VINDICATE-P

A Mnemonic for the Many Comorbidities of Atopic Dermatitis

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KEYWORDS

• Atopic dermatitis • Asthma • Food allergies • Allergic rhinoconjunctivitis
• Eosinophilic esophagitis

KEY POINTS

- Atopic dermatitis (AD) is a chronic inflammatory skin disease that is associated with many comorbidities that fall under a variety of subtypes.
- Comorbidities may vary with age, but almost every individual with AD will one day develop a comorbidity.
- Comorbidities of AD can be categorized under the mnemonic VINDICATE-P: *v*ascular/cardiovascular, *i*nfectious, *n*eoplastic and *n*eurologic, *d*egenerative, *i*atrogenic, *c*ongenital, *a*topic and *a*utoimmune, *t*raumatic, *e*ndocrine/metabolic, and *p*sychiatric.

INTRODUCTION

The concept of comorbidities was recognized in atopic dermatitis (AD) for many decades. A review article discussing "infantile eczema" published in 1946 wrote "eczematous infants may exchange their skin condition for asthma or hay fever, as they get older"[1] which has been coined the "allergic march."[2] Many of these eczematous infants with chronic AD of childhood, will later in adolescence and adult life have positive skin tests to proteins.[2] While the concept of comorbidities is certainly not new, our knowledge of specific comorbidities, the epidemiology, and burden certainly expanded over time. An early list of recognized comorbidities was considered minor AD criteria by Hanifin and Rajka in 1979.[3] To create a more organized scaffold of

This article originally appeared in *Dermatologic Clinics*, Volume 42, Issue 4, October 2024.
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Immunol Allergy Clin N Am 46 (2026) 465–477
https://doi.org/10.1016/j.iac.2026.04.005 **immunology.theclinics.com**

the myriad comorbidities, we developed a new mnemonic for this article—"VINDICATE-P": *v*ascular/cardiovascular, *i*nfectious, *n*eoplastic and *n*eurologic, *d*egenerative, *i*atrogenic, *c*ongenital, *a*topic and *a*utoimmune, *t*raumatic, *e*ndocrine/metabolic, and *p*sychiatric comorbidities (**Box 1**).

There are age-related differences in the epidemiology of comorbidities associated with AD. Overall, pediatric patients were found to more commonly have impetigo, folliculitis, seborrheic dermatitis, chronic and acute urticaria, lichen nitidus and lichn striatus, and bronchial asthma.[4] In particular, studies examining the frequency of minor Hanifin-Rajka criteria demonstrated infections to be more common in children with AD ages 2 to 12 versus less than 2 year old. Children and adolescents seem more prone to neuropsychiatric comorbidities, for example, migraines, and autoimmune conditions, for example, vitiligo, which is notably associated with AD in children under 12 years. In adulthood, AD was found to be associated with endocrine/metabolic disorders, for example, metabolic syndrome and type 2 diabetes; slight increase in risk for some neoplastic disorders, including non-cutaneous T-cell lymphomas (non-CTCLs) and skin cancers; and vascular/cardiovascular conditions, for example, hypertension, myocardial infarction, coronary artery disease (CAD), and stroke, particularly in moderate to severe AD. Geriatric patients with more severe AD may particularly have increased risk of dementia and osteoporosis. Psychiatric conditions, for example, depression and anxiety, are overrepresented in adults, while attention-deficit disorder is higher in teens. Traumatic and iatrogenic events can occur at any age. The wide array of comorbidities illustrates that AD can pervasively impact many aspects of health beyond the skin. The recent American Academy of Dermatology (AAD) guidelines on AD comorbidities in adults made clear statements of association of AD in adults with allergic conditions, immune-mediated conditions, mental health and substance abuse, cardiovascular disease, metabolic disorders, bone health, and skin infections.[5] We expect that this list will continue to grow over time and be a starting point, rather than a compendium.

VASCULAR AND CARDIOVASCULAR COMORBIDITIES

Although it is clearly a concern of adulthood, ultimately cardiovascular disease can shorten life expectancy and was the leading cause of death in the United States for 100 years.[6] Analysis of data from the United States population-based 2005 to 2006 National Health and Nutrition Examination Survey, 2010 and 2012 National Health Interview Surveys found associations of flexural eczema with increased odd of CAD, heart attack, congestive heart failure, peripheral vascular disease, and stroke in at least 1 study.[7] A Taiwanese population-based study found a 33% increase in the odds of ischemic stroke in AD patients overall, and 71% increased odds in patients with severe AD.[8] In the All of Us Research Program, hypertension (odds ratio [OR] = 1.56) and hyperlipidemia (OR = 2.29) were associated with AD in multivariate analysis, supporting an association with AD.[9] A systematic review of cardiovascular risk in children with AD found no significant association of AD with diabetes, hypertension, or ischemic heart disease.[10] Thus, it appears that increased screening for cardiovascular risk may not be warranted in children and may have a higher yield in late adolescence and adulthood.

INFECTIONS

Cutaneous and extracutaneous infections are quite common in young children with or without AD. *Malassezia* sensitization with the production of immunoglobulin E (IgE)[11] and *Molluscum contagiosum* infections[12] were linked to AD onset in infancy and early childhood, respectively. Wild-type varicella zoster virus (VZV) may protect against

Box 1
The VINDICATE-P mnemonic

Vascular/cardiovascular[6–8] (Risk begins in adulthood[9])
- Coronary artery disease
- Ischemic stroke
- Heart attack
- Congestive heart failure
- Hypertension

Infectious[10–18] (Risk is lifetime[18])

Bacterial
- Impetigo
- Abscesses
- Erysipelas/cellulitis
- Sore throat
- Strep throat
- Pneumonia
- Urinary tract infections
- Recurrent ear infections
- Sinus infections
- Bacterial conjunctivitis
- Septicemia

Fungal
- IgE to Malassezia

Viral
- Warts
- Molluscum
- Varicella
- Herpes zoster
- Extra-genital herpes
- Condyloma
- Eczema herpeticum
- Eczema coxsackium
- Eczema vaccinatum
- Head or chest colds
- Influenza

Neoplastic[19,20] (Risk occurs lifetime[19])
- Non-CTCL lymphoma
- Skin cancer

Neurologic[21,22] (Risk occurs lifetime[21,22])
- Epilepsy
- Headaches/migraines

Degenerative[18,23–26] (Risk identified in middle to late adulthood[27])

Osteoporosis
Enthesopathy
Intravertebral disk disorders

Iatrogenic[29]

Osteoporosis
Immunosuppression
Cancer from phototherapy
Ocular surface disease
Drug-induced cataracts

Congenital[2,30–32] (Risk begins at birth)

Ocular
- Keratoconus
- Anterior subcapsular cataracts

Cutaneous
- Ichthyosis vulgaris
- Xerosis
- Keratosis pilaris

Atopic and autoimmune[5,35–41] (Risk of atopic comorbidities continuous throughout lifespan)
- Asthma
- Food allergies
- Allergic rhinoconjunctivitis
- EOE
- Allergic contact dermatitis
- Chronic urticaria[42]
- Granuloma annulare[52]
- Rosacea[19]
- Vitiligo[47–49]
- Alopecia areata[19]

Traumatic[55,56]
Falls

Endocrine/metabolic[5,58–60] (Risk of comorbidity starts in early childhood and progresses through life)
Diabetes type 2
Metabolic Syndrome
Non-alcoholic fatty liver

Psychiatric[61–63] (Risk of comorbidity continuous through life)
Depression
Anxiety
Sleep disorder
Sleep apnea
ADHD
Dementia

Abbreviations: ADHD, attention deficit hyperactivity disorder; CTCL, cutaneous T-cell lymphoma; EOE, eosinophilic esophagitis.

developing AD[13,14] but is still associated with severe exacerbation of preexisting AD when generalized as a varicelliform eruption.[15] Cutaneous viral (warts, molluscum, herpesvirus) and bacterial (impetigo) infections, were linked to AD.[3] Analysis of the 2007 National Health Interview Survey showed higher odds of warts in US children with AD.[16] AD was also associated with extracutaneous infections including strep throat, sore throat, head or chest cold, influenza/pneumonia, sinus infections, recurrent ear infections, chickenpox, and urinary tract infections.[16] Recently, eczema coxsackium, a widespread severe spread of coxsackie lesions across the skin in children with AD, was more frequently observed.[17] IgE production to *Malassezia* increases with age and peaks at ages 20 to 30 years.[18] A large study of Finnish adults identified many comorbidities including abscesses, erysipelas/cellulitis, impetigo, herpes zoster, extragenital herpes, bacterial conjunctivitis, condylomas, and septicemia.[19] Similar pediatric and adult AD data in the US show higher odds of carbuncles/furuncles, impetigo, cellulitis, erysipelas, *Staphylococcus aureus* infection (methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible *Staphylococcus aureus*), molluscum, cutaneous warts, herpes simplex virus (HSV) and VZV, eczema herpeticum, dermatophytosis, and candidiasis of the skin/nails and vulva/urogenitals.[20] Specific to adults are the increased risk of genital HSV infections and genital warts.[20] Together, risk of cutaneous and extracutaneous infections is increased in persons with AD at all ages.

NEOPLASTIC

Linkage of neoplastic disease to AD is important. However, without understanding the baseline risk of neoplasms, it is difficult to appreciate the additional risk conveyed by various treatment modalities. Analysis of The Health Improvement Network from 1994 to 2015 found that children with severe AD had increased risk of non-CTCL lymphoma, and those with mild AD had increased non-melanoma skin cancer (NMSC) risk; adults had 2-fold increased odds of non-CTCL lymphoma and mild increases in NMSC.[21] A systematic review and meta-analysis also concluded that AD is associated with lymphoma due to high-potency topical corticosteroid usage.[21] AD was not found to be consistently associated with solid tumors. One study suggested there may even be a lower odd of solid tumors in patients with AD.[21]

NEUROLOGIC

The US population-based National Survey of Children's Health 2007 to 2008 found that children with an atopic disease, including asthma, AD, hay fever, and food allergies had higher odds of epilepsy; severe AD was associated with an even higher risk.[22] Migraines were linked to AD in children and adults, with potential mechanism of occurrence being interleukin-4 (IL-4) release.[19,23–26]

DEGENERATIVE COMORBIDITIES

Osteoporosis and degenerative disk disease were linked to AD in adults.[19] It is unclear whether this is a cumulative risk caused by long-term usage of topical high-potency and systemic corticosteroids.[27] However, recent data on short-term 2-week to 6-week usage of the class 2 topical corticosteroid betamethasone did not affect bone mineral turnover.[28] Osteoporosis and bone mineral alterations do not appear to be more common in young adults with AD.[29] Data in children are reassuring that usage of topical corticosteroids does not increase risk of fractures in AD patients.[30] However, osteoporosis is a well-established adverse event of systemic corticosteroids. Due to the terrible adverse event profile, systemic corticosteroids are not recommended for AD treatment. The role of vitamin D deficiency and supplementation is also being explored. Vitamin D may have immunomodulatory impact on inflammatory pathways activated by allergic responses. Some studies have suggested that vitamin D supplementation may help prevent allergic diseases.[31,32]

IATROGENIC COMORBIDITIES

One of the consequences of treating AD patients is that therapies can induce comorbidities, the so-called iatrogenic comorbidities. A list of all these adverse-effects is beyond the scope of this review, but merits consideration in the choice of therapeutic agents, and treatment decision-making to reduce risk of adverse events over time. Current guidelines for systemic medications and phototherapy in AD highlight some of the associated risks.[33]

CONGENITAL (AND EARLY-ONSET) COMORBIDITIES

The comorbid conditions of AD seen in early childhood include some of the minor features including ichthyosis vulgaris, keratosis pilaris, keratoconus, and subcapsular cataracts.

An Indian cohort of children highlighted several congenital comorbidities of childhood AD, including xerosis, Dennie-Morgan fold, palmar hyper-linearity, ichthyosis

vulgaris, keratosis pilaris, and orbital darkening.[34] These comorbidities of early childhood may be destined to occur from birth and promoted by environmental factors. Filaggrin null mutations are inherited in an autosomal semidominant manner and are associated with increased risk of palmar hyperlinearity; in fact, palmar hyperlinearity is often considered a sign of filaggrin mutations.[35] A recent study of 50 Saudi Arabian children with AD found that 92% had eye findings, including eyelid disease (54%) and keratitis (44%), suspected (16%) or moderate risk (8%) for keratoconus.[36] These findings support the need for regular eye examinations in children with AD. The frequency of keratitis demonstrates that many patients may already have keratitis even without the use of biologic therapy.

ATOPIC COMORBIDITIES

Children with AD have a greater risk of asthma, hay fever, and food allergy, a risk that increases in children with warts.[15] Adults bear the risk of comorbid asthma and hay fever in 8% and 7.5% of patients, respectively. The risk of atopic comorbidities in the setting of AD is sometimes conceptualized as the atopic march, in which cutaneous atopy progresses to systemic allergies and asthma. Mechanistically, percutaneous exposure to food antigens in dust or otherwise in the setting of AD is known to contribute to food allergy development. More formally, this is termed association of AD with the allergen-specific TH2 driven disorders, wherein AD onset and the associated barrier defects promote susceptibility to food allergy and asthma.[37] As some of the comorbidities can overlap in terms of the timing of occurrence, the march may be a cluster for some individuals. Studies that have examined the march/cluster include the Canadian Healthy Infant Longitudinal Development study, a study showing that the presence of AD and sensitization increased asthma risk in young children.[38] A UK study following patients longitudinally showed an increased asthma risk for early-onset AD when checking at age 23 and 44 years.[39] The Avon Longitudinal Study of Parents and Children found all types of AD were associated with asthma especially the persistent type and AD with evidence of the atopic march.[40] The Odense study addressed a cohort of eighth graders with AD and their course of illness. At age 29 years, 50% had persistent AD, 36.3% reported asthma ever, and 60.8% reported ever allergic rhinitis. Additional comorbidities in the allergic or atopic multimorbidities include eosinophilic esophagitis which can be triggered by food allergy and can trigger failure to thrive. This condition can occur at any age.[41] Chronic urticaria is also associated with AD; however, this can be either an allergic or an autoimmune comorbidity. Therefore, laboratory screening for autoimmune thyroid disease may be of benefit to the patient.[42,43] Early-onset and hand eczema were significant risk factors.[44] AD in infancy imparts an allergic risk over a lifetime. Interestingly, the shared importance of IL-4, and to an extent IL-13, in the pathophysiology of these conditions makes drugs impacting IL-4 and IL-13 an important therapeutic benefiting many, most, or all of the allergic comorbidities concurrently. The impact on long-term suppression of IL-4 and IL-13 on the atopic march is unknown but seems promising.[45]

AUTOIMMUNE COMORBIDITIES

In the past 15 years, the association of autoimmune disease with AD was explored in larger series. Alopecia areata (AA) is associated with AD. It was demonstrated that patients with AA and AD are more likely to have extensive hair loss and be refractory to therapy. Further, case reports demonstrate dupilumab has benefit in AD and AA, even demonstrating hair repigmentation.[46,47] Although the association of vitiligo with AD was reported in children under 12 years of age in survey, but not in adults.[47–49] We

also have no data on the lifetime impact of AD on course of disease in vitiligo, although AD specifically aggravates the risk of severe disease in AA.[50] We do have data demonstrating overlapping therapeutic benefits for some topical and systemic Janus kinase inhibitors. The current comorbidity guidelines of the AAD for AD acknowledge AA, but not vitiligo, as a common comorbidity.[51]

Although the association with urticaria was addressed under the allergic comorbidities, in fact, some cases are autoimmune, being associated with IgE autoantibody production against the FcER1 receptor. The association of chronic urticaria with AD was made in multiple population-based demographic studies.[42]

Granuloma annulare (GA) is linked to AD in some patients. In a case series of 47 children, 48.9% of children with GA had an atopic condition.[52] Interestingly, there were published case reports of dupilumab clearing GA, suggesting a shared role for IL-4 and IL-13 in GA and AD.[53,54]

TRAUMATIC COMORBIDITIES

Injuries and fractures have a multifactorial association with AD.[55] Injuries and fractures are more likely to happen in the setting of sleep disturbance and impaired daytime wakefulness, as well as in the setting of reduced bone mineral density (BMD) that can be seen in AD. Although conceptually, oral corticosteroids are a concern for BMD, in fact, one study linked low BMD to cyclosporine usage.[55,56]

ENDOCRINE/METABOLIC COMORBIDITIES

Again, the broad issue of metabolic syndrome and endocrine comorbidities of AD are beyond the scope of this article. However, there is evidence that metabolic syndrome can begin early in life for some AD patients. The authors have found linkage of childhood AD to metabolic syndrome, including increased blood pressure and waist circumference, and non-alcoholic fatty liver disease.[57] Overweight, obesity, and metabolic syndrome linkage to AD appears a particularly high risk in severe AD.[58] The role of adipocytes in inflammation and immune dysregulation was speculated as the reason for association with AD.[59] The recent AAD guidelines discussing comorbidity awareness stated that AD was not associated with diabetes but was linked to obesity, dyslipidemia, hypertension, and CAD.[5] Concerns for nutritional health particularly arise in children with food allergy or eosinophilic esophagitis–related dietary restrictions and linkage to malnutrition was observed.[55]

PSYCHIATRIC COMORBIDITIES

AAD guidelines on comorbidities awareness state that AD is associated with clinician-diagnosed depression, and anxiety, with lower certainty of evidence for suicidality and alcohol abuse. Additionally, attention deficit hyperactivity disorder (ADHD) was linked with low evidence.[5] However, we want to highlight that the neuropsychiatric effects of AD start in infancy with sleep disturbance and irritability associated with sleep disturbances.[60] As children get older, concentration can be impaired with greater sleep disturbance and severe AD being associated with ADHD.[61] ADHD can be associated with anemia, obesity, and headaches in children as well.[61] Preadolescents through adulthood can experience more anxiety and depression, with suicidality being the severe end of the spectrum.[62] All these associations are most common with severe AD.[5]

Comorbid environmental allergy may exacerbate risk of psychiatric comorbidities. In environmental allergies, the immune system overreacts overzealously and inappropriately to allergens in the surroundings. The culprit for these manifestations is that the

immune system releases proinflammatory and inflammatory mediators. These same inflammatory cytokine mediators were linked to depression.[63] Research has disclosed that cytokines released in allergic rhinitis can affect monoaminergic neurotransmission and that this may play a role as a risk factor in depression and other mood disorders.[63,64] Depressed individuals were noted to have increased amounts of acute phase proteins, proinflammatory cytokines, chemokines, and cellular adhesion molecules.[63,64] In addition to inflammatory mediators, changes in hormonal levels can contribute to depression and mood disorder. IL-1, IL-6, and tumor necrosis factor alpha are reported to affect corticotrope-releasing hormone which in turn increase adrenocorticotropic hormone and cortisol production via the hypothalamic-pituitary-adrenal pathway and systemic inflammatory markers can precede the appearance of psychiatric disease by a decade.[65–67] Cross-sectional studies and case-control studies showed a relationship between allergic rhinitis and environmental allergies with depression and mood disorders.[68–71]

There are studies where the effect of hormones and mediators are less supportive. These results attribute depression and other mental health sequelae to medications, behavior such as physical and emotional symptoms resulting from the atopic disease manifestations.[72] Exposure to pollen, dust, mold, and even pets can solicit symptoms such as itchy, congested, and runny nose; sneezing; itchy and watery eyes; and other prodromes. Such behavior can stigmatize an individual and disrupt social interactions leading to isolation as well as decrease a person's confidence. Eczema with concomitant unsightly scratching and intractable pruritus can disturb sleep patterns as well as interfere with daily functions. The discomfort of allergy sufferers can result in a negative quality of life which can culminate into anxiety and depression. Allergies impact an individual's well-being, which can interfere with ability to function which for adults is detrimental to work productivity and in children, school performance and scholastic achievements. A link between allergy and suicide was reported.[73,74]

SUMMARY

AD is a multisystem inflammatory disorder beginning in the skin but linking to a series of dominoes falling in the immune system triggering or aggravating tendency to a host of immune and inflammatory events, as well as the long-term outcomes of a lifetime of sleep disturbance. Now that we understand what we need to prevent, interventions can be assessed for their long-term benefits on general health.

CLINICS CARE POINTS

- VINDICATE-P is a mnemonic that captures a large number of the comorbidities of Atopic Dermatitis.
- VINDICATE-P stands for Vascular and cardiovascular, Infections, neoplastic/ neurologic, degeneritive, iatrogenic, congenital, atopy/ autoimmune, traumatic, endocrine/ metabolic, and psychiatric comorbidities.
- Vigilience is needed for early-recognition and control of comorbidites of atopic dermatitis.

DISCLOSURE

J.I. Silverberg has received honoraria as a consultant and/or advisory board member for Abbvie, Alamar, Aldena, Amgen, AObiome, Apollo, Arcutis, Arena, Asana, Aslan, Attovia, BioMX, Biosion, Bodewell, Boehringer-Ingelheim, Bristell-Meyers Squibb, Cara, Castle Biosciences, Celgene, Connect Biopharma, Corevitas, Dermavant, Eli Lilly,

FIDE, Galderma, GlaxoSmithKline, Incyte, Inmagene, Invea, Kiniksa, Leo Pharma, Merck, My-Or Diagnostics, Nektar, Novartis, Optum, Pfizer, RAPT, Recludix, Regeneron, Sandoz, Sanofi-Genzyme, Shaperon, TARGET-RWE, Teva, Union, UpToDate; speaker for Abbvie, Eli Lilly, Leo Pharma, Pfizer, Regeneron, Sanofi-Genzyme; institution received grants from Galderma, Incyte, Pfizer. Nanette Silverberg has received honoraria as a consultant, speaker, and/ or advisory board member for Incyte, Leo. Novan, Pfizer, Regeneron, Sanofi-Genzyme, and Verrica Pharmaceuticals.

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