosis of esophageal strictures in patients with these symptoms. Most EB strictures occur in the cervical esophagus [14], and radiologists

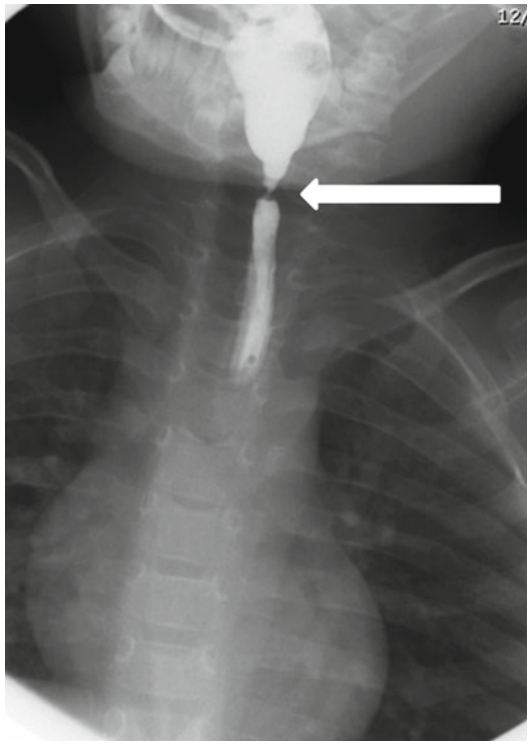

Fig. 12.1 Fluoroscopic esophagram showing a high-grade stricture in the cervical esophagus (*arrow*). This patient underwent emergent esophageal dilation which opened the stricture successfully

should be directed to focus on this anatomical area (see Fig. 12.1). The treatment of choice for strictures is balloon dilatation, guided by fluoroscopy [14] or endoscopy [15]. Relief of symptoms may last for months to years, and when symptoms recur, the procedure can be repeated. Less commonly used surgical treatments for advanced esophageal disease include resection and colonic interposition. Esophageal disease may be exacerbated by gastroesophageal reflux, and symptoms of reflux should be treated aggressively with acid-reducing medications. In addition, agents that coat erosions, such as sucralfate, can be used to minimize the discomfort associated with oral and esophageal disease.

Constipation can be an ongoing problem for patients with EB, regardless of the severity of cutaneous disease. Etiologies can include a component of encopresis – often initiated by painful defecation due to anal erosions, strictures, or fissures and dry hard stools due to decreased food and fiber intake and increased fluid losses through the skin. Fecal impaction and overflow incontinence may occur as a result of chronic constipation. Ensuring that patients have adequate amounts of free water and fiber in their diet is important. In addition, the liberal use of medications that retain moisture in the stool, such as polyethylene glycol, is encouraged. Polyethylene glycol is not habit forming, is tasteless, and odorless when dissolved in liquid, and patients can titrate the amount taken (up to 17 g daily) to maintain soft stools.

12.4 Anemia

Anemia is a common yet often insidious complication of JEB and RDEB. Most patients have some degree of anemia, and hemoglobin levels as low as 5–6 g/dl are not uncommon. Because the decline in hemoglobin levels can be slow, patients often accommodate to the symptoms of fatigue, lack of energy, poor endurance, and loss of appetite. In addition to contributing to poor quality of life, anemia can contribute to poor wound healing.

The pathophysiology of anemia in EB likely includes both iron deficiency and anemia of inflammation (i.e., chronic disease). Patients with EB may lose iron via skin sloughing and bleeding from open wounds. Involvement of the gastrointestinal tract may contribute to iron loss, and oral and esophageal disease can limit the ability to eat iron-rich foods such as meat. In addition, absorption of iron may be compromised by abnormal integrity of the mucosa. Finally, patients with JEB and RDEB can have chronically elevated markers of inflammation, likely the result of ongoing wound healing, which leads to inefficient utilization of iron in hematopoiesis and ineffectiveness of erythropoiesis [16].

Laboratory studies in patients with severe EB typically show microcytic anemia with reduced hemoglobin, hematocrit, and total iron levels. Ferritin levels are not a reliable indicator of iron deficiency in EB as they may be elevated due to inflammation. Any patient with EB with signs or symptoms of anemia (fatigue, pallor, tachycardia,

poor concentration) should have a complete blood count and iron studies performed. Vitamin B12, folate, and other mineral deficiencies should also be evaluated, if indicated. Screening complete blood cell count and iron studies are warranted every 6–12 months in patients with JEB and RDEB 1 year of age and older.

Treating the anemia of EB can be a challenge. Eating iron-rich foods and initiating daily multivitamins with iron at a young age may help to prevent anemia or minimize its severity. Oral iron is indicated for patients with mild anemia (hemoglobin (Hgb) of 10–12 g/dl), but unpalatable taste, gastrointestinal irritation, and constipation may limit compliance, and absorption from the gut may be inadequate. Concurrent supplementation with vitamin C may help improve the absorption of oral iron. Patients with more moderate anemia (Hgb 7–10 g/dl) are unlikely to improve significantly with oral iron, and intravenous iron is indicated to restore iron reserves. Although the published evidence is meager, newer forms of intravenous iron (iron sucrose and ferric gluconate) are well tolerated and improve hemoglobin levels in patients with EB [17, 18]. Optimal protocols of infusion frequency have not been determined, and the rate of dosing will depend on the severity of anemia and availability of intravenous access. Because intravenous-line starts can be difficult in patients with EB, our group relies on a strategy of infusing 5 mg/kg of iron sucrose (maximum dose 300 mg) after patients have procedures that require general anesthesia. The addition of erythropoietin is of unclear benefit in patients without renal disease, and using erythropoietin without iron supplementation is not beneficial. Red blood cell transfusions are indicated for EB patients with severe anemia (Hgb <7 g/dl) or for patients who require a rapid restoration of hemoglobin in order to tolerate surgery or procedures.

12.5 Musculoskeletal

Many of the skeletal abnormalities seen with RDEB are the result of chronic blistering and scarring. Pseudosyndactyly (mitten deformity) is the result of wounds on the hands and feet that heal with cutaneous fusion, scarring, and contracture of the digits. It can be a progressive change that limits the ability to perform daily activities requiring fine manipulation. Similarly, contractures affecting larger joints are not uncommon in EB and can hamper overall movement and the ability to perform activities of daily living. Although scarring may contribute to this process, inactivity due to pain, fear of causing injury, and/or fatigue likely contribute as well. Physical therapists and occupational therapists are an invaluable part of the EB care team. In infancy and early childhood, their involvement helps ensure that gross and fine motor development is progressing as normally as possible. Thereafter, prescribed exercises and adaptive devices can be helpful. Gentle stretching and range-of-motion exercises may help limit the impact of contractures. We have also found the practice of serial casting beneficial for heel-cord tightening. Other options that are not well studied but that could be valuable in the prevention of pseudosyndactyly include separating the digits by individually bandaging the fingers or using customized gloves and limiting contracture by wearing padded splints, particularly at night. Surgical correction of pseudosyndactyly can improve hand function, particularly if performed prior to the development of significant webbing, atrophy of the digital muscles, and partial resorption of the bones [19, 20]. However, patients must be cautioned that surgery is not a cure, that a commitment must be made to intensive postoperative care, and that pseudosyndactyly will eventually recur (Fig. 12.2).

Recent studies have shown that osteopenia, osteoporosis, and pathologic vertebral fractures are common in patients with JEB and RDEB [21–23]. The etiology is likely multifactorial and includes nutritional inadequacy, vitamin D deficiency, inactivity, hormonal abnormalities (e.g., delayed growth and puberty), and chronic inflammation. In a sizable retrospective study, Fewtrell and colleagues described bone density studies in 39 EB patients, showing that compared with healthy peers and those with EBS, RDEB and JEB patients tended to have lower bone mineral

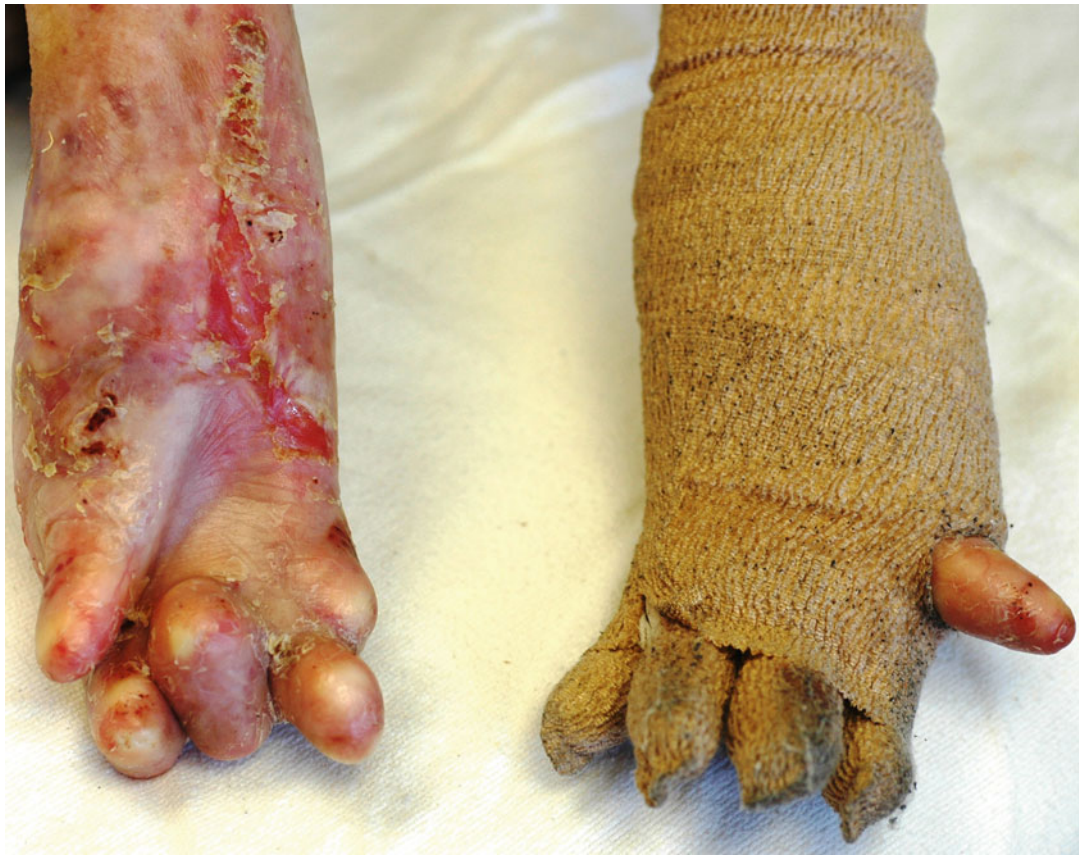

Fig. 12.2 The hands of an adolescent male with RDEB. This individual had prior surgery to correct pseudosyndactyly of both hands, although the right hand shows that contractures and webbing are recurrent. The left hand sports bandaging he devised to preserve separation of the fingers

density (BMD), even after adjustment for small body size [22]. Serologic evidence of bone pathology or vitamin D deficiency was not seen. Bruckner and colleagues performed a prospective study of 20 EB patients and confirmed that patients with severe, generalized RDEB have low BMD (see Fig. 12.3); correlates included short stature, delayed skeletal maturity, reduced mobility, greater extent of skin blistering, undernutrition, anemia, and chronic inflammation [23]. A follow-up study of a subset of these subjects showed that while many gained bone mineral content and BMD over a 1-year period, the gains fell short of expected increases for age, thereby resulting in reduced bone mass [24].

In order to reduce the risk for osteoporosis and pathologic fractures, healthy bone growth should be supported from infancy. Such efforts include optimizing nutrition, supplementing with calcium and vitamin D, and encouraging gentle weight-bearing activity as tolerated. Vibratory platforms, a non-traumatic means of providing mechanical loading to bones, have been found to be helpful in children with developmental disabilities [25] and may have a role in patients with EB. Routine-screening laboratories examining bone health (serum calcium and phosphate, 25-hydroxy vitamin D levels, and alkaline phosphatase) should be checked at least annually. The optimal frequency of dual energy x-ray absorptiometry (DXA) studies for patients with EB has not been determined, but for patients with RDEB and JEB, an initial DXA of the lumbar spine can be obtained when the child is able to hold still for the duration of the study (typically 5–6 years old) and then repeated every 1–2 years thereafter.

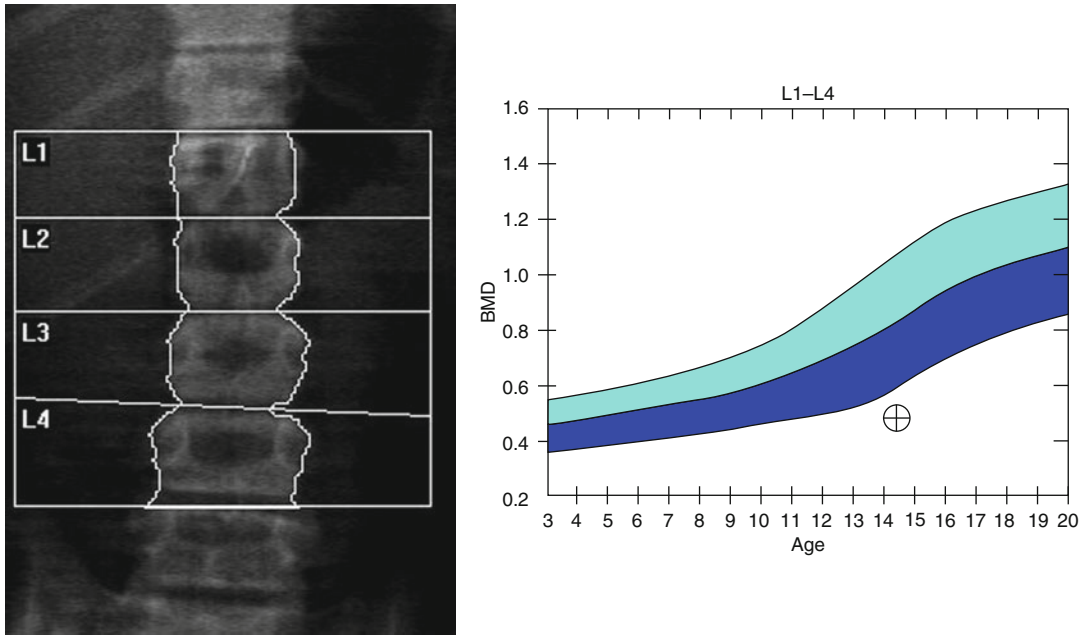

Fig. 12.3 Dual energy x-ray absorptiometry (DXA) study of the lumbar spine from an adolescent male with RDEB. Bone mineral density (*BMD*) of 0.483 g/cm^2 corresponded to a Z score of −2.9, consistent with low bone mass for age

Plain radiographs are used to evaluate for occult or pathologic fractures and are indicated in the evaluation of back pain. The use of bisphosphonates to treat low BMD in children is controversial. These medications should be for the treatment of disabling pathologic fractures and potentially, for disabling bone pain [26–28].

12.6 Dental

All patients with EB are at risk for bullous and erosive oral lesions, with patients with JEB and DEB being more severely affected. Patients with JEB have generalized enamel hypoplasia, leading to an increased risk for dental caries. While patients with RDEB have normal tooth enamel, they are also at increased risk for dental caries due to the difficulty of performing good oral hygiene, the consumption of a highly cariogenic, carbohydrate-rich diet, and from secondary scarring of the oral mucosa that limits normal clearance of food from the mouth [29]. Needless to say, the dental needs of patients with severe EB are high, and a preventive approach to care will help to maintain good oral health.

Best clinical practice guidelines for oral health care in EB patients were recently published [30]. Patients should begin seeing a dentist in the first year of life, primarily for education, and continue follow-up every 3–6 months thereafter. Brushing is possible, as long as modifications are followed for patients with oral mucosal fragility. Toothbrushes should have small heads and soft and short bristles. Rinsing the mouth with water after meals is also suggested. Topical fluoride, chlorhexidine solution, and other non-alcohol-based mouthwashes can also been used to prevent oral disease. Dental care may also include crowns and fillings to maintain the structure and function of their teeth, as well as extractions of severely affected teeth to decrease the incidence of oral infections [29, 30]. General anesthesia performed by a team experienced with EB may be needed for dental restoration.

12.7 Eye

Blisters and erosions can affect the ocular surfaces and eyelid skin, leading to significant pain. In addition, patients with JEB can develop

granulation tissue around the eyes, and patients with DEB are at higher risk for scarring, keratitis, and even visual impairment. Routine ophthalmologic evaluations, particularly for patients with JEB and RDEB, are recommended due to the potential for frequent ocular complications. Regular lubrication of the eye with hydrating gels or ointments is a key component in the prevention of ocular complications. Antibiotic ointments can be used in the setting of corneal erosions; however, if infiltrates are seen in the stroma, a culture should be obtained. Surgical lysis may be required if the patient develops significant adhesions of the eyelid and ocular surface (symblepharon), thereby restricting movement of the eyelids. In cases of advanced disease, limbal or corneal transplants with subsequent systemic immunosuppressive therapy may be considered. Newer techniques include tissue engineering and amniotic membrane transplants that promote reepithelialization of the cornea [31].

12.8 Pain and Itch

Pain impacts most aspects of daily life of patients with severe EB and can be a great source of anxiety. It complicates the ability to eat, bathe, participate in activities, and change wound dressings. Modern wound care dressings, designed to be nonadherent, have vastly improved the discomfort of removing bandages. These bandages also promote comfort by keeping wounds covered and by protecting the skin from additional trauma. Another useful intervention for skin care is the use of pool salts in the bathwater. Adding at least 1 pound of pool salt to the bath approximates normal saline and allows the water to be isotonic with open wounds, thereby decreasing the pain and anxiety patients associate with baths [32]. Shorter-acting narcotics (e.g., hydrocodone/acetaminophen elixir) and/or anxiolytic medications (e.g., lorazepam) prior to baths and dressing changes have also been helpful for some patients. Cognitive behavioral techniques allow patients to cope with the discomfort associated with many of their activities of daily living. A child life specialist can be used in clinic, and child psychologists, counselors, and social workers can work closely with affected families on an outpatient basis to provide distraction techniques and coping mechanisms that can help during dressing changes [33].

In addition to pain, many patients experience significant itching. Moisturizers, low-potency topical steroids, and oral antihistamines can be used to control mild to moderate itch. Some patients have discovered that handheld, vibrating massagers help decrease the sensation of itch and prevent them from scratching their skin, thereby reducing unnecessary trauma. The mechanism of itch in EB is poorly understood, but evidence from burn patients suggests the inflammation of wound healing is a factor, and gabapentin has been reported to be effective in this population [34]. Gabapentin may also have a role in treating pain in EB. We have found that for some of our patients, it has reduced the requirement for additional pain medication.

It must be remembered that for patients with severe EB, optimizing quality of life is the goal of care, and adequately treating pain is important in this regard. Some patients with EB will require daily pharmacologic interventions, such as opioid narcotics. Working with a pain management team skilled in pharmacologic and non-pharmacologic interventions is crucial for these patients.

12.9 Psychosocial Considerations

Many of the interventions made for patients with EB focus on the physical aspects of the disease, but the psychological and social aspects of health need to be kept in mind as well. EB is a demanding disease, and depression and caregiver fatigue are considerations to be addressed as they play a significant role in overall outcomes and quality of life. Patients and families should be referred to the Dystrophic Epidermolysis Bullosa Research Association (DEBRA, http://www.debra.org) or other patient-support organizations. Such groups provide lay information about EB, allow families to connect with others, and advocate for their financial and social needs. Even with insurance,

the financial burden of severe disease can be overwhelming. There are direct costs to consider (physician visits, procedures, admissions to the hospital, prescription medications, wound care supplies, and over-the-counter products such as emollients), as well as the indirect costs of lost time from work, or of giving up work in order to care for a child with EB. Having a skilled social worker as part of the EB team is important to providing support for EB families. Dedicated nurses and support staff who are familiar with EB patients are also invaluable in working with insurance companies and wound care supply companies to ensure patients' needs are being met. Charitable contributions and fundraising are other ways to help families bridge costs that are not covered by traditional sources.

Camps for children with skin disease, such as Camp Discovery, sponsored by the American Academy of Dermatology, can also be a liberating experience for patients and provide respite for parents. Most camps in the USA provide summer experiences. The EB program at Children's Hospital Colorado has sponsored a week-long winter camp, Camp Spirit, with the National Sports Center for the Disabled in Winter Park, Colorado. This camp allows patients with RDEB to participate in winter sports such as skiing. Both types of camp experiences provide an environment that helps children build social skills, friendships, and confidence and often empowers them to see beyond their EB.

12.10 Future Therapies

At this time, EB is incurable, and management centers on the supportive care described above. These interventions offer relief from symptoms and likely improve quality of life, but do not modify the overall course of the disease. New therapies targeting the pathogenesis of the disease are currently planned or under way. Bone marrow transplant has been shown to increase expression of collagen VII at the basement membrane zone and reduces the severity of disease, although there is significant risk with this approach [35]. Grafting autologous, genetically corrected keratinocytes [36] and local replacement of collagen VII [37, 38] are therapies that will hopefully be available on an experimental basis soon.

Conclusion

Severe forms of EB, such as JEB and RDEB, are effectively multisystem disorders, and their management must include a comprehensive, multisystem approach. The extracutaneous systems most likely to be affected are nutrition, the gastrointestinal tract, and hematologic (anemia), musculoskeletal, ophthalmologic, and oral health. In addition, addressing pain and itch and providing psychosocial support are important aspects of maintaining good quality of life for patients with severe epidermolysis bullosa.

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Part V

Other Growths and Tumors

Lymphoproliferative Disorders

13

Christian L. Baum and Dawn M. Davis

Key Points

- Information regarding lymphoproliferative disorders and their management in children is limited, in large part due to the rarity of most conditions in this population. Pityriasis lichenoides is the most common lymphoproliferative disorder affecting children.
- A dermatopathologist experienced in the interpretation of these disorders is imperative, especially if lymphoma is in the differential diagnosis.
- Gold standard treatment regimens are unavailable for these disorders. Treatment is often unnecessary, except for febrile ulceronecrotic Mucha-Habermann disease (FUMHD) and cutaneous lymphoma, where treatment is recommended.
- Treatment of these disorders may decrease symptomatology but is unlikely to alter or shorten the disease course (except for FUMHD). The risk-benefit ratio of the treatment modality and its side effects should be contemplated. Other factors such as disease severity, type of symptomatology, treatment availability, insurance coverage of off-label indications of medications, cost, and provider familiarity with the treatment modality should additionally be considered.

Abbreviations

ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma receptor kinase
bbUVB	Broadband Ultraviolet B
CLH	Cutaneous lymphoid hyperplasia
CTCL	Cutaneous T-cell lymphoma
FUMHD	Febrile ulceronecrotic Mucha-Habermann disease
LyP	Lymphomatoid papulosis
MED	Minimal erythema dose
MF	Mycosis fungoides
MTX	Methotrexate
MZL	Marginal zone lymphoma
nbUVB	Narrowband Ultraviolet B
PCBCL	Primary cutaneous B-cell lymphoma
PL	Pityriasis lichenoides
PLC	Pityriasis lichenoides chronica
PLEVA	Pityriasis lichenoides et varioliformis acuta
PUVA	Psoralen-ultraviolet A
UV	Ultraviolet
UVA	Ultraviolet A

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UVA-1 Ultraviolet A-1
UVB Ultraviolet B

The diagnosis of a lymphoproliferative disorder in a pediatric patient is often difficult. These rare conditions are frequently unrecognized by primary care providers, and access to subspecialty dermatology care is limited for many patients. Upon the establishment of a correct diagnosis, patient and parental concerns escalate while the dermatologist ponders the severity of the disease and the risks and benefits of each possible therapeutic option. Treatment modalities vary from observation with judicious follow-up to antibiotics, immunosuppressants, and phototherapy (Table 13.1). Many variables are balanced when the treatment regimen is enacted, including the following: the general health of the patient, patient and family ability for compliance, insurance coverage of off-label therapeutic medication usages, and geographic ease of in-office therapies and follow-up exams. Regardless of the treatment method chosen, a strong educational foundation for the patient, a patient-provider relationship of trust, and physician comfort with the treatment method(s) used are imperative for optimal patient outcomes. In this chapter, treatment modalities, from simple to complex, for lymphoproliferative disorders such as pityriasis lichenoides, lymphomatoid papulosis, plasmacytoma, and cutaneous lymphoma will be reviewed.

13.1 Pityriasis Lichenoides

Pityriasis lichenoides (PL) is an uncommon skin disease secondary to lymphohistiocytic infiltration of the epidermis and dermis. This leads to spongiosis, parakeratosis, vacuolar interface dermatitis, and dermal edema [1, 2]. Pityriasis lichenoides was once thought to be a form of parapsoriasis, but it is now recognized as a separate entity. Although the disease tends to be abrupt in onset, classification is based upon the characteristics of the individual skin papules. Pityriasis lichenoides et varioliformis acuta, more commonly known as PLEVA, demonstrates a more exuberant infiltration and secondary inflammatory response, evidenced by papules with a characteristic central crust and subsequent pox-like

Table 13.1 Treatments with supporting evidence, including dosing and side effects

Treatment	Dose	Side effects
Pityriasis lichenoides		
Continued observation	–	Monitor for lymphoma transformation
Topical steroids	QD to BID	Striae, atrophy, telangiectasias
Topical calcineurin inhibitors	0.03 or 0.1 % BID	Burning
Oral erythromycin	30–50 mg/kg/day	GI upset, diarrhea
nbUVB	70 % MED, inc 10–20 %/tx as tolerated, 3 days/week	Burning, actinic damage, increased risk of skin cancer
Febrile ulceronecrotic Mucha-Habermann disease		
Oral prednisolone	2 mg/kg daily	Irritability, increased appetite, hypertension, gastritis, osteopenia, aseptic bone necrosis
Methotrexate	Up to 15 mg/week	Immunosuppression, nausea, vomiting; may need folate supplementation
IVIG	2 mg/kg over 48 h	Fever, chills, nausea, vomiting, hypertension, urticaria
Cutaneous lymphoid hyperplasia		
Continued observation	–	Monitor for lymphoma transformation
Oral antibiotics	–	If onset was from infection, appropriate choice and dose for the infectious organism
Lymphomatoid papulosis		
Halobetasol proprionate 0.05 %	BID for 2–3 weeks	Striae, atrophy, telangiectasias
Clobetasol proprionate 0.05 %	BID for 2–3 weeks	Striae, atrophy, telangiectasias

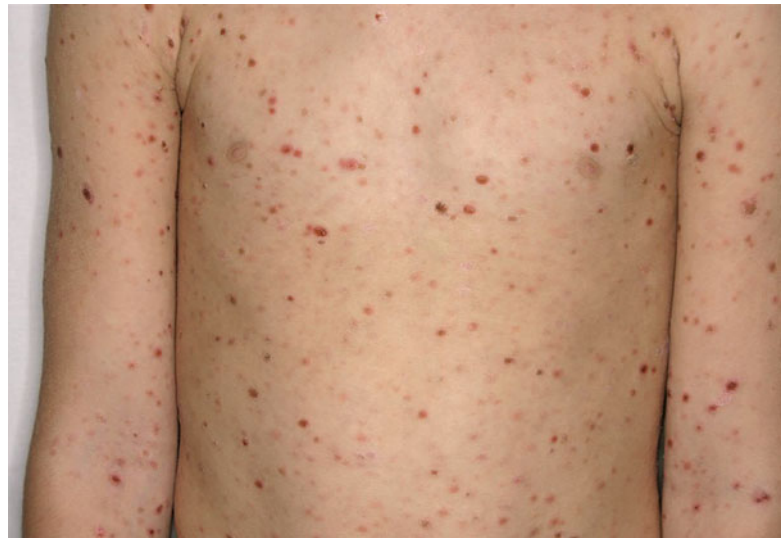

Fig. 13.1 Scattered papules with scale and ulceration in various stages of evolution, characteristic of PLEVA

scarring (Fig. 13.1). When the inflammatory cascade is extreme and leads to skin ulceration and true vasculitis, patients become systemically ill and have a poorer prognosis. This eruption is classified as a subtype of PLEVA named febrile ulceronecrotic Mucha-Habermann disease (FUMHD) in honor of its discoverers. The more subtle but chronic variant is known as pityriasis lichenoides chronica (PLC) because of its banal clinical course and eventual tendency towards regression.

Treatment is often sought for pityriasis lichenoides for numerous reasons. The eruption is usually extensive and unsightly, so even otherwise healthy patients seek options for improvement, even when there is lack of scarring and dyspigmentation. The eruption can last for years, such that patients who try to avoid treatment or wait a prolonged period to consult a dermatologist often want intervention due to frustration and emotional fatigue. PLEVA tends to scar and can become secondarily infected, so active intervention is warranted. The ulceronecrotic form (FUMHD) should be treated to alleviate systemic symptoms and resolve the vasculitis. Deaths have been reported from FUMHD [1, 3], making treatment even more urgent. Lastly, regardless of where in the spectrum of pityriasis the patient's inflammatory reaction lies, clonal T-cell populations are found in pityriasis lichenoides eruptions [1, 2, 4, 5]. This clonality, along with the prolonged natural disease course and secondary inflammatory cascade, argues that transformation to true malignancy is possible [4, 5], which would encourage proactive medical intervention.

When recommending treatment for pityriasis patients, it is important to remember this disease is frequently self-limited, making judgment of clinical efficacy of any modality questionable [1, 4]. However, one large, retrospective study by Ersoy-Evans and colleagues found 77 % of patients had a chronic and relapsing disease course, implying treatment efforts may be unsuccessful regardless of provider and patient efforts [2]. It is generally recommended, even if treatment is not pursued, that all pityriasis patients with active skin lesions seek regular follow-up examinations with a dermatologist because of the risk of malignant transformation [1].

Some patients with minimal disease, or those who are asymptomatic, may require only simple, supportive care. Oftentimes, the frequent application of a benign emollient is all that is necessary for such patients [2]. For patients with pruritus, oral antihistamines [5, 6] and topical tar preparations [2, 6] are helpful in improving the patient's quality of life, but patients should be informed that these do not alter the course of the disease. Since phototherapy has been shown in numerous studies to clear the skin in active pityriasis (as described below),

natural sunlight exposure in moderation should be recommended to patients when possible [2].

Topical steroids are often used as a first-line therapy in patients with pityriasis due to their ease of use, low cost, broad availability, and physician comfort with administration. While their use to alleviate pruritus in PL is known to be helpful [5, 6], their efficacy in disease clearance is debatable [1] to refuted [5]. The most commonly prescribed topical steroid in one large, retrospective review of pediatric PL patients was fluocinolone acetonide 0.025 % ointment [2]. Similarly, topical calcineurin inhibitors have been tried in place of topical steroids in various patients, including tacrolimus 0.03 and 0.1 % ointment BID [1], and are thought by some to be beneficial [5]. Administration of oral steroids is discouraged and considered ineffective [6] except in FUMHD [3, 6], where oral prednisolone at 2 mg/kg is suggested [3].

Oral erythromycin is considered by several authorities to be the true first-line therapeutic choice for pediatric patients with pityriasis lichenoides [1, 2, 6]. Dosing at 30–50 mg/kg/day for several months is typical [2, 4], although Gelmetti et al. found 20–40 mg/kg/day for 1–2 weeks to be "moderately effective" for their patients [7]. The response is marked at 66–87 % of patients [2, 5], but not guaranteed. Resumption at 30–50 mg/kg/day for recurrences is equally successful, with approximately 70 % of patients responding [4]. An alternate strategy entails long-term low-dose erythromycin to maintain remission [5]. Patients with partial improvement are frequently prescribed topical steroids, calcineurin inhibitors [1], or ultraviolet light (natural versus prescription) [6] in addition to the erythromycin to boost clinical improvement.

Alternative oral antibiotics have been sampled over time for pityriasis lichenoides with minimal success. Tetracycline at a dose of 2 g per day has been used in adult patients with positive outcomes, according to Bowers and Warshaw [1]. Some adults may require a maintenance dose of 1 g per day to maintain skin clearance. Although tetracycline is not traditionally recommended for the pediatric PL population, Lam and Pope do mention it as a therapeutic option in older children [5]. Two case reports have described clinical improvement of PLEVA in association with oral azithromycin [8, 9]. Other antibiotics, including cephalexin, amoxicillin-clavulanic acid, and cefaclor, do not show much benefit and are not recommended [2].

Phototherapy is a popular and effective treatment regimen for pityriasis lichenoides. Light treatment is considered second-line therapy for PL patients after oral antibiotics [1, 6]. Ultraviolet (UV) light, when administered in a controlled manner, is a safe and generally well-tolerated method for decreasing skin inflammation in the epidermis and dermis [10] and thus is used by dermatologists to alleviate such skin conditions as psoriasis, atopic dermatitis, vitiligo, and generalized pruritus[11]. But the side effects of UV exposure are well known and are accelerated in patients who receive the concentrated UV light via a light unit and should not be dismissed. These include carcinogenesis of the skin (actinic keratoses, squamous cell carcinomas, basal cell carcinomas), premature aging, lentigo development, fine wrinkling, and telangiectasias [11]. Patients should be educated about these side effects, and the risk-benefit ratio of treatment should be weighed against the burden of disease.

The most readily available phototherapy modality is narrow band ultraviolet B (nbUVB). Narrowband UVB is also the preferred light treatment method, relative to broadband UVB (bbUVB), because it is less erythemogenic and generally more effective at clearing skin disease [11]. Patients are treated three times a week, at a dose of 70 % of the minimal erythema dose (MED). Each UV dose is then increased by 10 % per treatment if the patient did not develop erythema from the prior dose. Pasic et al. used this protocol, along with nightly application of low-potency topical steroids, on their PL cohort with mixed success. For their patients with PLC, one-third had at least 90 % skin clearance, and another third had greater than 70 % skin clearance. Patients required a range of 14–24 light sessions, with a cumulative dose of 3–11 J/cm^2. No children developed side effects or required maintenance therapy. Unfortunately, PLEVA patients in this study showed no benefit (but did not have side effects). Ersoy-Evans and colleagues [12] used a similar protocol on five PLC patients,

using nbUVB 3 days a week. Initial UV dose was again 70 % of MED, but increases of 20 % per session were performed if tolerated. All five patients in this study noted skin clearance in an average of 22 sessions. Other dermatologists have found UVB treatment to decrease symptomatology and the number of acute flares but not alter disease course [7].

Ultraviolet A (UVA) light is a longer wavelength of light, with subsequent deeper penetration of the skin to the dermis. Its availability is limited, and provider comfort with administration varies widely. The addition of a topical or oral psoralen, known as PUVA, improves efficacy and is thought to be superior to UVA alone. The reported use of PUVA on pediatric patients for pityriasis lichenoides is scant. One author found it effective in 20 % of patients who used it, but the regimen was not defined [4]. The administration of topical PUVA for children with atopic dermatitis or scleroderma has been reported as successful [11]. All patients were hospitalized for monitoring and received topical PUVA 4 days a week (Monday, Tuesday, Thursday, Friday). The initial dose was 0.5 J/cm^2 UVA, and this dose was held for four treatments. Then doses were increased every third treatment as tolerated by 0.5 J/cm^2 to a maximum dose of 5 J/cm^2 UVA. The validity of this protocol for PL patients is unknown. Ultraviolet A1 (UVA-1) (340–400 nm) light therapy has been reported to improve pityriasis lichenoides in adults [10]. Eight adult patients received "medium-dose" UVA-1 of 60 J/cm^2 5 days a week (Monday through Friday), for an average of 18 treatments (range 10–27). All three PLEVA patients had disease remission and no relapses. Three PLC patients cleared, and the remaining two patients had 25 % residual involvement. Four of the five PLC patients flared within months of light discontinuation but responded to repeat treatment. The validity of this protocol and its practical application to pediatric patients is limited by the lack of pediatric use in the literature and the extreme scarcity of UVA-1 phototherapy units in the USA and elsewhere.

Methotrexate (MTX) administration for pityriasis lichenoides patients is suggested for special circumstances, including in children. While this antimetabolite drug is not recommended for young children or as first-line therapy [2], its utility in treating refractory or severe febrile ulceronecrotic Mucha-Habermann disease is well established [1, 3, 4]. The dose range for adults with FUMHD is 7.5–20 mg per week [1]. One toddler with life-threatening FUMHD was treated with 15 mg per week of MTX after failing multiple therapies, with improvement in 2 weeks [3]. This child was unable to taper off the MTX completely, requiring a maintenance dose of 5 mg by mouth weekly. Use for PLEVA and PLC has mainly consisted of several adult cases, but with benefit [1].

Assorted other medications and treatment methods have been attempted by providers for pityriasis lichenoides, but with minimal success. This includes dapsone [1, 3], cyclosporine [13], griseofulvin, penicillin, topical mechlorethamine, topical carmustine, grenz ray, electron beam, and X-ray therapy [6]. Refractory FUMHD in children has been treated with IVIG at 2 g/kg over 2 days with limited improvement [3].

13.2 Cutaneous Lymphoid Hyperplasia

Cutaneous lymphoid hyperplasia (CLH) is a reactive lymphoproliferative disorder with an interesting evolutionary nomenclature and challenging clinicopathologic features that may mimic cutaneous lymphoma. Considered in this regard as a "pseudolymphoma," it has also been referred to as lymphocytoma cutis, lymphadenosis benigna cutis, and pseudolymphoma of Spiegler and Fendt [14]. In adults, CLH generally occurs as reddish to violaceous, indurated, solitary or grouped, asymptomatic papule(s)/nodule(s) on the head and neck (Fig. 13.2). Reports of CLH in children are rare and have included both solitary lesions on the scalp [15] and, in a case resulting from feline scratches, multiple subcutaneous nodules [16]. Several entities have been associated with the development of this condition in adults, including tattoos [17], vaccination [18], chemotherapy [19], gold earrings [20], phenytoin [21], cobalt [22], and arthropod bites [23]. In areas such as Europe where *Borrelia burgdorferi* is endemic, tick bites have been reported as the most common cause of lymphocytoma cutis. In these

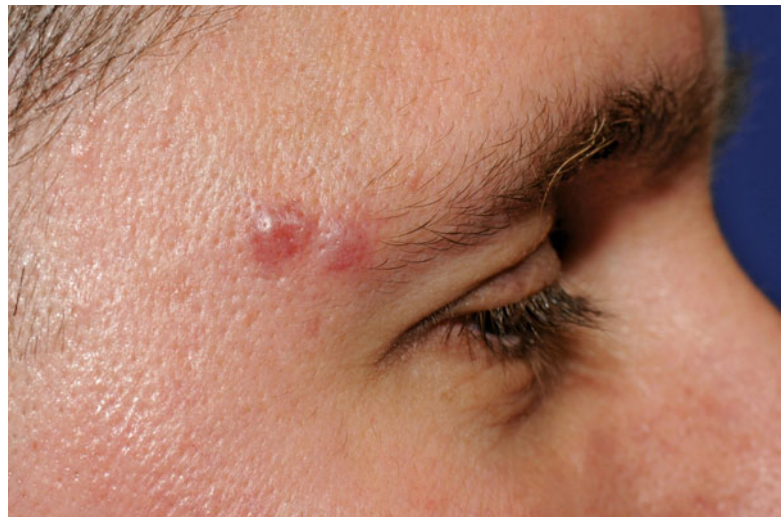

Fig. 13.2 Red solitary papule on the face, after arthropod bite, of cutaneous lymphoid hyperplasia

cases, serologic tests and PCR from skin biopsies may help narrow the diagnosis.

The histopathology of cutaneous lymphoid hyperplasia is generally described as a top-heavy infiltrate with a "grenz zone" consisting of a mixed lymphoid population commonly demonstrating lymphoid follicles with germinal centers. On histopathologic grounds alone, these features may be suggestive of a malignant B-cell lymphoma. Despite prior and ongoing studies to reliably distinguish these benign and malignant processes, no reliable histologic or molecular markers have been identified, and a discussion of these investigations is beyond the scope of this text. Thus, the greatest challenge associated with CLH often lies in the clinicopathologic correlation between the clinician and pathologist in order to render an accurate diagnosis and thereby avoid any unnecessary systemic therapy.

The natural history of CLH most often follows an indolent course and often results in spontaneous resolution. However, cases of malignant progression have been described [24–26]. Therefore, a necessary component of a treatment plan for this condition is close, long-term follow-up. When there is a clear association between an infectious cause, such as *B. burgdorferi* [27] or *Bartonella henselae* [16], appropriate antibiotics should be initiated. In cases where watchful waiting for spontaneous resolution is not feasible, one may consider either surgical excision or medical treatment with either intralesional or topical corticosteroids.

13.3 Cutaneous B-cell Lymphoma

Primary cutaneous B-cell lymphoma (PCBCL) is a form of non-Hodgkin lymphoma that has been recognized and classified by the World Health Organization- European Organization for Research and Treatment of Cancer (WHO-EORTC) classification of cutaneous lymphomas [28]. Within the larger category of PCBCL are subtypes that may be categorized by indolent behavior (primary cutaneous marginal zone B-cell lymphoma (MZL) and primary cutaneous follicle center lymphoma) or intermediate clinical behavior (primary cutaneous diffuse large B-cell lymphoma, leg type; primary cutaneous diffuse large B-cell lymphoma, other; primary cutaneous intravascular large B-cell lymphoma). It is estimated that PCBCL accounts for about 20 % of all primary cutaneous lymphoma [28, 29]. Occurrence of PCBCL in the pediatric population is rare. To date, the largest report of cutaneous lymphoma in children describes data collected over a 42-year period. A total of 69 patients were described, including 14 (20 %) with PCBCL. Although data are limited, it appears that most cases of pediatric PCBCL are characterized by indolent behavior, although aggressive forms have been reported [30].

The clinical lesions of PCBCL tend to be persistent, reddish to violaceous, solitary or localized groups of papules or nodules. A biopsy of the lesions will demonstrate a lymphoid infiltrate that raises a differential diagnosis of a reactive lymphoid process such as cutaneous lymphoid hyperplasia or B-cell pseudolymphoma. Indeed, retrospective analysis of cases originally diagnosed as cutaneous lymphoid hyperplasia has reclassified some lesions as PCBCL, many of which were marginal zone lymphoma [31, 32]. Thus, potential cases of pediatric PCBCL should be evaluated by a pathologist with experience in cutaneous lymphoma.

Due to the rare nature of pediatric PCBCL, data regarding management are limited to small case series and case reports or extrapolated data from the adult population. For cases of follicle center cell lymphoma and marginal zone lymphoma with an estimated 5-year survival rate of 95–99 % in adults, a cautious and balanced approach with close follow-up is warranted. For solitary lesions associated with indolent clinical behavior, surgical excision, intralesional corticosteroid injections, or radiotherapy may be considered [33, 34]. Topical nitrogen mustard application has been reported for diffuse cutaneous lesions with good results [33], and a recent report described the successful use of intralesional rituximab for MZL [35]. Since MZL in particular has been associated with *B. burgdorferi* infection, some encourage a trial of antibiotic therapy for this diagnosis in endemic areas [30].

Data regarding the management of aggressive forms of PCBCL are sparse and therefore best extrapolated from the adult population. For solitary or isolated lesions of diffuse large B-cell lymphoma, leg type, radiotherapy is considered first-line treatment. In cases of disseminated lesions or other aggressive forms of PCBCL, polychemotherapy or systemic rituximab are administered [34].

13.4 Cutaneous T-cell Lymphoma

Cutaneous T-cell lymphoma (CTCL) is also rare in the pediatric population, but it is the most common form of cutaneous lymphoma in children. The incidence of CTCL is approximately 0.35 per 100,000 persons per year, and pediatric cases are estimated to account for 4–11 % [36]. The WHO-EORTC classification for cutaneous lymphomas recognizes a number of different forms of CTCL, the most common of which is mycosis fungoides (MF). Although the data in these reports primarily reflects the adult population, a similar pattern has been reported in the pediatric population. The largest retrospective study to date included 69 pediatric patients with cutaneous lymphoma, including primary and secondary cutaneous involvement. In this series, the majority (75 %) of cases were CTCL and the most common form was mycosis fungoides (34.8 %), followed by the CD30+ cutaneous lymphomas (LyP and anaplastic large cell lymphoma (ALCL)) [30]. Other forms of CTCL such as subcutaneous "panniculitis-like" T-cell lymphoma and NK-T-cell lymphoma are exceedingly rare in children, and data are limited to single case reports and very small series.

13.4.1 Mycosis Fungoides

Mycosis fungoides usually manifests as scaly patches or plaques (Fig. 13.3) but may progress to erythroderma or tumors. Staging systems are based on the degree of body surface area involved. A recent report by the International Childhood Registry of Cutaneous Lymphoma corroborated previous data suggesting that most children with MF present at an early age (median age, 8 years) with early-stage disease (95 % in stage IA and IB) and a higher tendency to manifest with hypopigmented lesions compared to adult cohorts [37]. Indeed, the authors reported that 59 % of their patients presented with hypopigmented MF. This apparent tendency should no doubt influence the clinical differential diagnosis associated with hypopigmented dermatoses in children and may account, at least in part, for an underreporting of the true incidence of MF in children.

It is well established that a firm clinicopathologic diagnosis of MF may take several months, if not years, from the onset of lesions. This delay may reflect an evolution of clinical disease as

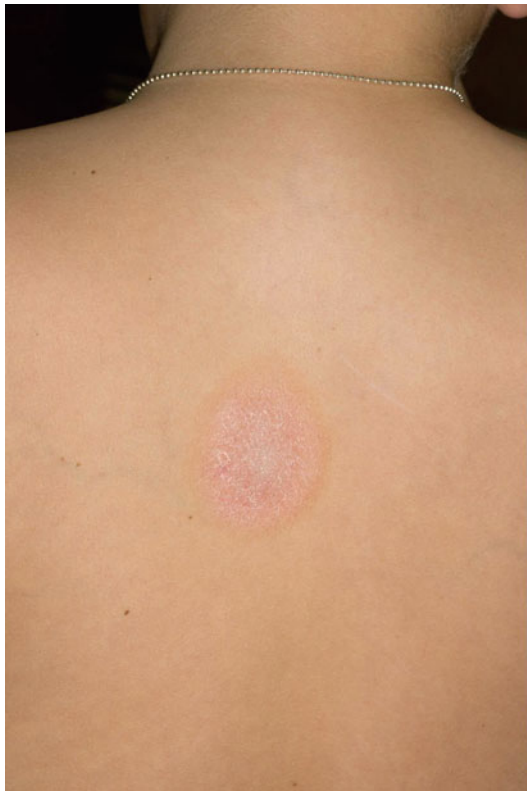

Fig. 13.3 Scaly, hypopigmented patch of mycosis fungoides on the trunk

well as of histopathologic features. Certainly other more common chronic dermatosis such as eczematous dermatitis or psoriasis may be favored on clinical grounds, and often a biopsy is not obtained due to a reasonable clinical diagnosis and/or reluctance to biopsy a young patient. A high index of suspicion, which may be strongly influenced by an inadequate response to appropriate treatment, may prompt a biopsy. Even so, multiple biopsies over time may be necessary before seeing hallmark histologic and molecular features such as atypical lymphocytes along the dermal-epidermal junction with epidermotropism, Pautrier's microabscesses, supportive immunohistochemical staining, and a monoclonal T-cell gene rearrangement.

Currently there are no guidelines for the work-up or management of pediatric patients with MF or other forms of CTCL. Suggested work-up, in addition to a complete physical examination, may include a complete blood count, chemistry panel, LDH, serologies (for Epstein-Barr virus, human T-lymphotropic virus (HTLV)-1, HTLV-2, human immunodeficiency virus), chest X-ray, and ultrasound of the abdomen and pelvis to look for internal involvement [5, 37].

The natural course of mycosis fungoides in the pediatric population is not fully characterized. This ambiguity adds to the challenge of developing a management plan, particularly when coupled with the data in adults that show no survival benefit from treatment [38]. Thus, a balanced approach that considers the chronic nature of the disease, practicality of treatment, cost, and side effects is encouraged. One institution in North America with experience in treating CTCL describes the use of topical steroids, topical retinoids, or imiquimod for patients with stage IA disease (<10 % of skin covered with papules, patches, or plaques) and UVB/PUVA for patients with stage IB (≥10 % of skin covered in papules, patches, or plaques) or IIA disease (≥10 % of skin covered in papules, patches, or plaques and clinical, but histologically normal, lymphadenopathy) [5]. For patients with early-stage MF, the consensus recommendations from the Joint British Association of Dermatologists and the United Kingdom include emollients with or without the addition of a moderate potency topical steroid [39]. Other topical treatment options have been reported in case reports and small case series or extrapolated from adults and include topical nitrogen mustard [40, 41], bexarotene, and BCNU (bis-chloroethylnitrosourea or carmustine) [39]. The use of these topical therapies may be limited by cost, availability, and irritation dermatitis. Radiotherapy or total skin electron beam has been described in the patient population [41], but the long-term side effects from radiation must be considered. For more advanced disease, more aggressive treatment options have been described, including methotrexate, CHOP chemotherapy, extracorporeal electrophoresis, interferon alpha, and autologous peripheral blood stem cell transplant [41].

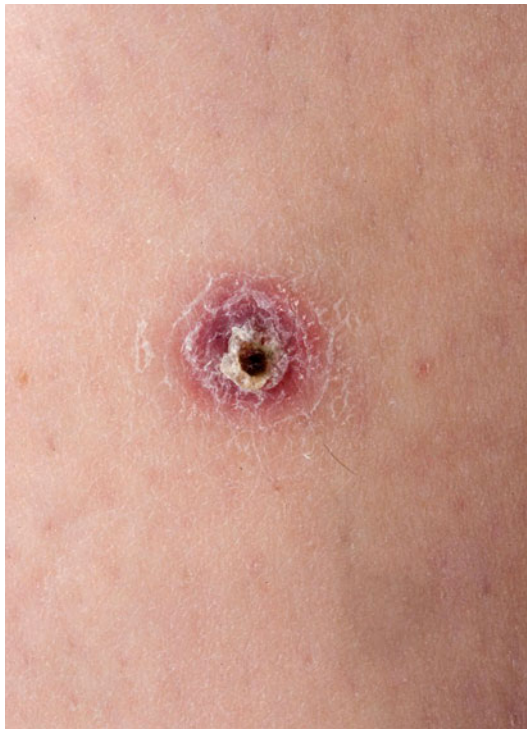

Fig. 13.4 Ulcerated, crusted papule characteristic of LyP

13.4.2 Primary Cutaneous CD30+ Lymphoproliferative Disorders

This subset of CTCL as recognized by the WHO-EORTC classification of cutaneous lymphomas includes lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large cell lymphoma (ALCL). According to the largest series of pediatric cutaneous lymphoma to date, 34.7 % are represented within the category of primary cutaneous CD30+ lymphoproliferative disorders [30]. Within this category, 54 % were diagnosed with ALCL and the remaining 46 % with LyP.

13.4.2.1 Lymphomatoid Papulosis

Lymphomatoid papulosis is an uncommon skin disease consisting of fluctuating eruptions of papulonecrotic nodules that resolve with punctate scarring (Fig. 13.4). Lymphomatoid papulosis histologically appears concerning, with CD30+ T-cell infiltration of the dermis and central ulceration. It is reported to have an associated lymphoid malignancy in about 20 % of adult patients [42, 43]. LyP is rare in children, where the malignancy potential is unknown [43, 44]. Due to its rarity, the diagnosis is often delayed until an evaluation by a dermatologist, increasing patient and parental anxiety. This factor, along with the potential for scar formation and malignancy, instigates therapy.

Some experts argue the main rationale for therapy of LyP is indeed parental anxiety [44] because treatment is not thought to alter disease course or reduce the rate of subsequent malignancy [45]. Also, current options only provide partial or temporary improvement [44]. Treatment should be sought to relieve symptoms such as itch or to address cosmetic concerns of scarring [43, 44]. Spontaneous remission of LyP in the pediatric population is quite common and swift, noted in 88 % of patients within 3 months of disease onset in a large study by Nijsten and colleagues [43]. This supports the motivation for clinical observation and psychosocial support for the patient and family in lieu of activate intervention.

Topical corticosteroids have been used in the treatment of pediatric lymphomatoid papulosis with mixed benefit. Some studies used topical steroids as the first-line treatment option [42, 43]. The range of clinical improvement was broad, and efficacy was consistently inferior to UV light when used. In contrast, Paul et al. report near-complete resolution of LyP flares in three children using strong topical corticosteroids as monotherapy [45]. Halobetasol proprionate 0.05 % ointment or clobetasol proprionate 0.05 % cream was applied to all nodules twice daily for 2–3 weeks. Thereafter, remaining lesions were treated weekly with a "pulse application" of the steroid, with application every 12 hours for three doses. Only a few persistent, ulcerated nodules remained, which successfully cleared with intralesional triamcinolone injection. The protocol was repeated during flares with consistent remission.

Ultraviolet light therapy is currently the most useful and reliable treatment modality for pediatric LyP in the literature. Although it is often considered a second- or third-line therapy after

topical steroids and oral antibiotics [43], some practices have recognized its efficacy and have made it the treatment option of choice if treatment is pursued [42]. Natural sunlight in moderation was noted to improve lymphomatoid papulosis in 19 of 35 patients in the Nijsten et al. cohort but was found to exacerbate the disease in one patient as well [43]. In this same study, eight patients received prescription UVB phototherapy, with clearance in seven; this proved to be more effective than antibiotics or topical steroids. The superiority of prescription ultraviolet light to other treatment methods was reiterated in a study by de Souza and colleagues as well [42]. The protocol for ultraviolet light administration in the phototherapy center was not delineated in either study. Wantzin and Thomsen have reported benefit of PUVA administration in adult patients with LyP refractory to various medications [46]. The frequency and dosage of light differed for each patient. Extrapolation of these findings to pediatric patients is dubious at best.

Numerous other medications for LyP have been tried unsuccessfully. Oral antibiotics, especially erythromycin and tetracycline, have been used in pediatric LyP patients as a corollary to its utility in pityriasis lichenoides (author's personal opinion). Unfortunately, despite their practicality, their use in LyP [42, 43, 45] does not alter disease progression or recovery and should be considered of no benefit [45]. Low-dose methotrexate for these children may accelerate skin clearance, but its use is cautioned due to the benign nature of the disease and the risk-benefit ratio of an immunosuppressant drug at a young age [43]. Other treatments including intravenous acyclovir, topical carmustine, intralesional interferon alpha, radiation, and serial surgical excision should be considered suboptimal and unrealistic [45].

13.4.2.2 Primary Cutaneous CD30+ Anaplastic Large Cell Lymphoma

In contrast to LyP with its characteristic grouped, waxing and waning papules, primary cutaneous CD30+ ALCL tends to present with solitary nodules. Reports in children are exceptionally rare and the natural history of the disease, therefore, is not completely understood in this population. However, this entity is associated with a favorable disease-specific survival rate of 95 % in the adult population [28].

As with other forms of cutaneous lymphoma, a biopsy is required for diagnosis and should be reviewed by a pathologist experienced in the interpretation of cutaneous lymphomas. The histology demonstrates a diffuse, dermal infiltrate consisting of large, atypical lymphocytes that stain with CD30. Critical to the work-up for these specimens is the application of ALK (anaplastic lymphoma receptor kinase) in order to rule out the potential of secondary cutaneous involvement from nodal anaplastic large cell lymphoma, which would demonstrate positive staining for ALK. Thorough clinicopathologic correlation is necessary to ensure the correct diagnosis and avoid potential misinterpretation as a nodal lymphoma.

Treatment of primary cutaneous ALCL may include simple excision. Radiation may also be considered, but as mentioned earlier, it must be considered in the context of long-term side effects [30]. Other treatment options that have been described with success in pediatric patients include low-dose methotrexate and local radiation [47], topical steroids, and multi-agent chemotherapy [48].

13.4.3 Other Forms of CTCL

Together, MF and the CD30+ lymphoproliferative disorders account for approximately 70 % of pediatric primary cutaneous lymphoma [30]. Case reports and small series have described other forms of CTCL in the pediatric population. These include aggressive entities such as subcutaneous panniculitis-like T-cell lymphoma and cutaneous gamma/delta T-cell lymphoma, which often require systemic chemotherapy or stem cell transplant [49]. A recent report described bexarotene as a potentially useful option as well [50]. Other entities such as primary cutaneous CD4+ small-/medium-sized pleomorphic T-cell lymphoma have been associated with a variable but generally favorable prognosis following treatment with excision, radiation, or topical steroids [51, 52].

Conclusion

The spectrum of lymphoproliferative disorders in the pediatric population includes indolent, banal conditions such as pityriasis lichenoides chronica as well as potentially life-threatening malignancies such as subcutaneous panniculitis-like T-cell lymphoma. Furthermore, the armamentarium for treating these conditions is expansive, as it ranges from observation to multi-agent chemotherapy and stem cell transplantation. An appropriate coupling of a diagnosis with a management strategy requires synthesis of a number of variables in order to optimize disease control, address parental expectations, and minimize potential long-term sequelae of the disease and therapy.

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Pediatric Mastocytosis

14

Julianne Mann, Sabra Leitenberger, and Alfons Krol

Key Points

- Children with mastocytosis usually have cutaneous disease only and a benign, limited course
- Management of cutaneous mastocytosis requires a multipronged approach, including thorough education of the family and other care providers, avoidance of triggers, development of a treatment plan for acute exacerbations, and consideration of chronic suppressive therapy for symptomatic patients
- Many cases of cutaneous mastocytosis can be managed conservatively, but systemic treatment may be needed if diffuse skin disease, multiple bullae, and/or significant local or systemic symptoms (e.g., wheezing, flushing, diarrhea)
- Bone marrow biopsy and further screening for systemic mastocytosis are not routinely recommended, but are indicated for cases with severe, recalcitrant symptoms that could be related to mast cell activation (abdominal pain, bone pain, flushing, pruritus, change in mentation), abnormality of complete blood cell count, organomegaly/lymphadenopathy, persistent skin lesions after puberty, significantly elevated tryptase level (>20 ng/mL), and/or persistently elevated tryptase level (above 15 ng/mL) after puberty
- KIT mutational analysis should be considered if symptoms or signs of concern for systemic mastocytosis are present. KIT mutation status may influence choice of specific therapy

Abbreviations

SCORMA SCORing MAstocytosis index

Mastocytosis is a group of rare, heterogeneous, myeloproliferative disorders characterized by abnormal mast cell accumulation in one or more organs. Mast cells are bone marrow-derived CD 34+ leukocytes which circulate in low numbers in the peripheral blood and mature in tissues in response to local growth factors and cytokines [1]. They survive for months to years in peripheral tissues and can be found in the physiologic state in the skin, the gastrointestinal and genitourinary tracts, respiratory mucosa, adjacent to blood and lymphatic vessels, and in proximity to peripheral nerves [2]. Ehrlich named them "Mastzellen" in

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1977, which means well-fed cells, because their cytoplasm is filled with granules [3]. These granules contain histamine, heparin, tryptase, prostaglandins, nitric oxide, endothelin, proteases, granulocyte-macrophage colony-stimulating factor (GM-CSF), and various cytokines which are critical to their role in inflammatory and allergic reactions. Mast cells express high-affinity immunoglobulin E (IgE) receptors and are the only terminally differentiated hematopoietic cells that express the stem cell factor receptor KIT, also known as c-kit. Release of mast cell granules may be triggered by (1) chemical toxins, venoms, and proteases, (2) endogenous proteases and proteins derived from other immune cells, and (3) antigens binding to the Fab portion of IgE receptors [2].

14.1 Epidemiology

Mastocytosis affects children approximately twice as often as adults [4]. Onset of disease in children typically occurs early, with 87 % of children presenting before 6 months of age [5]. Mastocytosis may be limited to the skin (cutaneous mastocytosis) or may involve the gastrointestinal tract, bone marrow, spleen, liver, and lymph nodes (systemic mastocytosis). Cutaneous mastocytosis is most commonly seen in children and usually has a benign and transient course. Systemic mastocytosis may be associated with multiorgan failure and shortened lifespan and is typically a disease of adults, although fatalities have been reported among children [6, 7]. Mutations found in codon 816 of exon 17 in the KIT gene occur in 86 % of patients with pediatric mast cell disease [8, 9].

14.2 Classification

The 2001 World Health Organization (WHO) classification of mastocytosis delineates the two major forms of mastocytosis: cutaneous and systemic [10]. Cutaneous mastocytosis is diagnosed based on the presence of typical cutaneous lesions and histology confirming the presence of mast cell aggregates in the skin. Three types of cutaneous mastocytosis have been delineated: (1) maculopapular type (47–84 % of childhood mastocytosis), of which urticaria pigmentosa and telangiectasia macularis eruptiva perstans are subtypes and which may present as numerous reddish-brown macules, multiple red-brown nodules, larger hyperpigmented patches and plaques (Fig. 14.1), or subtle telangiectatic patches; (2) diffuse cutaneous mastocytosis (1 % of childhood mastocytosis), which is rare and is characterized by diffuse erythema and peau d'orange consistency skin; and (3) solitary mastocytoma of the skin (6–20 % of childhood cases, Fig. 14.2) [5, 7]. Solitary mastocytomas are most often located on the trunk, head, or neck [5].

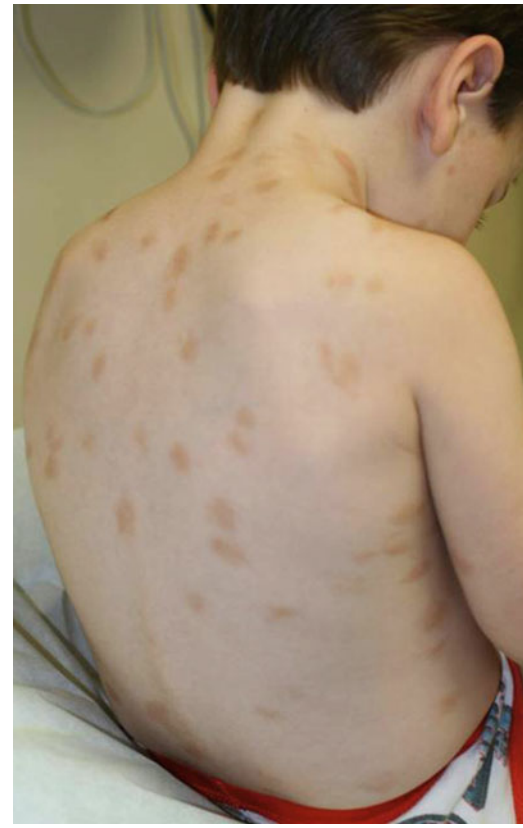

Fig. 14.1 Urticaria pigmentosa in a school-aged child

The major criterion for the diagnosis of systemic mastocytosis is demonstration of multifocal dense aggregates of mast cells in the bone marrow and/or other extracutaneous organs that are tryptase positive on immunohistochemical staining. Minor criteria include (1) detection of

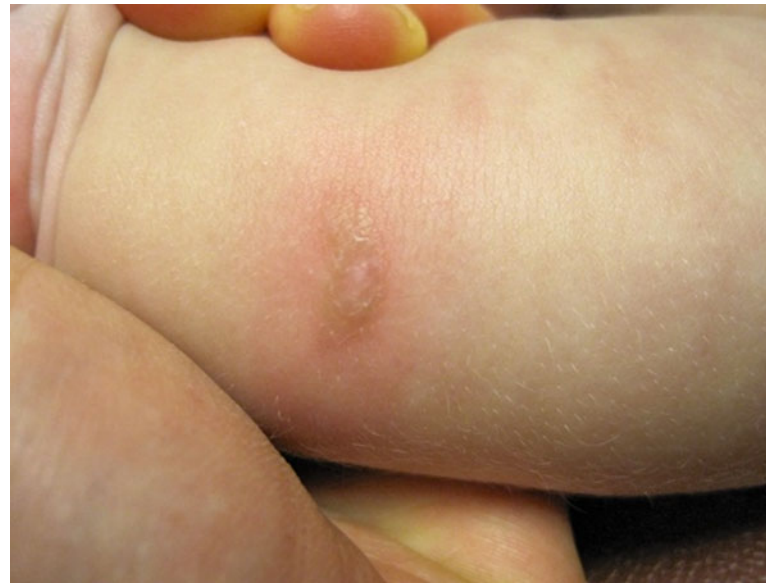

Fig. 14.2 Solitary mastocytoma in an infant

codon 816 c-kit mutation in bone marrow or blood, (2) expression of CD2 and/or CD25 by mast cells in extracutaneous organs, (3) more than 25 % of mast cells in extracutaneous infiltrates having spindle-shaped morphology, and (4) serum tryptase persistently elevated above 20 ng/mL [6, 7]. Systemic mastocytosis is diagnosed when one major and one minor or three minor criteria are met. Systemic mastocytosis is a very rare condition in children.

14.3 Physical Examination and Symptoms

Mechanical irritation of lesions of cutaneous mastocytosis leads to erythema and urtication, known as Darier's sign (Fig. 14.3). The formation of vesicles and bullae is most common in diffuse cutaneous mastocytosis but may also be seen in the maculopapular subtype [7]. The most common complaint of children with cutaneous mastocytosis is skin pruritus, which may persist for 30 minutes to several hours after mechanical trauma. Children with urticaria pigmentosa or diffuse cutaneous mastocytosis may develop widespread urticaria and constitutional symptoms.

Constitutional symptoms in children with mastocytosis, if present, are most commonly caused by the effects of uncontrolled release of mast cell mediators. Fewer than 10 % of children with a solitary mastocytoma have symptoms, compared to about a quarter (23 %) of those with urticaria pigmentosa [11]. In a review by

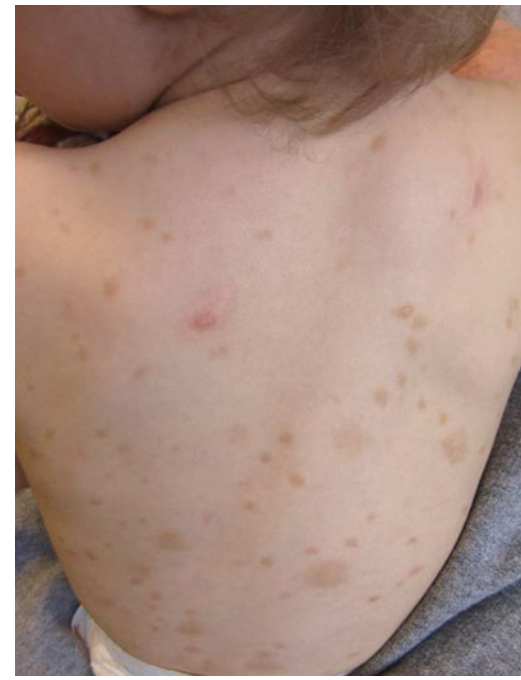

Fig. 14.3 Urticaria pigmentosa with positive Darier's sign in a 12-month-old

Ben-Amitai et al. [11], the most commonly reported symptom among patients with cutaneous mastocytosis was flushing. Bronchospasm was reported in 10 % of patients with urticaria pigmentosa but not in any children with a solitary mastocytoma. Additional symptoms may include fatigue, malaise, flushing, headache, cramping, diarrhea, abdominal pain, and loss of appetite [10]; however, gastrointestinal symptoms are uncommon in children [12]. Coagulation abnormalities may occur as the result of heparin release by mast cells. Rarely, syncope, hypotensive shock, osteoporosis/osteopenia, and peptic ulcer disease may occur. In rare instances of bony involvement, bone pain may be present. Skeletal lesions may occur in childhood mastocytosis but do not necessarily predict a poor outcome.

The SCORing MAstocytosis (SCORMA) index is a clinical scoring index which assesses the extent and activity of skin lesions in mastocytosis and incorporates subjective complaints [7]. SCORMA includes an approximation of the body surface area involved, the intensity of lesions (presence or absence of erythema, elevation, blistering, Darier's sign, and pigmentation), subjective complaints (flushing, wheezing, nausea, vomiting, or bone pain), and presence or absence of provoking factors. SCORMA has been found to correlate moderately well with serum tryptase levels, making it a useful tool for assessing the severity of mastocytosis. Comparing sequential SCORMA values in an individual patient may be a useful way to monitor disease progression and treatment efficacy [13].

14.4 Work-up

Work-up in children with mastocytosis is dependent upon the subtype of disease. Solitary mastocytomas can generally be diagnosed clinically, and a positive Darier's sign obviates the need for biopsy in most instances. Skin biopsy can help confirm the diagnosis of maculopapular cutaneous mastocytosis or diffuse cutaneous mastocytosis, and a complete physical examination should be performed to assess for the potential presence of organomegaly or lymphadenopathy. In cases where organomegaly is suspected on physical examination, evaluation with abdominal ultrasound is prudent [14]. Our preference is to check a complete blood count with differential, serum tryptase, and liver function tests on patients with extensive cutaneous involvement, hepatosplenomegaly, or any subjective constitutional symptoms (wheezing, flushing, diarrhea). A coagulation panel should also be performed in patients with hepatomegaly.

Serum tryptase levels have traditionally been used to assess burden of disease and help determine which patients will benefit the most from treatment. Among adult patients with mastocytosis, 13 % with cutaneous disease have tryptase levels greater than 20 ng/mL (and median level is 10 ng/mL), in comparison to 80 % of patients with systemic mastocytosis (and median level is 67 ng/mL) [15].

Bone marrow biopsy and further screening for systemic mastocytosis in coordination with a multispecialty approach are recommended for severe, recalcitrant symptoms that could be related to mast cell activation (abdominal pain, bone pain, flushing, pruritus, change in mentation), abnormality of complete blood cell count, organomegaly/lymphadenopathy, persistent skin lesions after puberty, significantly elevated tryptase level (>20 ng/mL) [16], and/or persistently elevated tryptase level (above 15 ng/mL) after puberty [14]. KIT mutational analysis should be considered for patients with symptoms or signs concerning for systemic mastocytosis. Patients with KIT mutations may have poorer prognosis, and KIT mutation status may influence choice of specific therapy (see below) [17].

Follow-up complete physical examination is recommended at least annually for pediatric patients with cutaneous mastocytosis. Repeat laboratory studies are indicated for patients with any concerning systemic symptoms or signs.

14.5 Treatment Options

The goal of treatment of cutaneous mastocytosis is control of skin and systemic symptoms by blocking mast cell activation and effects. Ideal

Table 14.1 Mast cell degranulators

Medications	Physical factors	Others
Aspirin, NSAIDs (nonsteroidal anti-inflammatory drugs)	Pressure or friction	Alcohol
Opiates/narcotics and derivatives	Skin temperature changes, heat more than cold	Insect stings, *Hymenoptera* and others
Polymyxin B	Fever	Snake venoms
Thiamine	Sunlight	Emotional stress
d-Tubocurarine	Surgery, endoscopic procedures, dental procedures	Intravenous high molecular weight polymers (dextran)
Cough medications: dextromethorphan and dimemorfan	–	Bacterial or viral infections
Cholinergic medications, such as scopolamine	–	Polypeptides against parasites, i.e., *Ascaris*
Vancomycin	–	Iodine-containing radiocontrast dye

management of this condition requires a multipronged approach, including avoidance of triggers, development of a treatment plan for acute exacerbations, and consideration of chronic suppressive therapy for symptomatic patients. Medical treatment of cutaneous mastocytosis may include topical therapies, systemic therapies, and phototherapy. The majority of patients with cutaneous mastocytosis or systemic indolent mastocytosis will have a favorable long-term course, and so treatment risks should be given careful consideration. Conversely, patients with aggressive systemic mastocytosis or systemic mastocytosis associated with another hematologic disease are managed with a multispecialty approach using cytoreductive and/or immunotherapy [18]. There are some exceptions to this general approach. Rare bullous mastocytosis cases with greater than 50 % of skin surface involvement may also warrant more intensive interventions even in the absence of internal organ involvement [16]. Patients with rapidly worsening or recalcitrant cutaneous mastocytosis are at risk of developing systemic mastocytosis, and in these patients cytoreductive and/or immunotherapeutic medications may be warranted to halt or stall disease progression.

Education of the family and other care providers is a critical piece of the equation in caring for children with cutaneous mastocytosis. School and day-care providers should be aware that the condition is not contagious, but it is chronic and has potential risks related to episodes of mast cell mediator release. Proper skin handling with avoidance of rubbing and hot temperatures is important, as is avoidance of other factors that cause mast cell degranulation (see Table 14.1).

Children with mastocytosis are at increased risk of anaphylaxis from bee and wasp stings, as well as from food allergies. Child care providers and parents should be taught to recognize signs and symptoms of anaphylaxis and should be prepared with a stepwise approach to the management of an acute anaphylactic emergency. Prescription and instructions on the use of a premeasured epinephrine delivery device, such as the EpiPen, may be considered for at-risk patients, particularly for those with history of recurrent severe hypotension after episodes of mast cell mediator release [19]. After such an event, the family should know to present to an emergency department for consideration of treatment with prednisone (20–40 mg/day for 2–4 days) to suppress acute recurrent reactions, which may occur in susceptible individuals in the hours following the initial event [17]. In the event of profound hypotension and/or shock, epinephrine, pressors, intravenous saline, corticosteroids, and antihistamines (both types 1 and 2) may be needed [20].

Wearing a medical alert bracelet is important for children with cutaneous mastocytosis who have known sensitivities to stings, medications, and/or foods. This intervention may also be suggested for children with cutaneous mastocytosis without known sensitivities, to alert medical

professionals about the condition and the associated increased risk of anaphylaxis [20].

Communication with other health care providers about the diagnosis and management is also essential. A question which frequently arises is which anesthetics are safe in children with mastocytosis. Injection of local lidocaine into the skin is considered to be safe in these patients [17]. Propofol, vecuronium, and fentanyl are considered to be relatively safe and well-tolerated anesthetics for patients with mastocytosis [21]. Despite theoretic concerns, two reviews suggest that the risks of anesthetics and pain relief medications in the setting of mastocytosis may be overstated, especially in children [22, 23]. There are no reports of anesthesia-related deaths in children with mastocytosis and only a few reports of anesthesia-related complications [14]. Carter et al. suggest administering medications which may increase histamine release, such as morphine and NSAIDS, incrementally instead of boluses [22]. This group also recommends against routine preoperative drug testing, deeming it unnecessary, and other authors have reported that intradermal medication testing is not sensitive or specific for systemic reactions [24]. Pretreatment regimens involving corticosteroids and antihistamines have been suggested [16]. Involvement of a pediatric anesthesiologist who is familiar with mastocytosis and its implications for anesthesia and pain control is widely recommended when caring for these patients.

Numerous medications are utilized for the management of mastocytosis. In this chapter, we will focus on systemic therapeutic agents; however, it bears mentioning that many cases of cutaneous mastocytosis can be managed conservatively. Children with cutaneous mastocytosis who have few to no bothersome symptoms can often be followed clinically, without any active intervention. For those with skin-limited symptoms, careful consideration should be given to use of topical therapy. Topical corticosteroids are most often utilized for this indication. In a report of 6 individuals with urticaria pigmentosa, including one child, betamethasone dipropionate 0.05 % ointment was applied under occlusion to a limited segment of the skin for 8 hours per day for 6 weeks [25]. All of the subjects had absence of pruritus and loss of Darier's sign in the treated segment of skin, and this effect lasted for at least 9 months. Two of these subjects also underwent intralesional injection of triamcinolone acetonide 40 mg/mL, with 0.25 mL injected into each lesion. There was loss of pruritus but also marked skin atrophy at the sites 4 weeks after the injections. Guzzo et al. reported 7 of 9 adult urticaria pigmentosa patients cleared at 6 weeks of betamethasone dipropionate 0.05 % ointment applied under occlusion nightly to half the body [26]. Lesions slowly recurred over months in these patients, so the authors suggested maintenance therapy with once weekly application of topical corticosteroid. Reduction of mast cell numbers appears to be mediated by corticosteroid inhibition of stem cell factor (c-kit ligand) production, at least in *in vitro* and murine models [27].

Pimecrolimus appears to both inhibit release of mast cell mediators and induce mast cell apoptosis [28]. A 14-month-old boy and a 26-month-old girl with biopsy-proven mastocytosis were treated with an oral antihistamine and pimecrolimus cream twice daily. In both patients, lesions cleared after 4 months of therapy and remained clear for 2 years of follow-up in one of the patients and 4 years in the other [29].

Antihistamines are the most commonly employed class of systemic medications for the treatment of mastocytosis. Histamine type 1 receptor antagonists decrease symptoms of pruritus, flushing, urticaria, and tachycardia [14]. The first-generation sedating type 1 antihistamine hydroxyzine may be dosed every 4 hours to help alleviate symptoms [20]. Alternatively, the less sedating second-generation type 1 antihistamines, including cetirizine, loratadine, and fexofenadine, can be used during the day [20]. A type 2 antihistamine (such as cimetidine, ranitidine, famotidine, nizatidine) may be added to the regimen for wider histamine blockage. This has been reported to lead to better symptomatic control [30, 31] There is a report of two cases of congenital bullous urticaria pigmentosa improving with cyproheptadine (0.25 mg/kg/day) and cimetidine (30 mg/kg/day) [32]. Addition of a type 2 antihistamine may be particularly helpful for those patients with gastric acid hypersecretion [17]. If gastrointestinal symptoms are not adequately controlled with an H2

antagonist, addition of a proton pump inhibitor can be considered [33]. The tricyclic antihistamine doxepin may also be helpful [17].

Several studies have reported decrease in pruritus, dermatographism, and bullae in mastocytosis patients treated with oral cromolyn sodium (200–800 mg/day) [34, 35]. It may also be helpful in alleviating the gastrointestinal symptoms associated with mastocytosis [17]. The mechanism of action of cromolyn sodium is inhibition of mast cell degranulation. The dosing of cromolyn sodium for children is 20 mg/kg/day divided in four doses for children under 2 years of age. Children between 2 and 12 years can be given 100 mg orally four times daily [20]. Introducing the medication at slowly increasing doses may help reduce side effects such as headache, fatigue, irritability, abdominal pain, and diarrhea [14]. There has been one case report of favorable response in systemic mastocytosis symptoms with addition of inhaled sodium cromoglycate to a regimen including oral sodium cromoglycate and type 1 and type 2 antihistamines [36]. In this report, 20 mg of pure sodium cromoglycate powder was administered four times daily using an Eclipse inhaler, and the dose was doubled during the time of menses, which was a known trigger for the adult female patient's symptoms.

Oral corticosteroids are used for angioedema and/or abdominal pain and diarrhea in mastocytosis patients resistant to cromolyn sodium [14]. Oral prednisone is important in the treatment of adults with mastocytosis-related malabsorption [33, 37]. Treatment with combined systemic corticosteroids and cyclosporine has been reported to result in improved symptoms, reduced serum tryptase, and reduced urinary histamine metabolite levels in a patient with systemic mastocytosis [38].

Ketotifen has both antihistamine and mast cell-stabilizing effects. It has shown promise in treatment of children and adults with cutaneous and systemic mastocytosis, alone or combined with ranitidine [38, 39]. Ketotifen is dosed 1 mg twice daily in children over 3 years old and 0.05 mg/kg twice daily in children ages 6 months to 3 years.

Montelukast has been reported to be helpful as an adjunctive therapy to combined antihistamine therapy and sodium cromoglycate [40]. Symptoms of urinary frequency and incontinence, flushing, angioedema, and abdominal pain were greatly ameliorated in an 8-year-old girl with systemic mastocytosis [40]. The dose used was 5 mg three times daily. Montelukast inhibits leukotriene receptors and has also been reported to inhibit leukotriene-mediated autocrine mast cell degranulation [41]. It has been used to treat adults with urinary symptoms related to detrusor mastocytosis [42]. In two other reports of systemic mastocytosis, treatment with montelukast led to an improvement in respiratory symptoms [43, 44].

Oral psoralen with UVA (PUVA) has been reported to be helpful in symptomatic and cosmetic improvement of diffuse cutaneous forms of mastocytosis with prominent bullae resistant to other therapies [45, 46]. PUVA appears to be most helpful in the setting of non-hyperpigmented diffuse cutaneous mastocytosis, while response in nodular and plaque forms is poor [16]. It does not alleviate other symptoms related to mastocytosis, however, and bath PUVA does not seem to have any effect [47, 48]. It is important to keep in mind that PUVA does have significant potential adverse effects, including ocular damage and cutaneous malignancy.

Phototherapy with narrowband UVB (NB-UVB) is an emerging treatment for mastocytosis. Seven patients with urticaria pigmentosa, four of whom were under the age of 16, were reported by Prignano et al. to have significant improvement in skin lesions and pruritus after 12 sessions of NB-UVB [49]. Similarly, in a case series of five patients with indolent systemic mastocytosis, all patients had complete remission of cutaneous lesions and pruritus after a median of 40.3 treatments, with a remission lasting more than 6 months [50]. NB-UVB is thought to have significantly better risk profile compared to PUVA, having been studied in the treatment of children with other skin disorders [51].

The recombinant humanized monoclonal antibody against IgE, omalizumab, alleviated symptoms in an adult woman with cutaneous mastocytosis [52]. She was treated with four biweekly treatment shots, initially, then with 6 monthly maintenance injections. Her cutaneous lesions persisted but she has had no further wheal

formation. Omalizumab has also been reported to be helpful in the treatment of unprovoked anaphylaxis in patients with systemic mastocytosis [53].

Use of chemo- or immunotherapeutic agents is mainly reserved for treating aggressive systemic mastocytosis or mastocytosis associated with an underlying hematologic disorder. As this usually falls outside of the realm of the dermatologist, treatment strategies for this subset of patients will be only briefly reviewed. The conventional treatments for these patients have been cladribine and interferon alpha [18]. Intravenous cladribine was reported to effectively clear skin lesions and improve bone marrow involvement in a patient with severe systemic mastocytosis [54]. Interferon alfa-2b, with or without prednisone, is helpful in adult cases of systemic mast cell disease [33, 55], though this treatment has not been well studied in the pediatric mastocytosis population [56]. For patients with bone pain, local radiation – at doses from 2,000 to 30,000 cGy over a 7–14-day period – may be helpful and lessen the need for analgesics [17].

Investigational and experimental therapies include kinase inhibitors (imatinib and nilotinib, as well as dasatinib, midostaurin, and masitinib), thalidomide, and daclizumab [57].

KIT mutations appear to mediate proliferation of mast cells in both cutaneous and systemic mastocytosis. A 2-year-old boy with progressive cutaneous mastocytosis who had mutations in D816V and codon 419 in exon 8 of c-kit was successfully treated with imatinib at a dose of 100 mg daily [58]. Symptoms ceased and disease progression was halted within 2 months of treatment, and the medication was well tolerated. After 13 months of treatment, imatinib was stopped but there was rapid recurrence of skin lesions and symptoms, so the medication was restarted after 5 days. Another 13-month course of therapy was given, followed by tapering to 100 mg every other day and eventual discontinuation of the medication 32 months after it was begun [58].

Mutational analysis is recommended prior to treating with imatinib, as patients who harbor only the common D816V mutation of KIT are not anticipated to be impacted significantly [57, 59], while those who have the PIPL1/PDGFRA fusion gene at exon 17 specifically targeted by imatinib may respond very well. Imatinib is approved by the US Food and Drug Administration for treatment of adults with aggressive systemic mastocytosis without the KIT D816V mutation or with unknown KIT mutational status. There are reports of patients with KIT mutations outside of exon 17 who were successfully treated with imatinib [17].

Rapamycin, an immunosuppressant medication that inhibits activation of the mTOR pathway, has been identified as a potential novel therapy for severe cases of mastocytosis. The Akt/mTOR pathway has been described as essential to downstream KIT signaling [60]. Rapamycin has been demonstrated *in vitro* to inhibit imatinib-resistant D816V KIT-expressing human mast cell lines [61].

14.6 Prognosis

The prognosis of mastocytosis in children is generally excellent. In most children with cutaneous mastocytosis, skin lesions regress by the time of puberty [5]. In a small subset of children, skin lesions persist into adolescence and these patients should be followed closely. Of children whose cutaneous mastocytosis persists until puberty, 15–30 % will develop internal organ involvement [62]. Progression to systemic disease may be heralded by the new onset of hepatosplenomegaly or lymphadenopathy [5]. In other cases, marked eosinophilia and extremely long-standing elevation of serum tryptase may be a clue to bone marrow involvement. Chantorn and Shwayder reported a young female with cutaneous mastocytosis diagnosed at age 5 which progressed to fatal mast cell leukemia at the age of 23, so the potential for evolution of limited skin disease into systemic, life-threatening disease should always be kept in mind [63].

Conclusion

When caring for a pediatric patient with mastocytosis, the first step is to confirm the diagnosis and rule out aggressive, systemic forms of the disease. Education about avoidance of

triggers and acute exacerbations is a must. For systemic treatment of cutaneous mastocytosis (see Table 14.2 for dosages and side effects), first line of therapy is a scheduled type 1 antihistamine. Addition of a type 2 antihistamine may be the next consideration. A proton pump inhibitor may be added for recalcitrant gastrointestinal symptoms. Addition of cromolyn sodium or ketotifen can be considered next for continued symptoms. Montelukast can be added to antihistamines and cromolyn sodium, if needed. For diffuse cutaneous forms of mastocytosis, narrowband ultraviolet B or PUVA may be considered in addition to these oral medications. More aggressive therapies, such as tyrosine kinase inhibitors, may be utilized in the multidisciplinary approach to patients with severe, recalcitrant disease.

Table 14.2 Systemic medications for pediatric cutaneous mastocytosis

Drug	Recommended dosage	Notes on usage, side effects (SE)
Oral Antihistamines		
(a) Type 1 – first generation		All are sedating, hydroxyzine can be dosed every 4 h
Hydroxyzine	0–1 year of age: 1 mg/kg/day in divided doses	SE: drowsiness, dizziness, constipation, urinary retention, dry mouth
	2–6 years of age: 2 mg/kg/day in divided doses	Doxepin specifically: do not administer concurrently with erythromycin or imidazole antifungals due to CYP3A4 inhibition. Avoid in patients with severe heart disease (rarely, may cause arrhythmias at high doses)
Diphenhydramine	5 mg/kg/24 h divided Q6h (max dose 300 mg/24 h)	
Doxepin	1–2 mg/kg/day	
Cyproheptadine	0.25 mg/kg/day	
(b) Type 1 – second generation		Less sedating which may be helpful for daytime dosing
Cetirizine	6 months to 23 months of age: 2.5 mg once daily, can be increased to 2.5 mg twice daily if 12 months to 23 months of age	SE: headaches, fatigue, dry mouth, sore throat, abdominal pain, insomnia, drowsiness in some
	2–5 years of age: 2.5 mg once to twice daily	
	6 years of age or older: 5 mg once to twice daily	
Loratadine	6 months to 23 months of age: 1.25–2.5 mg once daily	
	2–5 years of age: 5 mg once daily	
	6 years of age or older: 5 mg twice daily or 10 mg once daily	
Fexofenadine	6 months to 23 months of age: 15 mg twice daily	
	2–11 years of age: 30 mg twice daily	
	12 years of age or older: 60 mg twice daily or 180 mg once daily	
(c) Type 2		Adjunctive to increase the effect of type 1 antihistamines
Cimetidine	20–40 mg/kg/day in divided doses	May be particularly helpful for those patients with gastric acid hypersecretion as part of their condition; if still recalcitrant gastrointestinal symptoms, a proton pump inhibitor may be added

(continued)

Table 14.2 (continued)

Drug	Recommended dosage	Notes on usage, side effects (SE)
Ranitidine	2–4 mg/kg/day in two divided doses	SE: headache, nausea, transient diarrhea, agitation, nervousness; breast tenderness and mild gynecomastia reported with cimetidine and ranitidine
Famotidine	1–1.2 mg/kg/day in two divided doses, up to 40 mg twice daily	Ranitidine specifically: may decrease levels of ketoconazole and itraconazole Famotidine specifically: infants and young children may require Q8h dosing because of enhanced elimination
Oral cromolyn sodium	Under 2 years of age: 20 mg/kg/day divided in four doses 2–12 years of age: 100 mg orally four times daily	Given for gastrointestinal symptoms, may help pruritus, dermatographism, and bullae SE: headache, fatigue, irritability, abdominal pain, diarrhea (these may be reduced by introducing the medication at slowly increasing doses), throat irritation, cough, bronchospasm (rare), nasal congestion, bad taste in mouth
Oral ketotifen	6 months to 3 years of age: 0.05 mg/kg twice daily Over 3 years of age: 1 mg twice daily	Can be used alone or combined with ranitidine SE: may stimulate appetite and weight gain, drowsiness, dry mouth, irritability, and increased nosebleed
Oral montelukast	6 months to 23 months of age: one packet of 4 mg oral granules 2–5 years of age: one packet of 4 mg oral granules or one 4 mg chewable tablet daily 6–14 years of age: one 5 mg tablet daily (one report of an 8-year-old benefiting from 5 mg three times daily [40]) 15 years of age and older: one 10 mg tablet daily	Adjunctive therapy to combined antihistamine therapy and sodium cromoglycate for systemic symptoms SE: headache, cough, abdominal pain, behavior- and mood-related changes, increase in eosinophils, rarely systemic vasculitis
Systemic corticosteroids	20–40 mg/day for 2–4 days	Used for angioedema and anaphylaxis, also for abdominal pain and diarrhea in those resistant to cromolyn sodium Not generally used long term for the well-known SE: weight gain, sleep disturbance, hyperglycemia, osteopenia/osteoporosis, hypertension, striae, negative effect on growth in young children

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