PICO Search Assignment Worksheet Name__Lisette Romo_____

Brief description of patient problem/setting (summarize the case very briefly)

A 23-year-old Spanish-speaking male with no significant past medical history presents to the fast track section of the emergency department with four days of a painful and pruritic rash along his left hip, lower back, and inguinal region, confined in a single dermatomal pattern. He reports pain on a scale of 7/10. Despite using a medical interpreter, the history was limited, so the inquiry of a previous varicella infection or vaccination status was unknown. To provide relief of the symptoms, he took four tablets of over-the-counter Benadryl, which caused sedation side effects, without relief. Physical examination showed vesicles on an erythematous base on the left side, without crossing the midline. Given the clinical presentation and physical examination, he was diagnosed with herpes zoster. He was prescribed gabapentin and acyclovir. This highlights the need to choose appropriate antiviral medication while considering efficacy, cost, and patient adherence.

Search Question: In adult patients presenting with herpes zoster, do antivirals valacyclovir or famciclovir, in comparison to acyclovir, decrease the pain associated with this condition, along with the incidence of postherpetic neuralgia as a complication?

Question Type: What type of question is this?

□ **Treatment** □ Diagnosis □ Prognosis □ Screening □ Prevalence □ Harms

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)?
Please explain your choices.

If there were no highest level of evidence available, including systematic reviews or meta-analyses, then I would choose the next order of high-level evidence. Randomized controlled trials (RCTs) would provide sufficient comparison on antiviral medications, acyclovir, valacyclovir, and famciclovir. Choosing an RCT is beneficial when discussing treatment options since it can test these options on various demographics, leading to evaluating outcomes regarding efficacy in reducing pain and incidence of complications of herpes zoster. The next type of evidence to consider is prospective cohort studies to assess outcomes in settings such as the emergency department, where treatment plans are decided and given to patients at discharge. These studies are both relevant since they reflect comparisons and insight to management of herpes zoster. Other studies to consider are retrospective cohort and case-control studies. These can be used, but it is important to consider the bias potentially involved, and they may not be as strong in evidence in comparison.

PICO search terms:

P (Population)	I (Intervention)	C (Comparison)	O (Outcome)
Herpes zoster	Valacyclovir	Acyclovir	Post-herpetic neuralgia
Shingles	Famciclovir		Zoster-associated pain
	Antiviral therapy		

Search tools and strategy used:

Please indicate what databases/tools you used, provide a list of the terms you searched together in each tool, and how many articles were returned using those terms and filters.

Database	Search Terms Used	Number of Results	Filters/Limiters Applied	Notes/Observations
PubMed	(herpes zoster OR shingles) AND (valacyclovir OR famciclovir OR acyclovir)	870	Publication within the last 10 years, English language, and clinical trials	Initially, broad results, narrowing search terms improved specificity. The articles discussed similar efficacy amongst the antivirals.
Google Scholar	(herpes zoster OR shingles) AND (valacyclovir OR famciclovir OR acyclovir) AND (pain OR postherpetic	5,950	Publication within the last 10 years, English language, sorted by	Broad search results with a large number of articles. Filter applied for relevance and quality of studies. Results

	neuralgia)		relevance.	included a large mix of studies, with varying strengths in evidence.
CINAHL	herpes zoster AND (acyclovir OR valacyclovir OR famciclovir) AND pain	58	Publication within the last 10 years, English language, research articles.	Moderate number of results; more focused than Google Scholar, still broader than Cochrane. Articles included various study types with relevant findings on antiviral effectiveness.

Pubmed, CINAHL, and Google Scholar were my databases of choice to conduct research for articles to access various levels of evidence. PubMed was used to identify my primary studies, including randomized controlled trials comparing different antivirals. CINAHL demonstrated high-level evidence through systematic reviews. Lastly, using Google Scholar allowed me to broaden my search and assess other relevant studies. Using various search terms, I was able to choose articles that directly addressed my PICO question.

Results found:

Identify at least 3 articles (or other appropriate reputable sources) that answer your specific question with the highest available level of evidence.

1. **A Network Meta-Analysis of Randomized Clinical Trials to Assess the Efficacy and Safety of Antiviral Agents for Immunocompetent Patients with Herpes Zoster-Associated Pain**
   https://pubmed.ncbi.nlm.nih.gov/37535772/

   Liu Y, Xiao S, Li J, et al. "A Network Meta-Analysis of Randomized Clinical Trials to Assess the Efficacy and Safety of Antiviral Agents for Immunocompetent Patients With Herpes Zoster-Associated Pain." Pain Physician. 2023;26(4):337-346. PMID: 37535772

Abstract

Background: The most refractory symptom of herpes zoster (HZ) is pain. Approximately 90% of people who have HZ suffer from pain. Early use of antiviral medications has been found to reduce pain across all stages of the disease. Although many antiviral agents via oral or intravenous administration were recommended by clinical practice, the best approach to prevent HZ-associated pain remains uncertain.

Objectives: The purpose of this study was to compare the efficacy and adverse events of various antiviral agents used for the treatment of HZ-associated pain through a network meta-analysis.

Methods: Randomized clinical trials evaluating antiviral agents currently available for treating HZ-associated pain were included. We extracted data in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and conducted network meta-analyses with random-effects models. The primary outcome was the presence of acute pain at the end of anti-virus treatment, and the secondary outcomes included the presence of pain at 28-30 days after the onset of the acute herpetic rash, the presence of postherpetic neuralgia (PHN), and any other adverse events.

Results: A total of 17 randomized control trials with 5,579 participants were included in this study. According to the results of the network meta-analysis, for the treatment of acute pain, there was no significant difference between oral acyclovir and intravenous acyclovir. Furthermore, oral famciclovir was the most effective treatment concerning both the odds ratio (OR) (superior to placebo OR = 0.25; 95% CI: 0.13~0.48) and the surface under the cumulative ranking curve (SUCRA) values of 0.84 for the treatment of acute pain among all the oral antiviral agents. For the presence of pain at 28-30 days, no significant difference was observed in efficacy between all antiviral treatments and placebo concerning the OR; however, oral valaciclovir ranked first (SUCRA values of 0.96). For the presence of NPH, oral famciclovir was determined to be the most effective (SUCRA values of 0.77) treatment with an efficacy of 0.42 (95% CI: 0.18~0.99) versus placebo. For adverse events, there was no significant difference between oral antivirals and placebo; however, intravenous acyclovir ranked last with a score of OR 4.31 (95% CI: 1.26~14.75) versus placebo.

Conclusions: For the treatment of acute pain and PHN, oral famciclovir was the most effective treatment among all the oral antiviral agents. For alleviating pain after 28-30 days, oral valaciclovir appeared to be the most effective among all antiviral agents. Additionally, all oral antiviral agents were well tolerated.

Why I chose this article:

I chose this article because it is a network meta-analysis, which is the highest level of evidence. It comprises data from 17 randomized control trials with over 5,500 patients. This article applies to my PICO question since it compares antivirals: acyclovir, valacyclovir, and famciclovir. Since it compared all three at the same time, it demonstrated which antiviral was the most effective for pain reduction and prevention of postherpetic neuralgia, which are both outcomes in my question. The study found that famciclovir was the most effective of the antivirals for reducing pain and preventing postherpetic neuralgia, although valacyclovir was at the highest rank for reducing pain over an extended period of time, at 28-30 days. Additionally, this study was from 2023, making it very recent and applicable to current clinical practice. During my clinical rotation in emergency medicine, I was asked about treatment for herpes zoster, and I initially stated valacyclovir as first-line treatment. However, my preceptor educated me on prescribing acyclovir due to its affordability, highlighting the importance of clinical efficacy through patient access. This is relevant to the patient's case, who was treated with acyclovir, highlighting that it is used due to affordability, and how other antivirals such as valacyclovir or famciclovir improve pain and easier dosing compared to acyclovir.

Key Points:

i. This is a network meta-analysis of 17 RCTs with 5,579 participants, evaluating antiviral therapy for herpes zoster

ii. Famciclovir was the most effective in pain reduction and prevention of postherpetic neuralgia complications

iii. Valacyclovir was ranked the highest in reducing pain at 28 to 30 days

iv. The evidence supports using valacyclovir or famciclovir instead of acyclovir for better efficacy and easier dosing.

2. **Comparing Prodrugs with Acyclovir for Treating Postherpetic Neuralgia among Herpes Zoster Patients: A Systematic Review and Meta-Analysis** **https://pubmed.ncbi.nlm.nih.gov/35885708/**

Yeh CH, Chang KS, Huang SS, Tsay SL, Tsai JM, Wang YJ. "Comparing Prodrugs with Acyclovir for Treating Postherpetic Neuralgia among Herpes Zoster Patients: A Systematic Review and Meta-Analysis." *Healthcare*. 2022;10(7):1181. PMID: 35885708 doi:10.3390/healthcare10071181

Objective: The objective of this study was to compare the efficacy of prodrugs and acyclovir in treating PHN among patients with HZ.

Methods: This study took the form of a meta-analysis of RCTs that investigated the association between acyclovir and PHN. We conducted it in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) protocol. We searched relevant studies from the PubMed, Medline, and Cochrane Central Register of Controlled Trails databases through February 2022. We relied on the PICO framework to identify potentially relevant studies in the search, including both the indexed terms and Medical Subject Headings (MeSH) terms found in the titles and/or abstracts. The specific search terms were Population (P): herpes zoster; Intervention (I): acyclovir; Comparison (C): placebo or prodrugs; Outcome (O): PHN." Clinical studies and trials and RCTs involving acyclovir intervention for patients diagnosed with HZ were eligible for inclusion in this review. We compared the results of treatments with acyclovir and the prodrugs with placebos after the onset of HZ with PHN. The cut-off time for PHN varied across the studies. To include as many RCTs of the antiviral PHN treatments as possible in our sample, we used a cut-off time of one month after the onset of the rash (i.e., at least 30 days from the onset), which is consistent with the definition of acute PHN in the previous literature." We conducted the meta-analysis using ReviewManager software (version 5.3, Nordic Cochrane Centre, Cochrane Collaboration (London, UK) according to the manufacturer's guidelines. We also used this software to calculate the pooled risk ratios (RRs) with 95% confidence intervals (CIs) in a fixed-effect model across the eligible studies."

Results: Five RCTs with 1147 HZ patients met our eligibility criteria. Two studies, involving 860 participants in all, compared the effect of acyclovir with that of produgs (valaciclovir or famciclovir). The results of our meta-analysis showed that the RR for PHN events among the participants who received the prodrugs was significantly higher than among those who received acyclovir (RR = 0.86, 95%, CI: 0.75 to 0.98, p = 0.03). In other words, the prodrugs were significantly more effective than acyclovir in relieving PHN within one month after the onset of the rash. The results of a heterogeneity

assessment showed no significant heterogeneity between these two studies ($\chi 2 = 0.08$, $p = 0.77$, $I2 = 0\%$).The five studies, as discussed, compared the effects of acyclovir on the members of the treatment groups with the progress of PHN in the members of the control groups who received either a placebo or prodrugs (famciclovir or valaciclovir). Our meta-analysis showed that the incidence of PHN events among the members of the acyclovir groups was only slightly, and not significantly, higher than among the members of the control groups (RR = 1.13, 95% CI: 0.99 to 1.28, $p = 0.06$). In other words, acyclovir did not prevent PHN within one month after the onset of the rash. The results of a heterogeneity assessment showed no significant heterogeneity among the five studies ($\chi 2 = 1.56$, $p = 0.82$, $I2 = 0\%$). Three of the studies, involving 287 participants in all, compared the effects of acyclovir with the administration of a placebo. The results of our meta-analysis showed that the incidence of PHN events for the participants who received acyclovir was lower than for those who received the placebo or no treatment (RR = 0.98, 95%, CI: 0.71 to 1.35, $p = 0.89$), but the difference was not significant. In other words, again, acyclovir did not prevent PHN within one month after the onset of the rash. The results of a heterogeneity assessment showed no significant heterogeneity among these three studies ($\chi 2 = 0.52$, $p = 0.77$, $I2 = 0\%$). While none of the five studies in our meta-analysis reported any serious adverse events, some participants did experience mild nausea, headaches, constipation, dyspepsia, and vomiting.

Conclusion: Our meta-analysis found that the prodrugs valaciclovir and famciclovir were effective in relieving PHN among HZ patients. However, the evidence that we analyzed was insufficient to determine whether acyclovir can have this effect. We did find that the prodrugs were more effective than acyclovir for mitigating PHN. These agents have been in use for years, but relatively few recent RCTs have focused on them in this regard. We conclude that their efficacy in general and for especially susceptible populations such as the immunocompromised and those with DM in particular merits further investigation. More large-scale, multicenter RCTs with a wide range of participants are needed to verify and build on our findings.

Why I chose this article:

I decided to choose this article since it provides a high level of evidence, as it is a systematic review and meta-analysis of randomized controlled trials. It compares antivirals, acyclovir to valacyclovir and famciclovir, making it relevant to answer my PICO question. This article is also unique in comparison to other studies since it evaluates outcomes over 30 days after the rash onset, which essentially assesses long-term complications. What was also surprising was that although acyclovir is prescribed for shingles, it did not significantly reduce the likelihood of postherpetic neuralgia, versus a placebo; this demonstrates a possible flaw in its effectiveness. On the other hand, valacyclovir and famciclovir provided a significant reduction in postherpetic neuralgia, meaning these antivirals can also manage acute pain symptoms and be more effective in reducing long-term complications. Understanding this clear distinction in antivirals is necessary when making clinical decisions when considering choosing medication for symptomatic relief and long-term outcomes.

Key Points:

i. This is a systematic review and meta-analysis including 5 RCTs with 1,147 participants evaluating antiviral therapy for herpes zoster. It focused on postherpetic neuralgia, the most common complication.

ii. Valacyclovir and famciclovir were more effective in comparison to acyclovir in reducing postherpetic neuralgia

iii. Acyclovir did not reduce postherpetic neuralgia when compared to placebo, which emphasizes the limitation of this antiviral in preventing future complications.

3. Randomized Clinical Trial of Famciclovir or Acyclovir for the Treatment of Herpes Zoster in Adults https://pubmed.ncbi.nlm.nih.gov/29746903/

Pott Junior H, Bocchi de Oliveira MF, Gambero S, Amazonas RB. "Randomized Clinical Trial of Famciclovir or Acyclovir for the Treatment of Herpes Zoster in Adults." *International Journal of Infectious Diseases*. 2018;72:11-15. PMID: 29746903. doi:10.1016/j.ijid.2018.04.43

Background: This study investigated the safety and efficacy of famciclovir compared to acyclovir in patients with herpes zoster, to determine whether the two regimens are equally effective for the treatment of patients with uncomplicated herpes zoster over a period of 7days.

Methods: Patients were randomly assigned to receive either famciclovir 500mg (one tablet) three times daily or acyclovir 800mg (two capsules) five times daily for 7 days. The primary endpoint was defined as the time to full crusting of herpes zoster lesions. Secondary endpoints were the proportion of patients who achieved complete cure and the change in score of signs/symptoms (pain, vesicular lesions, loss of sensitivity, burning pain, and pruritus) according to the patient diary.

Results: One hundred and seventy-four patients were enrolled and randomized; 151 of these patients completed treatment (n=75 famciclovir, n=76 acyclovir). A similar proportion of patients who received acyclovir (94.74%) and famciclovir (94.67%) achieved complete cure. The mean time to full crusting of herpes zoster lesions was 15.033days in the acyclovir group and 14.840days in the famciclovir group (log-rank p-value=0.820). The most common adverse events in the pooled groups were headache, diarrhea, nausea, back pain, cold, and drowsiness, but none of these was deemed to be clinically important.

Conclusion: Both interventions obtained high rates of cure and had a similar time to full crusting of lesions. Analysis of the primary efficacy endpoint proved that famciclovir is non-inferior to acyclovir, as the confidence interval for the difference in efficacy did not violate the non-inferior margin. Therefore, the results are not different enough to be clinically relevant.

Why I chose this article:

I chose this article since it is a randomized controlled trial, which provided strong evidence when comparing antiviral therapy. The other two articles I chose are meta-analyses; this RCT study gives a direct comparison between famciclovir and acyclovir in a clinical setting. This allows for the evaluation of the efficacy and symptom improvement being reported by patients. This is important since medications are able to be assessed on how they perform in actual practice instead of just an accumulation of data. As a result, famciclovir and acyclovir are both effective in the treatment of herpes zoster. This RCT shows that these two antivirals provide the same efficacy in resolving the rash/ lesions, while other higher-level evidence studies take into account the other factors with pain management, long-term prevention, and dosing, and instead favor valacyclovir or famciclovir in comparison. Also,

the RCT mentioned common side effects, which the other two did not. This is relevant in applying this to the patient's case, who was prescribed acyclovir, as this article does support it as an effective treatment, and also considers other possible alternatives.

Key Points:

i. This was an RCT trial with 174 participants that lasted 7 days, and it compared famciclovir versus acyclovir in the treatment of herpes zoster.

ii.Supports that famciclovir and acyclovir have equivalent efficacy for acute lesion healing

iii. Most common side effects from antiviral medication included headache, diarrhea, nausea, back pain, and drowsiness.

iv. Famciclovir is dosed with a simpler regimen (3x daily), which provides better patient adherence.

What is the clinical "bottom line" derived from these articles in answer to your question?

Overall, these articles help to address what type of antivirals would provide better outcomes. Current evidence does suggest that acyclovir helps with better lesion healing, valacyclovir and famciclovir are far more effective in the reduction of pain and prevention of long-term complications, most commonly, postherpetic neuralgia, which is persistent nerve pain that occurs after the infection resolves. Moreover, the prodrugs, famciclovir and valaciclovir, offer simpler dosing regimens, which can essentially provide better patient adherence, and this will most benefit patients with barriers such as language differences or who struggle with following a medication schedule. Based on these sources, it can be concluded that the prodrugs are better and more preferred options for clinicians when available, providing better pain control and decreasing complications. However, acyclovir is still a reasonable option from a cost and accessibility standpoint. Ultimately, various factors must be taken into consideration when selecting a medication.