

帶狀皰疹和帶狀皰疹後神經痛(PHN)的治療及預防

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一、前言

水痘帶狀皰疹病毒感染(Varicella-zoster virus, VZV)會引起兩種臨床上型式不同的疾病。初次感染水痘帶狀皰疹病毒(VZV)，就是俗稱的水痘(varicella)：好發在臉部、軀幹和四肢。而帶狀皰疹(Herpes zoster)則是由潛伏在神經節內的水痘帶狀皰疹病毒(VZV)被刺激，而擴散至各個皮節(dermatome)

產生成帶狀分布的皮疹。罹患帶狀皰疹所導致的急性神經疼痛或者是皮疹消失後仍持續疼痛的帶狀皰疹後神經痛(post-herpetic neuralgia, PHN)，是最令患者困擾的症狀。這些疼痛的情況可影響到患者的睡眠情況、降低食慾甚至是性功能，且可能持續數個月至數年。

二、危險因子

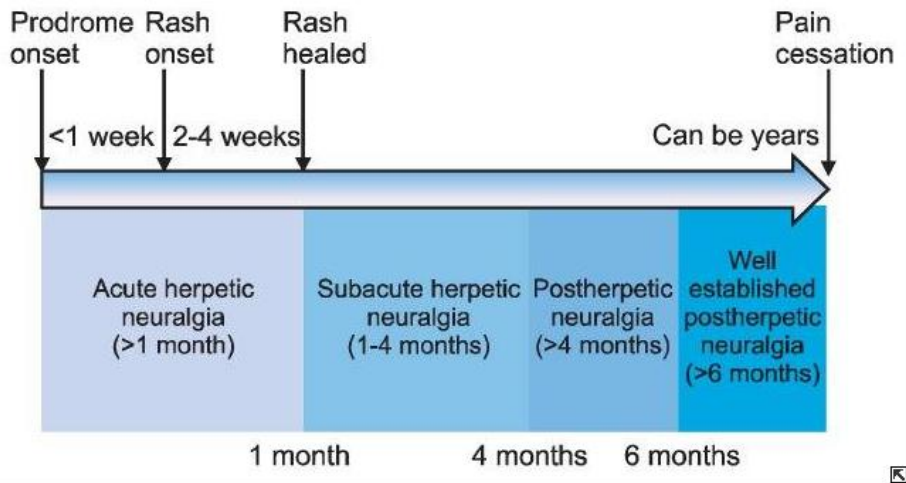
年紀增長所造成的免疫力下降是帶狀皰疹復發的最主要危險因子，另外免疫系統功能低下(ex: HIV)、使用免疫抑

制藥物、器官移植、有皰疹家族史者發生機率也略高。

三、臨床表現

帶狀皰疹的臨床症狀主要是皮疹(rash)及急性神經炎(acute neuritis)。高達75%的患者會有前驅性疼痛(prodromal pain)的情況；包括受感染的皮節感覺刺痛、燒灼及發癢，往往發生在爆發前幾天，集中在胸腰椎區域及臉部。過了2-3天出現紅色丘疹(圖一)，迅速在3-4天演變成成群的水疱或膿疱。

之後的7-10天會開始變得乾燥且結痂，並開始慢慢脫落，留下色素沉澱的痕跡(圖二)。少數的病例是屬於只出現急性神經炎的疼痛症狀，但無皮疹稱為zoster sine herpette。



資料來源: Herpes Zoster Vaccination



(圖一)



(圖二)

資料來源: Prevention of varicella-zoster virus infection: Herpes zoster

三、併發症

最常出現的併發症是帶狀疱疹後神經痛 (Postherpetic neuralgia, PHN)(7.9%)，定義是帶狀疱疹發生且皮疹消失後仍持續疼痛超過90天。PHN主要的特徵包括觸痛、灼熱感、刺痛、抽痛、劇痛，可能會持續數月及數年之久；PHN的發生頻率及嚴重程度會隨年齡而升高；在50歲以上的患者中，有25-50%的帶狀

疱疹病例可能會因為併發PHN而更加惡化；此外超過20%有PHN症狀的患者年紀大於80歲。隨機化雙盲安慰劑控制研究指出，為中老年人施打疫苗可以降低67%帶狀疱疹引起的PHN。其他的併發症包含帶狀疱疹病灶引起的蜂窩性組織炎(2.3%)、眼科併發症(1.6%)、運動神經性麻痺(0.9%)、腦炎及腦膜炎(0.5%)

五、預防

ZOSTAVAX為活性減毒的水痘帶狀皰疹病毒(Varicella-zoster virus, VZV)。目前美國FDA已允許此疫苗可應用在50歲以上民眾，以預防帶狀皰疹及其併發症，包括皰疹後神經痛。而我國衛生署於2008年也許可此疫苗可用於：預防50-79歲之成人帶狀皰疹。

Adults ≥ 60 years of age：帶狀皰疹疫苗可以有效的降低大於六十歲的人感染帶狀皰疹病毒的風險。帶狀皰疹預防研究(Shingles Prevention Study, SPS)是一個評估Zostavax之預防效果的安慰劑對照性雙盲臨床試驗：和對照組相比較，Zostavax可明顯降低帶狀皰疹的發生率，預防效果為51%(95% CI 0.44-0.48)(圖三)。

針對六十歲以上的成年人使用Zostavax減毒活性疫苗可以減少帶狀皰疹後神經痛(postherpetic neuralgia, PHN)發生率及嚴重程度(RR 0.36, 95% CI 0.48-0.79)(圖四)。和對照組相比疫苗組的帶狀皰疹後神經痛發生率降低67%。帶狀皰疹特异性抗體在接種疫苗後六週出現，而4年之後在降低皰疹及其併發症的發生機率仍有統計學上的顯著差異。

Adults 50 to 59 years of age：Zostavax效果與安全性試驗(Zostavax Efficacy and Safety Trial, ZEST)是一個評估Zostavax之療效及安全性的安慰劑

對照性雙盲臨床試驗。評估其接種疫苗所引起的免疫反應。接種6週之後，與安慰劑相比較，Zostavax可以誘發較高的VZV特异性免疫反應。然後監測他們接種疫苗後1.3年，帶狀皰疹疫苗施打組的帶狀皰疹發生率較安慰組降低70%(95% CI 0.54-0.81)。

Contraindications for vaccination：Zoster vaccine不建議用於會對明膠或neomycin過敏的人使用。雖然說Zostavax屬於減毒活性疫苗，但對於某些高風險的族群仍不建議使用，例如：懷孕、免疫不全者、接受化學藥物或放射線治療者、接受器官移植、接受高劑量corticosteroid治療者(dose ≥ 20 mg/day of prednisone for 14天)、T細胞免疫不全者(如HIV感染，CD4細胞數量 $< 200/\text{mm}^3$)。

目前Zostavax僅自費無健保給付，所費不貲且目前並不確定接種後的保護效果持續的最長時間(SPS僅確定4年的保護效果)。建議中老年人在接種疫苗之前，先行評估未來得到帶狀皰疹的風險及接種疫苗的成本效應。

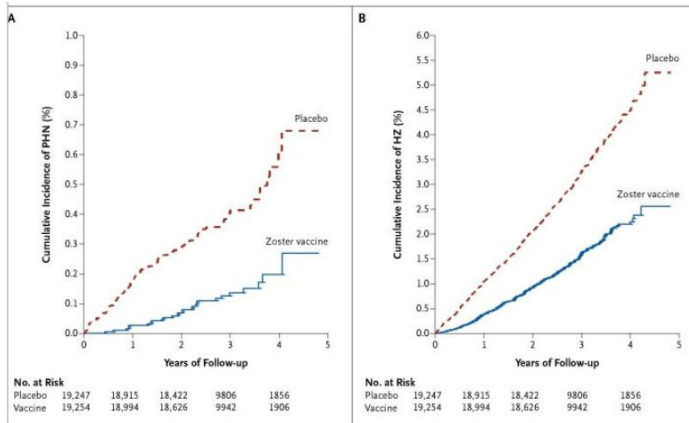


Figure 2. Kaplan-Meier Estimates of the Effect of Zoster Vaccine on the Cumulative Incidence of Postherpetic Neuralgia (Panel A) and Herpes Zoster (Panel B) in the Modified Intention-to-Treat Population.

Incidence rates of postherpetic neuralgia (PHN) and herpes zoster (HZ) were significantly lower in the vaccine group than in the placebo group ($P < 0.001$, by a stratified log-rank test that pooled the results of the log-rank test from the two age groups). Cumulative incidence, expressed as a percentage of the subjects at risk, is the probability of the development of the disease during the period from 30 days after vaccination to the follow-up time.

(圖四)

(圖五)

資料來源: A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults.

六、處理急性的帶狀疱疹感染

ANTIVIRAL THERAPY

適用於治療帶狀疱疹病毒的抗病毒藥物主要有acyclovir、famciclovir、valacyclovir。使用抗病毒藥物可以減少皮疹、降低併發症（包括帶狀疱疹後神經痛）的發生率。（圖六）

Corticosteroids

類固醇的使用是作為抗病毒藥物的輔助療法，可以縮短皮膚病灶癒合的時間，降低PHN的發生，提高生活品質。

Postherpetic Neuralgia：

帶狀疱疹後神經痛(PNH)相當複雜，不應該簡化成局部疼痛。因此臨床上通常選擇合併療法，配合可能出現的不良反應及患者的順從性來做藥物選擇的依據。（圖七）

阿片類(Opioids)、三環抗憂鬱藥物

(tricyclic antidepressants)、抗痙攣藥(anticonvulsants)可以單獨使用或組合使用來縮短PNH的時間以及降低PNH的疼痛程度。局部使用的lidocaine貼片和辣椒素鹼(capsaicin)軟膏，也可以適度的舒緩疼痛的感覺。針對持續時間較長的帶狀疱疹後神經痛(PNH)，且口服或局部使用的類固醇治療無效的PNH患者可以考慮在脊髓腔注射methylprednisolone acetate。（圖八）

Transmission感染控制：

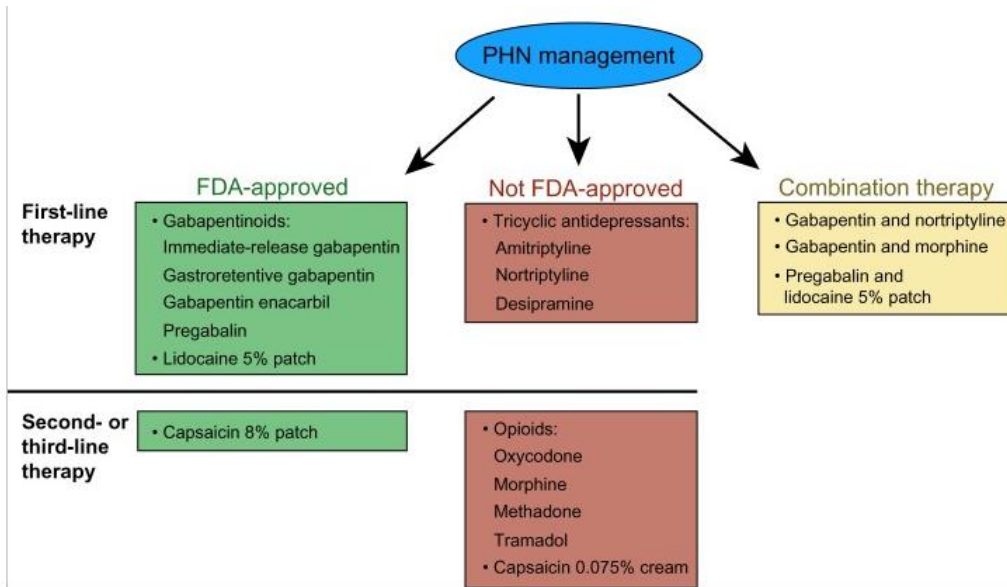
雖然帶狀疱疹的傳染性比水痘弱，但是仍然會經由接觸傳染的方式傳播。患者可以藉由覆蓋傷口、常常洗手，直到水疱結痂前儘量避免接觸孕婦、未得過水痘或接種過疫苗、免疫力低下的人。

Table 3. Antiviral Therapy for Herpes Zoster.

Medication	Dose	Effects Observed in Controlled Trials	Side Effects
Nonimmunocompromised persons			
Acyclovir (e.g., Zovirax)	800 mg orally five times daily for 7–10 days	Reduced time to last new-lesion formation, loss of vesicles, full crusting, cessation of viral shedding, reduced severity of acute pain ^{10,12}	Malaise
Famciclovir (e.g., Famvir)	500 mg orally three times daily for 7 days	Reduced time to last new-lesion formation, loss of vesicles, full crusting, cessation of viral shedding, cessation of pain ^{13,14}	Headache, nausea
Valacyclovir (e.g., Valtrex)	1 g orally three times daily for 7 days	Reduced time to last new-lesion formation, loss of vesicles, full crusting, cessation of pain ^{15,16}	Headache, nausea
Brivudin (e.g., Zostex, Helpin) [*]	125 mg orally once daily for 7 days	Reduced time to last new-lesion formation, full crusting, cessation of pain ¹⁷	Headache, nausea; contraindicated in persons receiving fluorouracil or other fluoropyrimidines
Immunocompromised persons requiring hospitalization or persons with severe neurologic complications			
Acyclovir (e.g., Zovirax)	10 mg/kg intravenously every 8 hr for 7–10 days	Reduced time to last new-lesion formation, full crusting, cessation of viral shedding, cessation of pain, reduced cutaneous dissemination, reduced visceral herpes zoster ^{18,19}	Renal insufficiency
Foscarnet (e.g., Foscavir) for acyclovir-resistant VZV [†]	40 mg/kg intravenously every 8 hr until lesions are healed	Not reported	Renal insufficiency, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, nausea, diarrhea, vomiting, anemia, granulocytopenia, headache

* Brivudin is not available in the United States and has not been approved by the Food and Drug Administration (FDA).
 † Foscarnet is not approved for this use by the FDA.

(圖六) 資料來源: Clinical practice: Herpes zoster.



Current postherpetic neuralgia (PHN) prevention and treatment options.

Abbreviations: FDA, US Food and Drug Administration; HZ, herpes zoster (shingles).

(圖七) 資料來源: Practical considerations in the pharmacological treatment of postherpetic neuralgia for the primary care provider

TABLE 2. TREATMENT OPTIONS FOR POSTHERPETIC NEURALGIA.

AGENT	INITIAL DOSE	COMMENTS	POTENTIAL ADVERSE EFFECTS
Opioids ⁴⁰	Oxycodone, 5 mg orally every 6 hours*	Total dose of 80 mg daily (or higher) potentially necessary for patients with severe pain	Sedation, nausea, dizziness, constipation, tolerance, abuse
Tricyclic antidepressants ^{36,38}	Nortriptyline or desipramine, 10 to 25 mg orally at bedtime*	Total dose of up to 75 to 150 mg daily potentially necessary; amitriptyline also proved effective but may be poorly tolerated by elderly patients; less experience with selective serotonin-reuptake inhibitors	Sedation, confusion, anticholinergic effects (dry mouth, blurred vision, constipation, urinary retention)
Gabapentin ³⁹	300 mg orally daily	Titration of dose as necessary over a 4-week period, to a total daily dose of 3600 mg (divided into 3 doses)	Somnolence, dizziness, ataxia, nystagmus
Capsaicin (0.025–0.075% cream) ⁴¹	Topically 3 to 4 times daily	Apply only to healed, intact skin; patients may start with low-potency preparation, advance to high-potency preparation as tolerated; may take days or weeks to achieve maximal benefit; available without a prescription	Localized skin irritation and burning sensation limit use for many patients
Lidocaine (5% patch) ⁴²	Applied to painful area; up to 3 patches can be used at a time for a maximum of 12 hours	Should be applied only to healed, intact skin; patches may be cut to size; rapid onset of pain relief	Localized skin irritation; systemic toxicity from cutaneous absorption of lidocaine very rare

*Other agents are also available for use.

(圖八) 資料來源: Postherpetic Neuralgia from updpe

七、結語

年齡增長是最重要的帶狀疱疹危險因子，由於免疫力隨者年齡而降低，發生帶狀疱疹的風險和嚴重程度也會升高。如果可以在紅疹發生後72小時內使用抗病毒藥物，治療效果會比較即時。針對帶狀疱疹患者最困擾的疼痛及神經痛後遺症，適當的

選擇止痛藥及配合的輔助療法，更可以協助患者度過不舒服的疱疹病程。

而如果從預防方面著手，接種帶狀疱疹疫苗可以降低發生帶狀疱疹的風險及相關併發症(ex PHN)的發生機率。

八、Reference

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