🩺 Physician Guide
Blau Syndrome: Quick Facts for Your Doctor

A Clinical Overview for Physicians and Specialists

🔬 What is Blau Syndrome?

Blau Syndrome is a rare **monogenic autoinflammatory disease.** Previously, this mutation was thought to be caused by **gain-of-function mutations in the NOD2 gene,** however ongoing research is examining the function. This mutation leads to dysregulated innate immune activation. It presents early in life, typically before the age of 4, and is characterized by **non-caseating granulomatous inflammation** in multiple organ systems.

It is inherited in an **autosomal dominant** pattern but may also arise from de novo mutations or somatic mosaicism. When there is no family history, it may sometimes be called **Early-Onset Sarcoidosis (EOS)**.

🧬 Genetic Cause

- **NOD2 gene mutation** (most commonly at R334Q or R334W accounting for 70% of population)
- Mutations are localized near the **NACHT/NBD domain**, causing autonomous NOD2 signaling
- Confirm diagnosis via molecular testing (sequencing of NOD2)
- Additional identified variants include, but not limited to:
    - R334Q/W, D382N, L454V, G481D, W490L, C495Y, H520Y, R587C, E600A, E600K, Q809K, L469F, A755V, N670K, E667K, T605N/P, H603R, R587C, Y563S/H, H520Y, M514T, M513R/T, D512H/V, L488V, E499_L500delinsV, H496L, W490L/S, H480R, G464W, D390V, E383K/G, D382E, R311W, P268S

⚠ Classic Clinical Triad

1. **Granulomatous arthritis/tenosynovitis**
    - 96% of patients with polyarticular arthritis
    - Symmetric, boggy joint swelling (esp. wrists, ankles)
    - Often misdiagnosed as JIA or RA
    - Camptodactyly may be present
    - Most involvement in PIP joints and tendon sheaths
    - Many adults misdiagnosed as sarcoidosis
    - Range of motion relatively preserved

2. **Uveitis**
    - Occurrence in 80% of Blau patients
    - Bilateral (97%) and chronic
    - Anterior, posterior, or panuveitis (55%)
    - High risk for complications (synechiae, cataracts, glaucoma, chorioretinal scarring)
    - Often leads to visual impairment or blindness if untreated
    - Typical fundus features of Blau posterior uveitis: pale optic disc, disc margins irregular, peripapillary pigement changes, nodular excrescensies (protrusions, bumps, prominences, swellings, border)
    - Multiple chorioretinal scars are visible
    - Most frequent anterior complications were cataract and synechiae (around 50%)
    - 25% increased intraocular pressure
    - One third of patients experienced moderate visual impairment already at baseline, with 15% of patients being legally blind

3. **Granulomatous Dermatitis**
    - Fine, scaly, monomorphic rash
    - Often appears in infancy or early childhood
    - Commonly misdiagnosed as atopic dermatitis
    - Characteristic of skin biopsy to show a non-caseating granulomatous inflammatory infiltrate located in the dermis

🧠 Expanded Systemic Involvement

In up to 50% of cases, inflammation extends beyond the classic triad:

- Liver, kidney, large blood vessels
- Lymphadenopathy
- Pulmonary involvement
- Neurologic symptoms (rare)
- Fever, hypertension, central nervous system, cranial nerve, large vessel, small vessel, and erythema nodosum
- Patient reporting of diagnoses with dysautonomia and mast cell activation syndrome (source: Cure Blau Syndrome Foundation)

🧪 Diagnostic Workup

- **Genetic testing** for NOD2 mutation and specific variant noted
- **Histopathology** (if biopsy): non-caseating granulomas
- **Ophthalmology evaluation** (slit lamp, fundus exam)
- **Imaging**: hand/wrist X-ray, chest X-ray if systemic symptoms
- **Laboratory**: CBC, ESR, CRP often normal; ACE may be normal or slightly elevated
- Consider urinalysis, liver and kidney function tests, echocardiogram

💊 Treatment Overview

Treatment for Blau Syndrome aims to control inflammation, manage symptoms, and prevent long-term organ damage. Most patients require a combination of therapies over time, tailored to their specific symptoms and disease activity. For a visual overview on treatment methods, please see this article, page 4.

1. Corticosteroids

- Oral (prednisone) for flares
- Topical or intraocular for uveitis

2. Immunomodulators

- Methotrexate, azathioprine, cyclosporine

3. Biologics

- **TNF inhibitors** (adalimumab, infliximab) – commonly used
- **IL-1 blockers** – less common
- **IL-17 inhibition** is under investigation

📈 Monitoring Recommendations

- **Rheumatology**: joint symptoms, mobility, growth
- **Ophthalmology**: full eye exams every 3–6 months
- **Referrals:** appropriate specialists as symptoms arise and may include pulmonology, orthopedics, nephrology, cardiology, endocrinology, etc.
- **General care**: BP, pulse, systemic signs
- **Labs**: CBC, ESR/CRP, LFTs, renal function
- Consider **imaging** (CXR, echocardiogram) based on symptoms

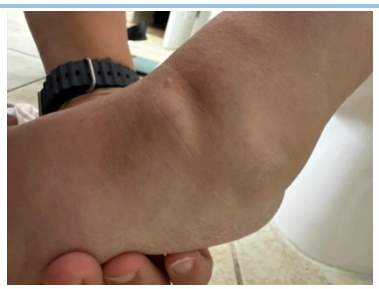
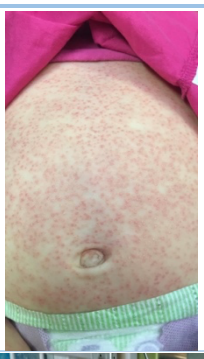
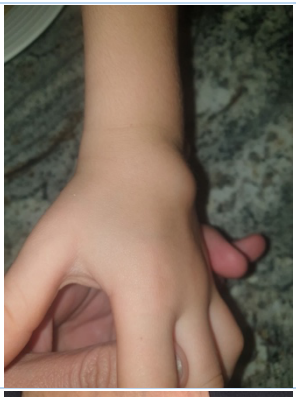
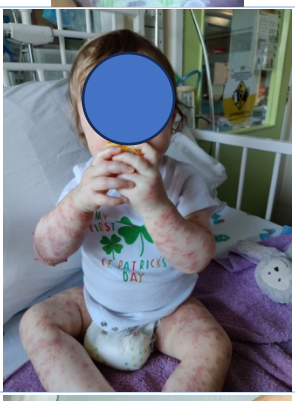
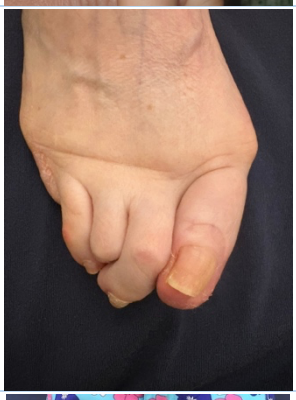
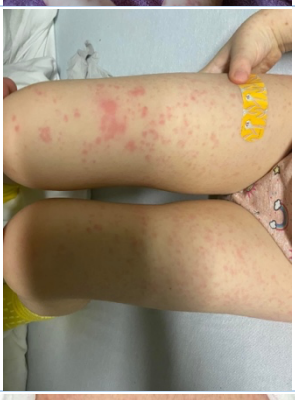
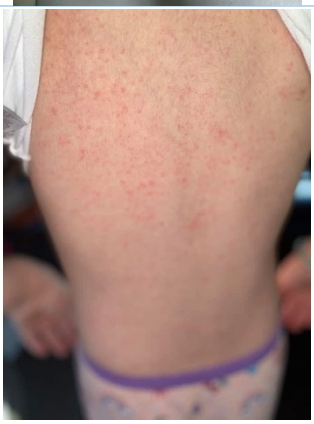
📌 Resources

• **Cure Blau Syndrome Foundation** – www.curebs.com
Your central hub for information, support, and updates about Blau Syndrome. Learn about current research, connect with the patient community, and explore educational materials for patients, caregivers, and healthcare providers.

• **Blau Syndrome International Registry** – www.curebs.com/registry
Join the first-ever global registry for Blau Syndrome. By enrolling, you contribute valuable data that helps researchers better understand the disease, identify trends, and accelerate the development of new treatments.

• **Patient Webinar Recording** – *Blau Syndrome Educational Forum Featuring Dr. Carlos Rose and Dr. Carine Wouters*- https://www.curebs.com/blau-education
Watch this in-depth educational session where two leading Blau Syndrome experts explain the disease, share current treatment approaches, and answer patient questions. A must-see for newly diagnosed patients, families, and clinicians.

- **Study Participation Opportunity** – *Mechanism of Disease of the Human Immune System:* Researchers Dr. Bryce Binstadt from the University of Minnesota and Dr. Ruth Napier from University of Colorado, Anschutz Medical Campus are looking for children and adults with immune-mediated diseases to participate in a study to learn more about how the novel or rare genetic mutations cause immune-mediated diseases.
Contact: ruth.napier@cuanschutz.edu

Arthritis	Granulomatous Dermatitis
	
	
	
	

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