**Pityriasis Rubra Pilaris**

## SYNONYMS

PRP

Devergie's Disease

Lichen Acuminatus

Lichen Ruber Acuminatus

Pityriasis Rubra Pilaire (Fr.)

Lichen Ruber Pilaris(1) (2) (3)

## SUBDIVISIONS OF PRP

Type 1 — Classical Adult Onset

Type 2 — Atypical Adult Onset

Type 3 — Classical Juvenile Onset

Type 4 — Circumscribed Juvenile Onset

Type 5 — Atypical Juvenile Onset

Type 6 — HIV-associated(1) (2) (3)

## SUMMARY

Pityriasis rubra pilaris (PRP) is a group of rare skin disorders that cause inflammation and shedding of the skin. The name means scaling (pityriasis), redness (rubra) and involvement of the hair follicles (pilaris).(4)

Typically, PRP appears first as a small spot somewhere on the body and then spreads elsewhere.(5)

It will impact different parts of the body in different ways for unpredictable periods of time. (5) The inflammation may cover the entire body or just parts of the body such as the elbows and knees, palms and soles. (6) The disease may progress and leave distinct areas of uninvolved skin, the so-called “islands of sparing” or “skip areas”.(7)

The disorder may start in childhood or adulthood. It affects males and females equally.(8)

There are several types of PRP, which are classified based on age of onset, body areas affected, and whether other associated conditions are present. PRP is usually sporadic (occurring randomly) but some forms may be inherited.(9)

With an estimated 800-plus “active” patients in the U.S. and less than 1900 in Europe, PRP is an ultra-rare skin disorder. The rarity of PRP notwithstanding, the signs and symptoms of PRP often mimic those of eczema (31.6 million patients) and psoriasis (8 million patients).(10) (11)

The treatment of PRP typically involves a combination of systemic and topical therapies combined. Topical therapies can help with the symptoms and may be enough for people with mild PRP. Topical treatments are usually combined with systemic therapy for PRP

that affects a large part of the body. Most people need systemic therapy to control the condition.

Currently there are no treatments approved by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) for use in PRP.(12)

PRP patients and their caregivers quickly learn that every case of PRP is unique.(4)

## INTRODUCTION

When James Shooter was admitted to St. Bartholomew's Hospital in London, England in 1828, he unwittingly became the world's first patient with what the medical community would eventually call *pityriasis rubra pilaris*. In 1828, however, Mr. Shooter's skin disorder did not yet have a name. Seven years passed before Claudius Tarral, a French dermatologist, wrote about the case in *Traite theorique et pratique des maladies de la peau (Treatise on Skin Diseases)* in 1835. Tarral saw it as a variant of psoriasis.(13) (14)

It would take another 21 years for Marie Guillaume Alphonse Devergie, a dermatologist and forensic doctor at St. Louis Hospital in Paris, to publish the most complete description of PRP. In fact, it was considered to be the "original description" of PRP by the medical community. Devergie's article was published in the Gazette *Hebdomadaire de Medecine et de Chirurgie* in 1856.(14)

While Devergie saw the skin disorder as a combination of "follicular lesions and psoriasis palmaris, pityriasis capillitii and pityriasis rubra", it would take yet another 21 years

before another Frenchman and dermatologist by the name of Richaud to recognize PRP as a distinct entity. Richaud published "Etude sur le pityriasis pilaris" in 1877.(15)

When Ernest Besnier presented nine cases in a 120-page article published in 1889 — 12 years after Richaud, 43 years after Devergie, and 54 years after Tarral, he forever fixed the name of the disease as *pityriasis rubra pilaris*. Besnier too, was a Frenchman and dermatologist. He was also the medical director of the St. Louis Hospital in Paris — the same hospital as Devergie.(16) The name comes from three Latin words: *pityriasis* (scalelike skin), *rubra* (red) and *pilaris* (hair follicles).(2)

Like many rare disease communities, the PRP community laments the snail's pace at which PRP research progresses. What should we expect — it took 61 years just to get the name right.

## SIGNS & SYMPTOMS

The terms "sign" and "symptom" are not redundant. A SIGN is subjective, eg, pain, itching, fatigue. The PRP patients must share that information with the dermatologist, dermatology physician assistant or dermatology nurse. In contrast, a SYMPTOM can be observed by others, including healthcare professionals. The following is a list of SIGNS and SYMPTOMS that define the PRP experience.

### *Pre-onset Signs*

Mild signs include dandruff and crusty scalp, limited red patches or scaling of the skin, eg, dime-sized red spot" on forehead. Duration varies from patient to patient. At some

point patient determines that intervention of a healthcare professional is warranted, eg, red spot has doubled in size in less than two weeks.

***Onset of Symptoms***

Depending on the advance of inflammation, a general practitioner or dermatologist will see symptoms including pink, red, or orange-red scaly patches on your skin. The patches are usually itchy. You may have the scaly patches only on some parts of your body. They most often occur on the elbows, knees, hands, feet, and ankles. The skin on the palms of your hands and the soles of your feet may also become red and thickened. The scaly patches may eventually spread over the entire body.(17)

Cracks may develop which can be painful and make walking and using the hands difficult. The nails may become thickened and discolored at the free nail edge and may show linear black streaks (splinter hemorrhages). The hair may thin considerably.(6) Shivering, heat and fluid loss may occur if the rash covers large areas of skin.(4) The onset of PRP may be further exacerbated if a misdiagnosis of psoriasis or eczema, for example, results in an improper treatment option.(5)

***Acute Stage Signs and Symptoms***

The dermatologist will be able to see the symptoms of a body engulfed by dry, red, and flaking skin, swollen feet and legs, and cracked and bleeding feet. There may be serious issues related to impaired mobility, eyes and vision, and dexterity. The PRP patient will see signs of PRP from a different perspective, eg, pain of motion, unrelenting itch, inability to sweat, overheating, the impact of cold, heat and sleep deprivation. The Acute Stage poses the greatest challenge to body, mind, and spirit and can last less than a month or months longer. This is the time in the PRP journey that PRP patients and caregivers

should seek support from patient support groups. It is also a time to address issues of depression.(5)

***Management Stage***

After the Acute Stage, the journey of a PRP patient takes on a new focus — mitigating symptoms. All the potential irritants are waiting on the roadside, eg, joint pain, clogged ears, disability claims, etc. While 90% of the PRP patient population can look forward to full remission within one to four or five years, the timetable is not certain. Those diagnosed with Atypical Adult Onset and Atypical Juvenile Onset, the chronic versions of PRP, must develop long-term coping skills. For everyone, the daily routine associated with medications, moisturizing, and dealing with the unpleasantries of this skin disorder cannot be ignored.

***Remission & Healing Milestones***

There does not appear to be an official definition of remission as it applies to pityriasis rubra pilaris. For some it means no meds, no signs, and no symptoms. Others are told they are in remission by their dermatologist during their last clinic visit. Other believe that sustained improvement with an acceptable quality of life is all that is required for a declaration of remission. The PRP community, however, has adopted a more celebratory approach with recognition of healing milestones, eg, the return of sweat, the first trip to Walmart for groceries, dark hardwood floors that don’t need hourly vacuuming. These milestones are signs of healing that PRP patients and caregivers feel and symptoms that everyone else observes.

## CAUSES

The specific underlying cause of PRP is unknown, although genetic factors, an abnormal immune response, or vitamin A deficiency may be involved. (18), (19), (20), (21), (22)

PRP is an autoinflammatory disease according to the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), "a relatively new category of diseases that are different from autoimmune diseases. However, autoimmune and autoinflammatory diseases share common characteristics in that both groups of disorders result from the immune system attacking the body's own tissues, and they also result in increased inflammation."(23) When your body is attacked — perhaps by a virus or other germs — your immune system defends you. It "sees" and kills the germs that might hurt you.

*"But when the system doesn't work right, this process can cause harm. Immune cells can mistake your body's own cells as invaders and attack them. This "friendly fire' can affect almost any part of the body. It can sometimes affect many parts of the body at once. This is called "autoimmunity' (meaning "self-immunity').*

*"The part of the immune system that orchestrates all of this develops as a person grows and is known as the acquired immune system. It "remembers" foreign antigens, or proteins, so that it can fight them if they come back. It employs white blood cells called lymphocytes.*

*"But the body also has an innate (inborn) immune system that is more primitive. It employs types of white blood cells called granulocytes and monocytes to destroy harmful substances. In autoinflammatory diseases, this innate immune system causes*

*inflammation for unknown reasons. It reacts, even though it has never encountered autoantibodies or antigens in the body.*

*"Autoinflammatory disorders are characterized by intense episodes of inflammation that result in such symptoms as fever, rash, or joint swelling. These diseases also carry the risk of amyloidosis, a potentially fatal buildup of a blood protein in vital organs."*(23)

## AFFECTED POPULATIONS

Based on conversations within the PRP community, we can say with metaphysical certitude that PRP isn't a punishment for misbehavior or forgetting to put the seat down on a toilet (loo in some parts of the world). There are thousands of perfectly wonderful people who have — or had — PRP. Moreover, there are many very bad people who don't have it. Who then gets the short end of this rare disease stick?

*Prevalence:* In March 2003, Dr Andrew Griffiths delivered a "Dowling Oration" to members of the British Association of Dermatology assembled in Liverpool, England. Dr Griffiths reflected on 35 years of diagnosing, treating and researching pityriasis rubra pilaris. He unilaterally fixed the PRP prevalence rate at one in 400,000. While the methodology used by Dr Griffiths is subject to debate, dermatologists worldwide have accepted his estimates.(1)

*Age:* Pityriasis rubra pilaris is a rare disorder that may develop during childhood or adulthood. Juvenile Onset accounts for 45% of the "active" patient population while Adult Onset accounts for 55%.(6)

Although PRP may occur at any age (10), it most commonly affects those in their first, second, fifth, or sixth decades of life.(24)(2)

*Gender:* PRP appears to occur in males and females in relatively equal numbers. However, in childhood, the male to female ratio is 3:2.(25)

*Race:* Persons of any race may be affected.(2)(7)

*Acquired or Inherited:* PRP is usually sporadic (occurring randomly) but some forms may be inherited.(6)(2)

## RELATED DISORDERS

Symptoms of the following disorders can be similar to those of pityriasis rubra pilaris. Comparisons may be useful for a differential diagnosis:

***Psoriasis****:* According to the National Psoriasis Foundation, "psoriasis is an immune-mediated disease that causes raised, red, scaly patches to appear on the skin. It typically affects the outside of the elbows, knees or scalp, though it can appear on any location. Some people report that psoriasis is itchy, burns and stings. Psoriasis is associated with other serious health conditions, such as diabetes, heart disease and depression." More information is available at the NPF website.(26)

***Atopic dermatitis (Eczema & Dermatitis)****:* There are different types of eczema that collectively affect more than 30 million Americans: atopic dermatitis, contact dermatitis,

dyshidrotic eczema, hand eczema, neurodermatitis, nummular eczema and stasis dermatitis. For more information contact the National Eczema Foundation.(27)

***Allergic reaction**:* Most allergic reactions are minor, such as a rash from poison ivy, mosquito or other bug bites, or sneezing from hay fever. The type of reaction depends on the person's immune system response, which is sometimes unpredictable. For more information about allergic reactions, go to eMedicineHealth.(28)

***Pityriasis rosea**:* Pityriasis rosea (PR) is a benign rash, a common skin disorder observed in otherwise healthy people, most frequently children and young adults. It can easily mimic types of similar skin eruptions including lichen planus, psoriasis, and pityriasis rubra pilaris. Pityriasis rosea has a very specific and recognizable rash. It does, however, begin with a "herald mark". Follow the link for additional information at Medscape.(29)

***Fungal infection**:* Fungal infections of the skin are also known as 'mycoses'. They are common and generally mild. However, in very sick or otherwise immune suppressed people, fungi can sometimes cause serious disease. Fungi are parasites or saprophytes, ie, they live off living or dead organic matter. Mycologists identify and classify fungi according to their appearance by microscopy and in culture, and by the method of reproduction, which may be sexual or asexual.(30)

***Lupus**:* Lupus is a chronic autoimmune disease that can damage any part of the body (skin, joints, and/or organs). "Chronic" means that the signs and symptoms tend to last longer than six weeks and often for many years. In lupus, something goes wrong with the immune system, which is the part of the body that fights off viruses, bacteria, and germs ("foreign invaders," like the flu). Normally our immune systems produce proteins called "antibodies" which protect the body from these invaders. "Autoimmunity" means your

immune system cannot tell the difference between these foreign invaders and your body's healthy tissues ("auto" means "self"). As a result, it creates autoantibodies that attack and destroy healthy tissue. These autoantibodies cause inflammation, pain, and damage in various parts of the body.(31)

***Cutaneous T-cell lymphoma**:* On occasion, the diagnosis of a PRP patient has been changed to cutaneous T-cell lymphoma. The PRP community recommends that biopsy be performed to rule out CTCL. Inclusion of CTCL is an appropriate warning to PRP patients, caregivers and dermatologists.(32)

## DIAGNOSIS

A medical diagnosis is based on information from sources such as findings from a physical examination, an interview with the patient or family or both, a medical history of the patient and family, and clinical findings as reported by laboratory tests and radiologic studies.

A *differential diagnosis* is a process of weighing the probability of one disease versus that of other diseases. It represents an alternative diagnosis that precedes the enlightened diagnosis of pityriasis rubra pilaris.

Pityriasis rubra pilaris is not easy to diagnose. In March 2003, English dermatologist Dr Andrew Griffiths reinforced that fact when he titled his Dowling Oration to the British Association of Dermatologists "Pityriasis Rubra Pilaris — The Scarlet Pimpernel". Griffiths quoted Baroness Orczy's character who says: "They seek him here, they seek

him there, that damned elusive Pimpernel." We agree with Griffiths, "This disease remains an enigma."(1)

***The Diagnostic Role of the Dermatologist***

CLINICAL OBSERVATION is where it all begins. What symptoms are visible to the dermatologist during the examination? A dime-sized red spot on a forehead can reasonably be diagnosed as *seborrheic dermatitis*. Similarly, a patient "in full bloom" presenting with 90% coverage, islands of sparing, and other key indicators might be more than enough to awaken a memory of a grand rounds experience six years earlier in medical school, a textbook or a prior patient.

***The Diagnostic Role of the Dermatopathologist***

THE MICROSCOPE is where the clinical observations are either supported or not. Biopsies sent to a dermatopathologist are often used to "rule out" specific skin maladies or causes. The PRP community has learned from shared experiences — albeit anecdotal — that when the dermatologist suspects PRP and instructs the dermatopathologist to "consider PRP," that the findings support the clinical observations.

***Differential Diagnosis***

A differential diagnosis is the method by which a physician determines what disease process has caused a patient's symptoms. The physician considers all relevant potential causes of the symptoms and then eliminates alternative causes based on a physical examination, clinical tests and a thorough case history.(33)

"A differential diagnosis is a quest for a diagnosis. What is wrong with the patient internally? It is not, inherently, a search for the ultimate cause (critical to liability) of that

disease process or disorder." (34) It is "the process of weighing the probability of one disease versus that of other diseases possibly accounting for a patient's illness."(35)

## STANDARD THERAPIES

Treatment of pityriasis rubra pilaris (PRP) is mainly based on reports of patients' experiences. No controlled trials have been done, so the effectiveness and safety of treatments is unclear. Currently there are no treatments approved by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) for use in PRP. (9)

PRP tends to follow a natural waxing and waning course, with episodes in which there is periodic worsening (exacerbation) or cessation (remission) of symptoms. As a result, according to many researchers, it may be difficult to evaluate the effectiveness of particular therapies. (9)

The value of treatment is difficult to assess, as the clinical course is so variable for each of the different types of PRP. Patients with classical adult onset PRP, for example, may present with intense and widespread reddening of the skin (erythroderma). Hospital admission for skin care, fluid replacement and other supportive care may be warranted. (6)

From the patient perspective, there are two major objectives in the treatment of pityriasis rubra pilaris:

* relieving symptoms as they present

✻ achieving long-term remission, if possible. The mantra heard within the PRP community is simple but deafening: What works for one doesn't work for all.

***Treatment Options***

Management of PRP often involves systemic and topical therapies combined. Topical therapies can help with the symptoms and may be enough for people with mild PRP. Topical treatments are usually combined with systemic therapy for PRP that affects a large part of the body. Most people need systemic therapy to control the condition. (9)

Treatment options will vary based on age, geography, and cost to the patient. Moreover, laboratory tests are important to monitor the effects of medications on the body — especially the liver — and to manage and monitor the side effects of drugs.

Some of the medications used to treat PRP can harm a developing fetus and are not recommended for use right before or during pregnancy. (9)

People seeking information about specific treatment options for themselves or family members should speak with their health care provider. (9)

Oral retinoids are derivatives of vitamin A that slow the growth and shedding of skin cells. Treatment options include acitretin / Soriatane® and isotretinoin / Accutane®. Oral retinoids (synthetic vitamin A derivatives) are usually preferred as a first-line systemic treatment for PRP. (9)

Immunosuppressants to slow down the body's immune system. Often used when oral retinoids are ineffective. Treatment options include (oral and injection) include methotrexate and cyclosporine.

Biologicals, with generally fewer side effects, are targeted to reduce inflammation. These are injectable or intravenous (IV) medications that affect the immune system. Treatment options include adalimumab / Humira®, etanercept / Enbrel®, infliximab / Remicade®, ustekinumab / Stelara®, secukinumab / Cosentyx® and apremilast / Otezla®

**Other therapies**

✻ Ultraviolet light therapy. This is normally given in combination with psoralen (a drug that makes you less sensitive to the sun) and a retinoid. (8)

✻ Topical creams that contain urea or lactic acid. These go directly on your skin. (8)

✻ Oral vitamin A. This may be helpful in some people, but only in very high doses. Retinoids are more effective and more commonly used than vitamin A. (8)

✻ Traditional Chinese Medicine and other Alternative Medicines with varying degrees of success.

***Referrals***

Depending on the severity, duration and array of signs and symptoms, PRP patients seek the expertise of specialized healthcare professionals:

✻ Opthamologist: ectropion and impaired vision

✻ Podiatrist: impaired mobility

✻ Otorhinolaryngologist (ENT specialist): impaired hearing, removal of cerumen from ear canal.

✻ Hepatologist: monitor impact of PRP treatment on the liver.

✻ Psychiatrists/Clinical Psychologist: depression and mental wellness

✻ PRP patient support resources: (see Resources) For further information on patient care and tools see www.survivalguide.org

## INVESTIGATIVE THERAPIES

The Department of Dermatology and Cutaneous Biology located at Sidney Kimmel Medical College at Thomas Jefferson University (Philadelphia) began genetic research in October 2012 studying *CARD14* gene mutations in relation to PRP. Dr Jouni Uitto, Chair, was part of an earlier research effort in Tel Aviv that did not find a causal relationship between these mutations and PRP, but did discover a "genetic basis" for PRP. In July 2014, the genetic analysis research effort was expanded to include a clinical analysis component. The PRP Alliance helped recruit a cohort of over 100 PRP patients and Thomas Jefferson University has the full cooperation and support of the PRP community. Thomas Jefferson University is also seeking separate funding to build a PRP Patient Registry. No start date has been established. For information about PRP research, contact: www.prpSurvivalGuide.org. (36)

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government web site. For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD; Contact the NIH Patient Recruitment Office: Toll free: (800) 411-1222TTY: (866)

411-1010E; mail: prpl@cc.nih.gov. For information about clinical trials sponsored by private sources, contact: www.centerwatch.com.

## NORD MEMBER ORGANIZATIONS

*EURORDIS — Rare Diseases Europe*

Plateforme Maladies Rares

96 rue Didot

Paris, 75014 France

Website: http://www.eurordis.org

Email: eurordis@eurordis.org

*Foundation for Ichthyosis & Related Skin Types (FIRST)*

2616 N Broad Street

Colmar, PA 18915 (USA)

Phone: (215) 997-9400 Toll-free: (800) 545-3286

Email: info@firstskinfoundation.org

Website: http://www.firstskinfoundation.org

*PRP Alliance, Inc.*

1500 Commerce Drive

Plano, TX 75093-2640 USA

Phone: (214) 205-0574

Email: bill.mccue@prpalliance.com

Website: http://www.prpAlliance.org

## OTHER ORGANIZATIONS

*Genetic and Rare Diseases (GARD) Information Center*

PO Box 8126

Gaithersburg, MD 20898-8126, USA

Phone: (301) 251-4925 Toll-free: (888) 205-2311

Website: http://rarediseases.info.nih.gov/GARD/

*PRP Community on RareConnect*

Zürich, Switzerland; Barcelona, Spain

Website (PRP): www.rareconnect.org

Email: rareconnect@prpSurvivalGuide.org

*PRP Facebook Support Group*

Virginia Beach, VA, USA

Website (PRP): www.facebook.com

Email: facebooksg@prpSurvivalGuide.org

*PRP Survival Guide*

Plano, TX, USA

Email: editor@prpalliance.com

Website: http://www.prpSurvivalGuide.org

## REFERENCES

In the FINAL DRAFT, the references under the NORD-required headings: Textbooks, Journal Articles and From the Internet.

(1) Griffiths WA. Edited version of the Dowling Oration delivered to the British Association of Dermatologists in Liverpool, England. March 2003. http://prpsurvivalguide.org/wp-content/uploads/2017/05/Dowling-Oration-2003-Liverpool-England.pdf Accessed August 7, 2017.

(2) Paravina M, Ljubenovic M, Milosavljevic M, et.al. Pityriasis rubra pilaris: A report of two cases and literature review. https://www.degruyter.com/downloadpdf/j/sjdv.2015.7.issue-4/sjdv-2015-0016/sjdv-2015-0016.pdf. Serbian J Dermatol Venereol. 2015; 7 (4): 181-194 DOI: 10.1515/sjdv-2015-0016. Accessed August 7, 2017.

(3) ICD!)Data.com. http://www.icd10data.com/ICD10CM/Codes/L00-L99/L40-L45/L44-/L44.0 Accessed August 7, 2010.

(4) British Association of Dermatologists. Pityriasis rubra pilaris leaflet. http://www.bad.org.uk/shared/get-file.ashx?id=116&itemtype=document Updated May 2016. Accessed August 7, 2017.

(5) PRP Survival Guide. Chapter 1 — The Basics. http://prpsurvivalguide.org/2017/05/19/yayaya/?trashed=1&ids=3 Accessed August 7, 2017.

(6) DermNet New Zealand. Pityriasis rubra pilaris. www.dermnetnz.org/topics/pityriasis-rubra-pilaris/ Updated October, 2015. Accessed August 7, 2017.

(7) Medscape.com. Pityriasis rubra pilaris. http://reference.medscape.com/article/1107742-overview Updated April 17, 2017. Accessed August 7, 2017.

(8) Healthline.com. Pityriasis rubra pilaris. http://www.healthline.com/health/pityriasis-rubra-pilaris#Introduction1 Reviewed June 9, 2016. Accessed August 7, 2017.

(9) Genetic and Rare Disease Information Center. Pityriasis rubra pilaris. https://rarediseases.info.nih.gov/diseases/7401/pityriasis-rubra-pilaris Updated August 1, 2017. Accessed August 7, 2017.

(10) National Eczema Association. Eczema Facts. https://nationaleczema.org/research/eczema-facts/ Accessed August 7, 2017.

(11) National Psoriasis Foundation. About the National Psoriasis Foundation. https://www.psoriasis.org/about-us Accessed August 7, 2017.|

(12) Genetic and Rare Diseases Information Center. Pityriasis rubra pilaris. https://rarediseases.info.nih.gov/diseases/7401/pityriasis-rubra-pilaris#ref_7262 Accessed August 7, 2017.

(13) Tarral C. *Observation CXVIII. In Rayer P : 'Traite theorique et pratique des maladies de la peau'*, Paris: Bailliere:1835: 2,158-9.

(14) Devergie MGA. *Pityriasis rubra pilaris, maladie de peau non decrite par les dermatologists*. Gazette Hebdomadaire de Med. et de Chirurg. 1856;3:197-201.

(15) Richaud A, Féré C. *Etude sur le pityriasis pilaris [dissertation]*. Paris: A Parent; 1877.

(16) Besnier E. *Observations pour server a l'histoire clinique du pityriasis rubra pilaire (pityriasis pilaris de Devergie et de Richaud).* Ann Dermatol 2nd series 1889;10: 253-87, 398-427, 485- 544.

(17) Healthline.com. Pityriasis rubra pilaris. http://www.healthline.com/health/pityriasis-rubra-pilaris#causes3 Reviewed June 9, 2016. Accessed August 7, 2017.

(18) Healthline.com. Pityriasis rubra pilaris. http://www.healthline.com/health/pityriasis-rubra-pilaris#types2 Reviewed June 9, 2016. Accessed August 7, 2017.

(19) Genetic and Rare Diseases Information Center. Pityriasis rubra pilaris. https://rarediseases.info.nih.gov/diseases/7401/pityriasis-rubra-pilaris Accessed August 7, 2017

(20) Medscape.com. Pityriasis rubra pilaris. http://reference.medscape.com/article/1107742-overview#a5 Updated April 17, 2017. Accessed August 7, 2017.

(21) MedlinePlus, US National Library of Medicine. Pityriasis rubra pilaris. https://medlineplus.gov/ency/article/001471.htm Updated July 5, 2017. Accessed August 7, 2017.

(22) New Medical.net. Pityriasis rubra pilaris skin condition. http://www.news-medical.net/health/Pityriasis-Rubra-Pilaris-Skin-Condition.aspx Updated May 26, 2016. Accessed August 7, 2017.

(23) National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Understanding autoinflammatory diseases. https://www.niams.nih.gov/Health_Info/Autoinflammatory/default.asp January 2017. Accessed August 7, 2017.

(24) Judge MR, McLean WHI, Munro CS. Disorders of keratinization. In: Burns T, Breathnach S, Cox N, Gri ths C, editors. *Rook's textbook of dermatology*. 8th ed. Oxford: Blackwell Publishing Ltd; 2010. p. 19.1-19.122.

(25) Sehgal VN, Srivastava G. (Juvenile) Pityriasis rubra pilaris. https://www.ncbi.nlm.nih.gov/pubmed/16650174 Int J Dermatol 2006;45(4):438-46. Accessed August 7, 2017. |

(26) National Psoriasis Foundation. https://rarediseases.org/organizations/national-psoriasis-foundation/ Accessed 2017.

(27) National Eczema Association. https://nationaleczema.org Accessed 2017

(28) eMedicineHealth. Allergic reaction. http://www.emedicinehealth.com/allergic_reaction/page2_em.htm#what_causes_an_allergic_reaction ; 2017

(29) eMedicine Medscape. http://emedicine.medscape.com/article/1107532-overview ; Reviewed April 12, 2016. Accessed August 7, 2017.

(30) DermNet New Zealand. Introduction to fungal infections. https://www.dermnetnz.org/topics/introduction-to-fungal-infections/ 2003. Accessed August 7, 2017.

(31) Lupus Foundation of America. http://www.resources.lupus.org/entry/what-is-lupus Accessed August 7, 2017.

(32) Cutaneous Lymphoma Foundation. https://www.clfoundation.org; Accessed August 7, 2017.

(33) Committee on the Development of the Third Edition of the Reference Manual on Scientific Evidence, Committee on Science, Technology, and Law Policy and Global Affairs, FEDERAL JUDICIAL CENTER, National Academic Press, Washington, DC, page 214. https://www.fjc.gov/sites/default/files/2015/SciMan3D01.pdf Accessed August 7, 2017.

(34) International Center for Toxicology and Medicine. From symptoms to liability: The distinct roles of differential diagnosis and causation assessment. http://www.ictm.com/Downloads/dri-causation.pdf. Accessed August 7, 2017

(35) MedicineNet.com. Medical definition of differential diagnosis. http://www.medicinenet.com/script/main/art.asp?articlekey=2991 Reviewed May 13, 2016. Accessed August 7, 2017.

(36) PRP Survival Guide. Chapter 7 — PRP Research. http://prpsurvivalguide.org/2017/05/21/chapter-6-prp-research/ Updated August 1, 2017; Accessed August 7, 2017.