



PRURITUS

CLINICAL ASPECTS

- The cause of uremic pruritus is unknown.
- It occurs in 25-33% predialysis patients and 60-86% of dialysis patients.
- It is not dependent on age or gender.
- There is about 10-14% reduction in incidence of pruritus in CAPD patients versus hemodialysis patients.
- It can be localized or generalized. It occurs most frequently on the forearm and upper back.

POSSIBLE TRIGGERS

Histamine

- Regardless of the mechanism, the symptom of pruritus is thought to be related to the release of histamine from skin mast cells.
- Only histamine H1-receptors are involved.
- The number of basophils and mast cells are increased

Proteases

- Proteases are potent histamine releasers.

Leukotrienes

- Leukotrienes are modulators of pruritus.

Prostaglandins

- Prostaglandins are modulators, which lowers the threshold for histamine-induced itching.

Substance P

- Substance P is a neurotransmitter that transmits the sensation of itch.

POSSIBLE CAUSES

The mechanism of uremic pruritus is poorly understood.

Uremic Skin

- Uremic skin is atrophic, xerotic and has a yellowish discoloration.
- It occurs in 67-93% of patients.
- It may not be relieved by topical emollients.

Cutaneous Mast Cell Proliferation

Atrophy of the Sebaceous Glands and Sweat Glands

- There are decreased surface lipids.
- Diminished sweating may aggravate decreased cutaneous hydration & impair the normal excretion of electrolytes, lactate, urea, and other pruritogenic substances.

Increased Skin pH

- Skin pH of the hemodialysis patients is significantly higher than normal, which may predispose patients to fungal dermatitis and, consequently, pruritus.

Secondary Hyperparathyroidism

- Secondary hyperparathyroidism causes increased calcium and phosphate levels leading to soft-tissue calcification (see mineral metabolism section)

Divalent-ion Abnormalities

- Renal failure patients can experience accumulation of calcium, magnesium and phosphate in the skin.
- There can also be microprecipitation of mineral salts.

Hypervitaminosis A

- Hypervitaminosis A can cause drying & peeling of the skin.
- Fat-soluble Vitamin A is not removed by hemodialysis.

Iron Deficiency Anemia

- Renal failure patients can experience iron deficiency in the early stages after initiation of erythropoietin.

Peripheral Neuropathy

- Patients may experience peripheral neuropathy due to nerve fibres sprouting into the epidermis.

Middle Weight Molecules

- Porphyrins and beta-2 microglobulins may contribute to pruritus.

Bile Acids

- Increased serum bile acid concentration has been shown to induce pruritus.

TREATMENT

Effective therapy remains a clinical challenge:

- Regular, intensive dialysis eliminates or markedly improves pruritus. Patients report more severe pruritus just before the dialysis session and the least the day after hemodialysis.
- A Kt/V urea value > 2.1, which represents efficient dialysis, is optimal, if the patient can tolerate it.

- It is preferable to use highly permeable membranes and biocompatible membranes for hemodialysis. Some patients may be allergic to the dialysis membrane sterilant ethylene oxide.
- Restricted diet reduces phosphate intake (see mineral metabolism section).
- Calcium or aluminum containing phosphate binders bind dietary phosphate in the gut (see mineral metabolism section).
- Erythropoietin (see anemia section)
 - The antipruritic effect begins in 1 week but may take 4 weeks for maximum response.
 - Decreased histamine levels may be noted.
 - The antipruritic effect only lasts 7 days after stopping erythropoietin.
- Iron supplementation is recommended if iron deficient anemia is present (see anemia section).
- For xerosis, emollients & topical corticosteroids can be used.
 - Eg. 1% HC,
 - 3% Salicylic Acid,
 - 5% Propylene Glycol,
 - 10% Urea,
 - in glaxal base
- UVB
 - UVB therapy can be performed 3 times a week for 3 weeks. Remission time is about 3 months.
 - UVB therapy causes photo-inactivation of pruritogenic substances or inactivation of Vitamin D, thus altering skin content of divalent ions.
 - UVA & UVB also decrease epidermal Vitamin A.
 - Phototherapy decreases skin mast cell numbers.
 - Patients should be counselled to avoid photosensitive drugs.
 - Phototherapy produces variable results.
- Antihistamines
 - A 2-3 week trial of one of the following antihistamines is recommended:
 - hydroxyzine 25-50 mg po q6-12h
 - diphenhydramine 25-50 mg po q8-12h
 - cyproheptadine 2-4 mg po q8-12h
 - clemastine fumarate 1.34-2.68 mg po q8-12h
 - Antihistamines provide variable relief.
- Cholestyramine - 4 g po bid

- Patients should be monitored for hyperchloremia as cholestyramine exchanges chloride for bile acids.
 - Side effects of cholestyramine include constipation, nausea & vomiting, and cramping.
 - Cholestyramine decreases the absorption of some medications (eg. digoxin, warfarin, phenytoin and vitamins) so it is important to space medications at least 1 hour before or 4-6 hours after cholestyramine.
- Activated charcoal
 - Activated charcoal in a dose of 6 g/day in 4-6 divided doses for 8 weeks can be tried.
 - It is necessary to watch for decreased absorption of medications
- Combination UV and cholestyramine or activated charcoal can also be tried.
- Subtotal parathyroidectomy
 - Subtotal parathyroidectomy often provides relief of pruritus in 24-48 hours.
 - Vitamin D and calcium supplementation is required.
 - PTH is not pruritogenic, but it may act as a marker for some unknown pruritogenic substance.
- Heparin, lidocaine, naloxone (50 mg po daily), ondansetron (4 mg po bid for 3 months), thalidomide, and azelastin HCl (2 mg po daily) have also been reported in the literature with varying results.
- Acupuncture
 - Acupuncture treatment has been shown to provide relief persisted for months after a series of treatments.
- sauna bath
 - Some patients are asymptomatic for several weeks after a sauna bath.
- Oatmeal baths, baking soda (1 full box), salt water baths, and bath oil therapy have also been tried.
- A 100% cotton sheet over the dialysis chair and 100% cotton clothes may also provide relief.

Pruritus: Useful References

1. Andersen, LW, et al. Naloxone in the treatment of uremic pruritus: a case history. *Clin Nephrol* 1984 Jun;21(6):355-6.
2. Balaskas, EV, et al. Histamine and serotonin in uremic pruritus: effect of ondansetron in CAPD-pruritic patients. *Nephron* 1998;78(4):395-402.
3. Balaskas, EV. Uremic pruritus in CAPD patients. *Perit Dial Int* 1997 Sep-Oct;17(5):440-1.
4. Balaskas, EV, et al. Uremic pruritus is a poor prognostic factor of outcome. *Perit Dial Int* 1995;15(2):177.
5. Balaskas, EV, et al. Pruritus in continuous ambulatory peritoneal dialysis and hemodialysis patients. *Perit Dial Int* 1993;13 Suppl 2:S527-32.
6. Bencini, PL, et al. Cutaneous abnormalities in uremic patients. *Nephron* 1985;40(3):316-21.
7. Blachley, JD, et al. Uremic pruritus: skin divalent ion content and response to ultraviolet phototherapy. *Am J Kidney Dis* 1985 May;5(5):237-41.
8. Cho, YL, et al. Uremic pruritus: roles of parathyroid hormone and substance P. *J Am Acad Dermatol* 1997 Apr;36(4):538-43.
9. Cohen, EP, et al. Mast cells and calcium in severe uremic itching. *Am J Med Sci* 1992 Jun;303(6):360-5.
10. Marchi, S, et al. Relief of pruritus and decreases in plasma histamine concentrations during erythropoietin therapy in patients with uremia. *N Engl J Med* 1992 Apr 9;326(15):969-74.
11. Denman, ST. A review of pruritus. *J Am Acad Dermatol* 1986 Mar;14(3):375-92.
12. Dimkovic, N, et al. Uremic pruritus and skin mast cells. *Nephron* 1992;61(1):5-9.
13. Duo, LJ. Electrical needle therapy of uremic pruritus. *Nephron* 1987;47(3):179-83.
14. Francos, GC, et al. Elevated plasma histamine in chronic uremia. Effects of ketotifen on pruritus. *Int J Dermatol* 1991 Dec;30(12):884-9.
15. Gilchrest, BA, et al. Clinical features of pruritus among patients undergoing maintenance hemodialysis. *Arch Dermatol* 1982 Mar;118(3):154-6.
16. Giovannetti, S, et al. Oral activated charcoal in patients with uremic pruritus. *Nephron* 1995;70(2):193-6.
17. Hiroshige, K, et al. Uremic pruritus. *Int J Artif Organs* 1996 May;19(5):265-7.
18. Hiroshige, K, et al. Optimal dialysis improves uremic pruritus. *Am J Kidney Dis* 1995 Mar;25(3):413-9.
19. Kanai, H, et al. The effect of azelastin hydrochloride on pruritus and leukotriene B4 in hemodialysis patients. *Life Sci* 1995;57(3):207-13.
20. Masi, CM, et al. Dialysis efficacy and itching in renal failure. *Nephron* 1992;62(3):257-61.
21. Mettang, T, et al. Uremic pruritus in patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). The role of plasma histamine and skin mast cells. *Clin Nephrol* 1990 Sep;34(3):136-41.
22. Ponticelli, C, et al. Uremic pruritus: a review. *Nephron* 1992;60(1):1-5.
23. Robertson, KE, et al. Uremic pruritus. *Am J Health Syst Pharm* 1996 Sep 15;53(18):2159-70; quiz 2215-6.
24. Schultz, BC, et al. Uremic pruritus treated with ultraviolet light. *JAMA* 1980 May 9;243(18):1836-7.
25. Schwartz, J, et al. Clonidine for painful diabetic-uremic leg cramps and pruritus -- a case report. *Angiology* 1993 Dec;44(12):985.

26. Silva, SR, et al. Thalidomide for the treatment of uremic pruritus: a crossover randomized double-blind trial. *Nephron* 1994;67(3):270-3.
27. Smith, EC. The uremic itch. *Int J Artif Organs* 1980 Mar;3(2):64-6.
28. Stahle-Backdahl, M. Uremic pruritus. *Semin Dermatol* 1995 Dec;14(4):297-301.
29. Stahle-Backdahl, M. Uremic pruritus. Clinical and experimental studies. *Acta Derm Venereol Suppl (Stockh)* 1989;145:1-38.
30. Stahle-Backdahl, M. Pruritus in hemodialysis patients. *Skin Pharmacol.* 1992;5(1):14-20.
31. Szepietowski, JC, et al. Uremic pruritus. *Int J Dermatol* 1998 Apr;37(4):247-53.
32. Tan, JK, et al. Identifying effective treatments for uremic pruritus. *J Am Acad Dermatol* 1991 Nov;25(5 Pt 1):811-8.
33. Tercedor, J, et al. Erythropoietin therapy for uremic pruritus. *N Engl J Med* 1992 Sep 3;327(10):734; discussion 734-5.