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Treatment overview:

- zoster is self-limited and usually resolves without complications; treatment goals are to reduce symptoms, speed rash resolution and prevent complications
- treatments that may reduce acute pain
    - corticosteroids may reduce acute zoster pain and improve quality of life at 1 month **(level 2 [mid-level] evidence)**, but have no benefit for postherpetic neuralgia
    - other treatments that may reduce acute pain **(level 3 [lacking direct] evidence)** include cool compresses, calamine lotion, analgesics, tricyclic antidepressants
- limited evidence that any treatments prevent postherpetic neuralgia, but famciclovir, valacyclovir or amitriptyline may be considered
- antiviral treatment
    - antiviral treatments achieve modest reduction in time to full healing of rash if started within 3 days of initial rash (e.g. full crusting may occur in 10 days without antiviral agent and 8 days with antiviral agent)
    - antiviral agents should be initiated in ophthalmic zoster, disseminated zoster, and ill severely immunocompromised patients
    - antiviral treatment options
        - valacyclovir (Valtrex) 1 g PO 3 times daily for 7 days $185.64
        - famciclovir (Famvir) 500 mg PO 3 times daily for 7 days $178.71
        - acyclovir (Zovirax) 800 mg PO 5 times daily for 7-10 days $224.70, generic $121.45
        - Reference - Treatment Guidelines from The Medical Letter 2005 Apr;3(32):23
    - parenteral antiviral agents indicated for some cases of ophthalmic zoster, immunocompromised hosts, and disseminated zoster
        - in immunocompromised host, acyclovir (Zovirax) 10 mg/kg IV every 8 hours for 7 days (20 mg/kg IV every 8 hours for 7-10 days in children age 12 years and younger) $2,236.20, generic $1,602.00
        - for acyclovir-resistant zoster, foscarnet (Foscavir) 40 mg/kg IV every 8 hours for 10 days $1,050.00, not FDA approved
        - Reference - Treatment Guidelines from The Medical Letter 2005 Apr;3(32):23
- ophthalmic zoster
    - all patients with ophthalmic zoster (irrespective of age or illness severity) should be prescribed antiviral agents at first sign of disease and re-examined within 1 week
    - ophthalmology referral indicated if Hutchinson's sign (skin lesions extending to tip of nose and at inner corner of side of nose), visual complaints or red eye

Medications:

- analgesics or tricyclic antidepressants for acute pain
- antiviral treatment

- useful for hastening of healing of acute zoster (modest benefit)
- valacyclovir and famciclovir also have been shown to reduce duration of postherpetic neuralgia in randomized trials, but most patients (especially those aged < 50) do not develop postherpetic neuralgia
- ophthalmic zoster should be treated with oral antiviral agents in consultation with ophthalmology consultants
    - **famciclovir 500 mg PO 3 times daily and acyclovir 800 mg PO 5 times daily for 7 days appear to have equivalent efficacy (level 2 [mid-level] evidence)** in randomized trial of 454 patients with ophthalmic zoster of trigeminal nerve, 58% of both groups had one or more ocular manifestations over 6 months, 43 patients in acyclovir group were excluded from analysis because initial study participants used acyclovir dosing that was not commercially available (Br J Ophthalmol 2001 May;85(5):576)
    - **valacyclovir 1,000 mg PO twice daily and acyclovir 800 mg PO 5 times daily for 7 days had equivalent efficacy (level 1 [likely reliable] evidence)** in randomized trial of 110 immunocompetent patients with herpes zoster ophthalmicus diagnosed within 72 hours of skin eruption (Ophthalmology 2000 Aug;107(8):1507)
    - **oral antiviral therapy associated with lower complication rate in patients with acute herpes zoster ophthalmicus (level 2 [mid-level] evidence)**; retrospective study comparing 202 such patients treated with oral antivirals vs. 121 who were not, 0 vs. 3.3% had neurotrophic keratitis (p = 0.02, NNT 30), 2.1% vs. 8.9% had adverse outcome (visual acuity 20/200 or worse, trichiasis, or surgery for eyelid malposition) at 5-10 years (p = 0.009, NNT 15) (Arch Ophthalmol 2003 Mar;121(3):386)
- for localized zoster in immunocompetent adults (start within 48-72 hours of onset of rash)
    - valacyclovir (Valtrex) 1 g PO 3 times daily for 7 days
        - generally well tolerated
        - adverse effects may include gastrointestinal symptoms, headache, rash, hallucinations, confusion
        - renal dosing (7-day course)
            - creatinine clearance 30-49 mL/minute - 1 g every 12 hours
            - creatinine clearance 10-29 mL/minute - 1 g every 24 hours
            - creatinine clearance < 10 mL/minute - 500 mg every 24 hours
        - **valacyclovir associated with earlier pain relief than acyclovir (level 1 [likely reliable] evidence)**; 1,141 immunocompetent adults > 50 years old with zoster randomized to valacyclovir 1 g PO 3 times daily for 7 or 14 days vs. acyclovir 800 mg PO 5 times daily for 7 days and followed for 6 months; median duration of zoster-associated pain was 38 or 44 days vs. 51 days; comparing both valacyclovir groups vs. acyclovir group, 19.3% vs. 25.7% had postherpetic neuralgia at 6 months (NNT 16);

no significant differences in pain intensity, quality of life, or adverse events (Antimicrob Agents Chemother 1995 Jul;39(7):1546 PDF)

- famciclovir (Famvir) 500 mg PO 3 times daily for 7 days
  - generally well tolerated
  - adverse effects may include headache, nausea, diarrhea
  - renal dosing
    - creatinine clearance 40-59 mL/minute - 500 mg every 12 hours
    - creatinine clearance 20-39 mL/minute - 500 mg once daily
    - creatinine clearance < 20 mL/minute - 250 mg once daily
    - hemodialysis - 250 mg after dialysis
  - famciclovir 500 mg 3 times daily for 7 days within 72 hours is effective and reduces median duration of postherpetic neuralgia from 4 months to 2 months; study of 323 patients with 500 mg or 750 mg of famciclovir 3 times daily or placebo for 7 days; all study patients were immunocompetent and were treated within 72 hours of the appearance of the rash; famciclovir accelerated rate of lesion resolution (by an average 1-2 days), reduced duration of viral shedding, and reduced duration (but not incidence) of postherpetic neuralgia; both doses were equally effective (Ann Intern Med 1995 Jul 15;123(2):89 **EBSCO*host* Full Text** in QuickScan Reviews in Fam Pract 1996 Feb:18); further noted that at 6 months after rash in patients > 50, 40% on famciclovir vs. 70% on placebo still had pain; no benefit in patients < 50; most common side effects were headache and nausea (POEMs in J Fam Pract 1996 Apr;42(4):350)
- acyclovir (Zovirax) 800 mg PO 5 times/day for 7-10 days
  - generally well tolerated
  - adverse effects may include gastrointestinal symptoms, headache, rash, rarely encephalopathy (tremors, hallucinations, seizures, coma)
  - renal dosing - see literature

o in immunocompromised host (or patients with disseminated zoster)
- acyclovir (Zovirax) 10 mg/kg (500 mg/m^2 in children) IV every 8 hours for 7 days
- adverse effects with IV administration may include phlebitis, extravasation, reversible renal failure (crystalline nephropathy), encephalopathy (tremors, hallucinations, seizures, coma)
- famciclovir and valacyclovir not available in parenteral form

o for acyclovir-resistant VZV
- foscarnet (Foscavir) 40 mg/kg IV every 8 hours for 10 days, not FDA approved
- adverse effects may include renal failure, nausea, vomiting, anemia, fatigue, headache, genital ulceration, CNS disturbances, hypocalcemia, hypercalcemia, hypophosphatemia,

hyperphosphatemia, hypokalemia, hypomagnesemia

- corticosteroids
  - **steroids may have a role in zoster, based on review of small amount of evidence available**; steroid use reasonable in healthy patients > 50 with herpes zoster; corticosteroids can reduce acute zoster pain and improve quality of life at 1 month, but have no effect on development or severity of postherpetic neuralgia; theoretical risk of viral dissemination not supported in small trials of immunocompetent patients; side effects of nausea, vomiting, dyspepsia, edema, hot flushes; pooled dropout rate about 14% with steroids; 21-day prednisone taper costs < $10, cost-effectiveness unknown (J Am Board Fam Pract 1998 May-Jun;11(3):224)
- combination antiviral and corticosteroid
  - **combination acyclovir and prednisone hastens healing more than single therapy or placebo**; study of 201 immunocompetent patients > 50 with localized zoster < 72 hours; patients with cancer, hypertension, osteoporosis, or diabetes mellitus were excluded; patients given acyclovir 800 mg 5 times/day for 21 days or placebo, and prednisone tapered from 60 to 15 mg/day (60 mg/day for 1 week, 30 mg/day for 1 week, 15 mg/day for 1 week) or placebo; combination therapy improved more outcomes more quickly than either single therapy; acyclovir associated with earlier crusting and healing of lesions and earlier return to usual activities; prednisone associated with cessation of acute pain, discontinuation of analgesics, and return to uninterrupted sleep and usual activities during first month only; at 6 months, no differences; 22-27% side effects with any therapy; steroids did not prevent postherpetic neuralgia; suggestion to consider acyclovir without corticosteroids for patients with severe pain or involvement of first trigeminal branch, and those at high risk of developing postherpetic neuralgia (Ann Intern Med 1996 Sep 1;125(5):376 **EBSCO*host* Full Text** in J Watch 1996 Oct 1;16(19):152 and in POEMs in J Fam Pract 1996 Dec;43(6):539); discussion by authors suggests limiting acyclovir < 10 days since another study showed no difference between 7 and 21 days of acyclovir (N Engl J Med 1994 Mar 31;330(13):896)
- treatments for prevention of postherpetic neuralgia (PHN)
  - limited evidence (from randomized controlled trials) that current treatments prevent or shorten PHN
  - famciclovir and valacyclovir have each been shown to reduce duration of PHN in single published trials of 419 and 1,141 patients, respectively
  - percutaneous electrical nerve stimulation (PENS) more effective than famciclovir in single trial of 50 patients
  - pre-emptive amitriptyline (25 mg PO once nightly for 90 days) reduced incidence of PHN in placebo-controlled trial of 80 patients
  - steroids had no effect on PHN
  - acyclovir had marginal benefit at best with 4 trials of mixed quality having inconsistent results
  - treatments to prevent PHN not recommended for patients younger than 50 as incidence of PHN is low
  - for details, see Prevention section in postherpetic neuralgia
- miscellaneous treatments

- topical antibiotics for secondary bacterial infection
- cimetidine has been reported in 4 cancer patients to improve pain and pruritus, and heal inflammatory skin lesions within 48 hours; dose reported for one patient was 300 mg PO 4 times daily for 7 days (N Engl J Med 1984 Feb 2;310(5):318)
- topical application of povidone-iodine associated with rapid crusting and pain resolution in case report of zoster lesions at 7 days of age (Lancet 2004 Aug 7-13;364(9433):502 **EBSCO*host* Full Text**)
- topical Preparation H anecdotally reported to improve zoster in 1 patient (Cortlandt Forum 1996 Sep;9(9):109,103-31)

Consultation and referral:

- refer patients with red eye, ocular foreign body sensation, tearing, blurry vision or photophobia to ophthalmologist

Prevention and Screening

Prevention:

- avoid primary varicella infections (chickenpox)
- **exposure to varicella in previously exposed patients may reduce risk for subsequent zoster**; case-control study comparing 244 patients recently diagnosed with zoster and 485 controls with no history of zoster; social contacts with many children outside the household and occupational contacts with ill children were associated with protection against zoster in dose-response fashion, increasing number of known varicella contacts associated with reduced risk for zoster; study method inadequate to exclude recall bias (Lancet 2002 Aug 31;360(9334):678 **EBSCO*host* Full Text**), commentary can be found in Am Fam Physician 2003 Jan 1;67(1):162
- varicella-zoster vaccine
  - Zostavax FDA approved to reduce risk of herpes zoster in people age 60 years and older (FDA Press Release 2006 May 26)
  - CDC Advisory Committee on Immunization Practices recommends zoster vaccine (Zostavax) for all persons age 60 years and older, including those with history of zoster (CDC Press Release 2006 Oct 26)
  - Zostavax overview
    - live attenuated varicella zoster virus vaccine to prevent zoster
    - at least 14 times more potent than Varivax (vaccine used to prevent varicella)
    - given as single subcutaneous injection
    - costs about $150
    - contraindicated in immunosuppressed patients, including patients taking prednisone 20 mg/day for > 2 weeks
    - Reference - Prescriber's Letter 2006 Jul;13(7):37
  - **potent zoster vaccine prevents zoster and postherpetic neuralgia in previously unvaccinated elderly (level 1 [likely reliable] evidence)**
    - 38,546 immunocompetent adults > 60 years old (at 22 US medical centers) with history of varicella (or at least 30 years residence in continental US), no history of zoster, no history of zoster or varicella vaccination were randomized to investigational live attenuated Oka/Merck VZV vaccine 0.5 mL vs. placebo subcutaneously once in nondominant arm, minimum estimated potency of study vaccine was > 14 times that of Varivax
    - follow-up and case definitions

        - median follow-up 3.12 years, 0.6% withdrew or lost to follow-up, 4.1% died during study
        - suspected cases of zoster were confirmed or excluded by polymerase chain reaction testing for VZV DNA when possible or determined by expert panel blinded to randomized assignment
        - PHN defined as pain at least 3 on 0-10 scale persisting or appearing > 90 days after zoster rash onset
    - comparing vaccine vs. placebo
        - 315 (1.63%) vs. 642 (3.33%) confirmed cases of zoster ($p < 0.001$, NNT 59), 1.67% vs. 3.43% in intent-to-treat analysis (NNT 57)
        - 27 (0.14%) vs. 80 (0.42%) cases of postherpetic neuralgia ($p < 0.001$, NNT 364)
        - adverse events (based on substudy of 6,616 patients)
            - 58.1% vs. 34.4% any adverse event (NNH 4)
            - 1.9% vs. 1.3% any serious adverse event (NNH 166)
            - 48.3% vs. 16.6% adverse event at injection site (NNH 3)
    - Reference - N Engl J Med 2005 Jun 2;352(22):2271, editorial can be found in N Engl J Med 2005 Jun 2;352(22):2344, commentary can be found in CMAJ 2005 Aug 2;173(3):249, commentary can be found in J Fam Pract 2005 Sep;54(9):757 or in BMJ 2005 Sep 17;331(7517):584, commentary can be found in N Engl J Med 2005 Sep 29;353(13):1414, 1414, commentary can be found in ACP J Club 2005 Nov-Dec;143(3):61
- revisions to CPT codes include code 90736 for zoster (shingles) vaccine, live, for subcutaneous injection (Fam Pract Manag 2006 Jan;13(1):28 PDF)
- inactivated varicella vaccine prevents zoster in patients undergoing hematopoietic cell transplantation; 119 patients scheduled to undergo autologous hematopoietic cell transplantation for lymphoma were randomized to heat-inactivated live attenuated varicella vaccine (within 30 days before and 30, 60 and 90 days after transplantation) vs. no vaccine; 111 patients had transplantation and were analyzed; 13% vs. 33% developed zoster over 12 months ($p = 0.01$, NNT 5); 10% had induration, erythema or local pain at injection site (N Engl J Med 2002 Jul 4;347(1):26), commentary can be found in N Engl J Med 2002 Nov 14;347(20):1624
- unknown if varicella vaccine will prevent zoster in general population
- cost-effectiveness of zoster vaccine unclear (Ann Intern Med 2006 Sep 5;145(5):317 **EBSCO*host* Full Text**), editorial can be found in Ann Intern Med 2006 Sep 5;145(5):386 **EBSCO*host* Full Text**
- additional information regarding Zostavax administration
    - Zostavax must be kept frozen, with average temperature < -15 degrees C (+5 degrees F) in freezer with separate door from refrigerator, Zostavax must be reconstituted and given immediately once out of freezer
    - if Varivax given by mistake, Zostavax should be given

immediately or wait 28 days
        - avoid Zostavax in immunosuppressed patients
        - Reference - Prescriber's Letter 2006 Dec;13(12):67
        - drug reimbursed in United States by Medicare under Part D but administration of drug reimbursed under Part B
            - pharmacists can bill Part D for administration but administration in physician office may require patient to pay for it (about $150) and get reimbursed
            - vaccine and administration fee will both be covered under Part D in 2008
            - Reference - Prescriber's Letter 2006 Dec;13(12):67, Prescriber's Letter 2007 Feb;14(2):10
    - review of varicella-zoster vaccine for prevention of zoster can be found in N Engl J Med 2007 Mar 29;356(13):1338

References including Reviews and Guidelines

General references used:

- The Medical Letter 1999 Dec 3;41(1067):113
- review of managing ophthalmic zoster in primary care (BMJ 2005 Jul 16;351(7509):147)
- herpes zoster ophthalmicus (Can Fam Physician 2001 Mar;47:493, 503, summary can be found in Am Fam Physician 2001 Sep 1;64(5):867)

Reviews:

- review can be found in BMJ 2007 Jun 9;334(7605):1211
- review can be found in Am Fam Physician 2006 Mar 1;73(5):882
- review can be found in Am Fam Physician 2005 Sep 15;72(6):1075, commentary can be found in Am Fam Physician 2006 Aug 1;74(3):378
- review can be found in Am Fam Physician 2000 Apr 15;61(8):2437
- review can be found in BMJ 2003 Apr 5;326(7392):748