



# COLUMBIA UNIVERSITY MEDICAL CENTER

DIVISION OF GENERAL MEDICINE

Senior Medicine Rotation: Evidence-Based Medicine Project

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Case SIGNOUT:

57 y.o. Caucasian M with a history of mild intermittent asthma, psychotic depression, anxiety, pre-diabetes, pre-HTN, and an unknown history of varicella exposure presenting with a three-day unilateral, burning, erythematous vesicular eruption in the L. V1 distribution following a four day prodrome of dizziness, myalgias, and L. conjunctival injection. The patient's presentation was deemed consistent with L. herpes zoster ophthalmicus with overlying dermatoblepharitis and sparing of the globe. Treatment was initiated with 850 mg IV acyclovir tid, bacitracin ointment qid, and neurontin 100 tid for treatment of acute lesions and neuritis and prevention of bacterial superinfection and postherpetic neuralgia. It was noted that corticosteroids have also been variably administered for acute herpes zoster.

**Clinical Question:** *Are corticosteroids indicated in the treatment of herpes zoster to promote resolution of lesions, treat acute neuritis and/or prevent postherpetic neuralgia?*

## Background:

- ❖ Herpes Zoster:
  - Dermatomal vesicular rash and acute neuritis, which can precede/ occur simultaneously with the rash
  - Results from reactivation of endogenous latent VZV infection within the sensory ganglia
  - Estimated lifetime incidence of 10-20%, with incidence doubling each decade past 50 years
  - <20% patients have systemic sx of HA, fever, malaise, fatigue, but 75% of patients have prodromal pain in the dermatome where the rash subsequently appears.
- ❖ Zoster Complications
  - Postherpetic neuralgia:
    - Pain lasting at least 120 days from rash onset, but likely representing a continuum of pain that never resolves following an acute episode of zoster
    - Most common complication: occurs in 10-15% of patients with acute zoster
    - Factors predicting development of PHN:
      - Age, severity of neuritis or rash at clinical presentation, history of prodromal symptoms, ophthalmic zoster, immunocompromised state
  - Others: Bacterial skin infxns, ocular complications (uveitis and keratitis), motor neuropathy, meningitis, encephalitis, stroke, and herpes zoster oticus
- ❖ Goals of Therapy:
  1. Treatment of the acute viral infection
  2. Treatment of the acute neuritis
  3. Prevention of PHN-Treatment initiated with antivirals ideally within 72 hrs, analgesics, agents for prevention of PHN
- ❖ Role of Corticosteroids
  - Pathophysiology of PHN is unclear:
    - Damage to sensory nerves, sensory dorsal root ganglia and dorsal horns of the spinal cords
    - ? Represent persistence of low amounts of VZV with continued inflammation, providing rationale for treatment with acyclovir and corticosteroids.
  - Recently published Cochrane review on *Corticosteroids for Preventing Postherpetic Neuralgia*
    - Pooled data from 5 randomized controlled trials conducted between 1970-1996
    - Conclusions:
      - Corticosteroids are ineffective at preventing PHN
      - Risks of administration of corticosteroids are not great in people with acute zoster
      - Corticosteroids have been recommended to relieve acute phase pain
      - Long-term follow-up should observe the effect on corticosteroids on the transition from acute pain to PHN.
      - Future trials should include measurement of function and quality of life.

## Search Strategy

Database: PubMed

((Herpes zoster[Title]) AND steroids[MeSH Terms]) AND "randomized controlled trial"[Publication Type]) AND English[Language] => 9 results

Wood MJ, Johnson RW, Mckendrick MW, Taylor J, Mandal BK, Crooks J. A randomized trial of acyclovir for 7 days or 21 days with and without prednisolone for treatment of acute herpes zoster. *New England Journal of Medicine* 1994;**330**(13):896-900.



*Multicenter randomized, double-blind, placebo-controlled parallel study.*

Group	Criteria or definition	n
Population screened	Patients at four centers in the United Kingdom (Birmingham, Bristol, Manchester, and Sheffield)	?
Inclusion criteria	Adults over 18 yrs of age presenting with a clinical diagnosis of herpes zoster as confirmed by one of the investigators, having a rash for 72 hours or less, and having at least moderate pain.	400
Exclusion criteria	Immune dysfunction due to cancer or immunosuppressive therapy, being a pregnant woman/woman of childbearing potential who was not adequately protected by contraception; having renal insufficiency (serum Cr > 1.8 mg/dL); HTN (DBP > 110 mmHg); IDDM or a random blood glucose > 216 mg/dL; hx of peptic ulceration, severe psoriasis, or hypersensitivity to acyclovir; receiving barbiturates, anticonvulsant drugs, systemic steroids, rifampin, or specific antiviral therapy for the present infection.	?
Treatment groups	<b>A: 7 Days of acyclovir therapy</b> (800 mg acyclovir 5x/day x 7 days, followed by matching placebo until day 21 and matching prednisolone placebo tablets for 21 days)	101 (39M, 62 F, mean age 58)
	<b>B: 7 Days of acyclovir therapy</b> (800 mg acyclovir 5x/day x 7 days, followed by matching placebo until day 21) <b>and 21 days Prednisolone</b> as follows: 40 mg days 0-6, 30 mg days 7-10, 20 mg days 11-14, 10 mg days 15-18, and 5 mg days 19-21 (total dose, 535 mg).	99 (37 M and 62 F, mean age 59)
	<b>C: 21 days of acyclovir therapy</b> (800 mg 5x/day x 21 days with matching prednisolone placebo tablets for 21 days)	101 (38 M, 63 F, mean age 59)
	<b>D: 21 days of acyclovir therapy</b> (800 mg 5x/day x 21 days) <b>and 21 days of Prednisolone</b> as follows: 40 mg days 0-6, 30 mg days 7-10, 20 mg days 11-14, 10 mg days 15-18, 5 mg days 19-21 (total dose, 535 mg).	99 (39 M, 60 F, mean age 60)

**Primary endpoints:** Last day with new lesions, first day without new vesicles, first day with full crusting, time to 100% healing of the rash, time to first cessation of pain, time to complete cessation of pain, change from base line in pain-intensity score.

**Secondary endpoints:** Adverse events

• **Are the Results of the Trial Valid?**

- **Randomized?** YES; computer-generated randomization code was employed at each center
- **All patients accounted for at end?** YES, 349 patients completed study as specified
  - 51 withdrawals balanced equally amongst groups: 10 in 7 day acyclovir, 14 in 7 day acyclovir plus prednisolone, 14 in 21 day acyclovir, and 13 in 21 day acyclovir plus prednisolone
  - Reasons: deviation from protocol, adverse events, loss to follow-up, no reason given, and death.
- **Intention to treat?** YES
- **Blinding:** YES: double-blinded with use of placebos
- **Groups similar at start of trial?** YES
  - Groups well- matched for sex, age, duration of prodrome, duration of rash, and base-line pain score with the following deviation noted:
    - Median duration of rash for 7-day acyclovir noted to be 48-72 hrs, whereas other groups noted to be 24-48 hrs. Nevertheless, means comparable at 55 vs ~50 hrs.
- **Equal treatment of groups?** Yes
  - Rash and pain intensity assessed on days 0, 1, 2, and 3; then twice weekly until 21 days (or until all lesions crusted if longer); and on day 28. Then monthly visits until 6 months to assess PHN
  - Rash assessed for new lesions, vesicles, crusts, and percentage of rash healed.
  - Patients kept a pain diary describing intensity, quality, and pattern of pain and whether it interfered with sleep.
  - Blood samples obtained prior to study and on days 7 and 21. Adverse events recorded.
- **Did randomization work?** Yes

- **Are the Results of the Trial important?** Important? YES. Significant? YES & NO. Administration of corticosteroids resulted in a significantly higher proportion of the rash area healed on days 7 & 14 (P=0.02) and greater pain reduction during the acute phase on days 7 and 14 (P<0.01 for both). Nevertheless, corticosteroid administration did not result in any significant difference in time to a first or complete cessation of pain. Additional primary endpoints consisting of time to last day with new lesions, first day with no new vesicles, first

day with full crusting, and first day with 100% healing were not statistically different between groups treated with and without prednisolone. Lastly, steroid recipients experienced more adverse outcomes.

Endpoint	Result		Significance
	Acyclovir plus steroid	Acyclovir Alone	
Last day with new lesions	1	1	HR: 0.985 (0.79-1.23) P: 0.89
First day with no new vesicles	2	2	HR: 0.860 (0.69-1.07) P: 0.18
First day with full crusting	7	7	HR: 0.856 (0.68-1.07) P: 0.17
First day with 100% healing	19	21	HR: 0.924 (0.75-1.14) P: 0.40
Morbidity	Result		Significance
% of patients reporting ≥ 1 adverse event <i>(dyspepsia, nausea, vomiting, diarrhea, depression, dizziness, HA, paresthesia, hot flushes, sweats, edema, HTN, rash, biochemical/ hematologic abnormality, other)</i>	38	26	RR: 1.46 p: 0.1

Endpoint	Result		Significance
	Acyclovir Alone	Acyclovir plus steroid	
Time to first cessation of pain (median day)	84	91	0.876 (0.69-1.11) P: 0.27
Time to complete cessation of pain (median day)	140	137	1.043 (0.81-1.34) P: 0.74

Table 3. Changes from Base Line in Pain-Intensity Scores.

DAY	7-DAY ACYCLOVIR		21-DAY ACYCLOVIR		P VALUE*	
	STERIOD	NO STERIOD	STERIOD	NO STERIOD	7-DAY VS. 21-DAY ACYCLOVIR	STERIOD VS. NO STERIOD
	score (95% confidence interval)†					
0	3.8 (3.7–3.9)	3.9 (3.8–4.0)	3.8 (3.7–3.9)	3.8 (3.7–3.9)	—	—
7	1.3 (1.0–1.5)	0.8 (0.6–1.0)	1.5 (1.3–1.8)	1.2 (0.9–1.4)	0.02	<0.01
14	1.7 (1.5–2.0)	1.4 (1.1–1.6)	1.9 (1.6–2.1)	1.6 (1.4–1.9)	0.17	<0.01
21	1.9 (1.6–2.2)	1.9 (1.6–2.2)	1.9 (1.6–2.2)	2.0 (1.7–2.3)	0.63	0.96
28	2.0 (1.7–2.3)	2.1 (1.8–2.4)	2.1 (1.8–2.3)	2.2 (1.9–2.5)	—	—

\*By the Wilcoxon rank-sum test.

†Values shown for day 0 are mean base-line pain-intensity scores, and remaining values are mean changes from the base-line scores.

• **Can I apply these results to my patient?**

- **Comparison of my patient to trial patients:**
  - Duration of patient’s rash was at least 72 hours; presentation complicated by zoster ophthalmicus; history of pre-diabetes, pre-HTN, and psychotic depression/anxiety
- **All clinically important outcomes considered:** Three goals of therapy (resolution of rash, resolution of acute pain, prevention of postherpetic neuralgia) were all considered, but quality of life indicators like return to usual activity, return to uninterrupted sleep, analgesia requirement, and persistent scarring/ changes in pigmentation from rash were not assessed.
- **Likely benefits outweigh potential harms and cost?**
  - Although it appears that a short course of prednisolone in addition to acyclovir promotes the acute healing of rash and pain severity during the first two weeks, its ineffectiveness in preventing PHN begs the question of whether this reported short-term benefit merits the many known adverse systemic effects of corticosteroids.
  - Especially in this patient, the possibilities of hyperglycemia, HTN, mood disorder/ psychosis, and exacerbated gastritis are particularly concerning.
  - Thus, it appears that the benefits do not outweigh the harms, but ultimately more studies investigating the effects of corticosteroids on more practical quality of life indicators are necessary.

**References:**

Wood MJ, Johnson RW, Mckendrick MW, Taylor J, Mandal BK, Crooks J. A randomized trial of acyclovir for 7 days or 21 days with and without prednisolone for treatment of acute herpes zoster. *New England Journal of Medicine* 1994;330(13):896–900.

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