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MANAGEMENT OF INFECTIONS DUE TO THE VARICELLA-ZOSTER VIRUS

11TH CONSENSUS CONFERENCE ON ANTI-INFECTIOUS THERAPY OF THE FRENCH SOCIETY OF INFECTIOUS DISEASES (SPILF- Société de Pathologie Infectieuse de Langue Francaise)

The reasons for conducting a consensus conference on the treatment of infections due to VaricellaZoster viruses (VZV) in 1998 are epidemiological, clinical, therapeutic and prophylactic.

1. In the USA, UK and in some countries in Asia, the increasing incidence of varicella in patients aged 15 years or more has resulted in an increase in severe forms and in mortality. Moreover, infections of the VZV group are a matter of concern in immunocompromised patients, and, due to specific therapeutic advances or a specific epidemiological evolution, this patient population is steadily increasing. Furthermore, cases of resistance to classic antiviral treatments, which are exceptional in the general population, seem more frequent in HIV-infected patients.

2. Unusual forms of varicella and zoster are occasionally encountered even in non immunocompromised patients. In such cases it remains to be decided **whether antiviral treatments** can be administered even though these are not officially-approved indications. This is the case of

- - extensive cutaneous lesions or neurologic and thromboembolic complications of varicella in an otherwise healthy child who is the last affected member among siblings,
- - the rare severe or lethal forms seen in asthmatic children,
- - severe interstitial lung disease in adults and pregnant women,
- - perinatal varicella due to maternal infection started 5 days prior to, or 2 days after delivery (mortality in the range of 30%),
- - zoster of the nasociliary branch,
- - long-lasting painful zoster in adults under 50 years of age.

Not surprisingly, physicians interviewed during this conference admitted that they used antiviral drugs in one third of the cases even though these indications differ from those officially approved. These facts merit being taken into consideration.

3. From the therapeutic point of view, antiviral chemotherapy, that had long been non-existent or limited to intravenous aciclovir, now offers a larger choice of drugs some of which, administered orally, are available for outpatient use. All these drugs inhibit the viral DNA-polymerase, i.e. the enzyme responsible for replication of viral DNA strands. These are virostatic agents, effective only on actively-replicating virus.

These new efficacious and reasonably-well tolerated antiviral drugs include three nucleosidic analogues: oral aciclovir (800 mg), valaciclovir (a precursor molecule of aciclovir) and famciclovir, the last two showing interesting pharmacokinetic properties.

Intravenous aciclovir is presently indicated for severe forms of varicella or zoster in healthy or immunocompromised patients, and oral aciclovir for the prevention of ocular complications of ophthalmic zoster.

It is desirable that the efficacy of these new antiviral drugs be evaluated for the curative treatment in other forms of VZV infections (complicated varicella, varicella in the course of pregnancy or immunodeficiency states), and for prophylaxis following close exposure in non immune persons at risk (siblings of the propositus, medical personnel). However, extending the use of these products should not be envisaged unless the development of viral resistance is closely monitored.

4. Apart from antiviral agents, the treatment of VZV infections is commonly administered with other therapeutic agents, all of which should be discussed.

For local symptomatic treatment several agents (antiseptics, talc, dyes) have been used for a long time, but their use may be hazardous.

Steroid treatment, often prescribed for zoster, is highly controversial.

The use of analgesics for pain during or after zoster is delicate and warrants good knowledge of the pathophysiology and the semeiology of pain.

5. Prophylaxis in VZV infections is difficult. It relies on one or several of the following measures: vaccination, passive immunotherapy, chemoprophylaxis and patient isolation. All of them are only partly efficacious and are not frequently used.

In France, vaccination with a living, attenuated virus is nowadays indicated only for children suffering from haemopoietic malignancies, but this indication has been extended in other countries to all children. This policy relies more on economic than on medical grounds, and has not been adopted in France. Before the vaccination policy is changed, the following facts should be considered:

- the usually benign course of varicella in children,
- the risk of not obtaining an adequate vaccinal coverage, implying ageing of the non immune population that develops more severe disease,
- the uncertainty concerning prevention of zoster with vaccination.

Anti-VZV immunoglobulins (VZIG) have not been available in France since 1994. They have been proven efficacious for reducing the incidence and severity of varicella in immunocompromised children. It is desirable that VZIG once again becomes available when safety problems have been resolved. Polyvalent immunoglobulins (IVIG) have not been shown to reduce transmission to persons at risk.

Indications for antiviral chemoprophylaxis have not been validated.

Exclusion from school has a rather limited effect in the control of an epidemic since varicella is contagious during the pre-eruptive period.

Finally, the problem of nosocomial VZV transmission exists. Let us remember that, according to surveys performed in departments caring for adult patients, this risk is taken into consideration by physicians only in the case of severely immunodeficient patients.

QUESTION 1. WHO ARE THE PERSONS AT RISK OF COMPLICATED AND/OR SEVERE VZV INFECTIONS?

Varicella corresponds to the primary infection and results from exposure of a non immune host to the virus: 90% of the cases occur in children aged between 1 and 14 years, with a very low mortality (1.42 per 100,000 cases). Mortality increases after the age of 45 years (0.1-0.5%). Zoster represents the recurrence of VZV and affects 20% of the population.

VARICELLA

Definition of severe and complicated forms

Severe forms are those with very extensive and/or haemorrhagic lesions as well as those with immediate visceral involvement (pneumonia, myocarditis, acute thrombopenia, purpura fulminans).

Complicated forms include:

- bacterial superinfections: these are the commonest, affect the skin and soft tissues and are due to *Staphylococcus aureus* and to *Streptococcus pyogenes*. Necrotising fasciitis and bacteraemia may be life-threatening because of septic shock;
- neurological complications: the most severe is meningoencephalitis (1/40,000), which is a significant cause of mortality and of secondary lesions both in infants and adults. Reye's syndrome, associating acute encephalopathy and liver involvement, is exceptional in France.
- varicella pneumonia: this occurs mainly in infants under six months of age and in adults.
- the remaining complications are exceptional, including hepatitis, secondary thrombopenia, nephropathy, arthritis, thromboses, ocular complications, pericarditis, pancreatitis, orchitis.

Immunocompetent persons at risk

Infants and young children.

The incidence of complicated forms is 5% in infants. In infants under one year of age the mortality rate is increased fourfold as compared with children aged between 1 and 14 years.

The main cause of death before the age of six months is pneumonia; between six months and one year encephalitis predominates. Infectious complications, namely soft tissue bacterial infections - including necrotising fasciitis - occur mainly before the age of 5 years.

In the case of contagion within families or communities, fever and eruption severity in secondary cases is higher than in the propositus.

Children (>5 years to 13 years).

The course of varicella is usually benign in this age group. The existence of chronic cutaneous lesions, namely atopic dermatitis, does not increase the risk for severe forms.

Asthma seems to induce a significant risk of invasive infection, especially due to streptococci, independently of the use of steroids.

Adolescents and adults up to the age of 50 years.

In the USA and the UK, the proportion of cases affecting patients aged 15 years or more has increased from 7% in 1967 to 20% in 1995, with an increase in mortality rate. The risk of death is increased 25-fold in adults compared with children.

Varicella pneumonia (VP) is the commonest complication. It accounts for 30% of deaths due to the disease. The only recognised risk for VP in adults is smoking.

Adults over 50 years of age and elderly individuals.

Varicella is very rare in this age group. It is often more severe than in children, causing severe malaise, and may produce pulmonary and neuromeningeal complications.

Foetuses.

The prevalence of VZV primary infection during pregnancy is low. Foetal varicella syndrome variably associates atrophic cutaneous lesions, neurologic disease, ocular, muscle and skeletal lesions.

The rate of varicella foetopathy increases during pregnancy and reaches 2% between the 13th and 20th week of amenorrhoea. The main risk thereafter is the development of zoster within the first weeks or months of life.

No foetal varicella has been reported following zoster in the mother.

Newborns (0 to 28 days).

Perinatal varicella: newborns contaminated between 5 days before and 2 days after delivery may present severe varicella (bronchopneumonia, ulcers of the gastrointestinal tract, meningoencephalitis, hepatitis) that is fatal in 30% of cases,

- Post-natal varicella: the risk of severe forms occurring within the first month of life renders hospitalisation advisable.

- Nosocomial varicella: in hospital neonatology departments the risk of contamination from a propositus is high.

Pregnant women.

The risk of overt varicella pneumonia in pregnant women is not different than in other adults. Deaths in utero and premature deliveries are increased, namely in the course of severe forms with lung involvement.

Immunocompromised hosts

Congenital immunodeficiencies.

Children with congenital immunodeficiencies may develop severe varicella.

Acquired immunodeficiencies.

In adults, varicella may represent primary infection or exogenous or endogenous reinfection rendered possible because of the immunosuppression. Varicella is especially severe in children with malignant lymphoproliferative diseases, or more rarely, with solid tumours. GVH disease is a risk factor for varicella but only acute GVH increases the risk of viral dissemination. Allogeneic bone-marrow grafts induce an increased

risk for dissemination and death compared with autologous grafts. Kidney and heart transplant recipients are less susceptible than bone-marrow graft recipients. Immunosuppression induced by systemic steroid treatment increases the frequency of viral dissemination. However, the risk of severe varicella following steroid treatment by inhalation remains highly controversial. HIV infection does not seem to worsen the prognosis of varicella in adults, but the scarcity of such cases renders this assessment difficult. Atypical cutaneous forms presenting diagnostic difficulties may delay the onset of the treatment in the case of VP. In HIV infected children, CD4 lymphopenia does not seem to be predictive of viral dissemination, particularly in VP. However, CD4 counts below 200/mm³ and/or the presence of more than 400 skin lesions per ml seem to be associated with a more protracted eruption.

HERPES ZOSTER

The clinical expression of zoster is generally limited to the dermatome corresponding to the sensory ganglion where reactivation of the virus occurred. The disease may be complicated and severe forms also exist.

Definition of severe and complicated forms

These correspond to generalised or haemorrhagic forms with systemic involvement and visceral complications (of the lungs, liver and brain). This form, very rare in immunocompetent hosts, is more frequent in the presence of underlying immunodeficiency or cancer.

The most important complication is zoster-associated pain. In the acute phase this is almost invariably present. After healing, some patients still complain of neuralgic pain, also known as post herpetic neuralgia, that may cause significant reduction in the quality of life. The incidence increases with age, reaching 50% of patients after the age of 50 years and more than 70% after the age of 70. The presence of pre-eruptive pain, the severity of pain in the initial phase of the disease and the severity of cutaneous lesions are predictive factors for the development of post herpetic neuralgia.

The specific case of ophthalmic zoster

Ophthalmic zoster affects mainly adults aged 50 years or more; it causes post herpetic neuralgia which is often protracted, and frequent ocular complications that may be severe. Scarring lesions may cause anatomic loss of the eye or irreversibly diminish visual acuity. Ophthalmologic examination should be regularly performed in the following cases:

- - ophthalmic zoster extending over the lateral sides of the nose (nasociliary area),
- - eyelid oedema,
- - reduction of visual acuity,
- - conjunctival hyperhaemia,
- - immunodeficiency.

Forms according to age

Young children.

Foetal contamination or varicella within the first months may be responsible for zoster within the first years of life.

Zoster is rare before the age of four years and is not severe.

Children and adults under 50 years.

In children and immunocompetent adults, zoster remains localised and heals without noticeable scars. Serologic screening for HIV infection should be proposed to young adults.

Adults over 50 years of age and elderly people.

The incidence of zoster increases with age; it is maximal after the age of 75 years, affecting 1.4/100 people/year.

The frequency and severity of pain persisting beyond one month after disease onset increase with age. In patients aged 50 years or more, the prevalence of post herpetic neuralgia is increased 15-fold at day 30 and 27-fold at day 60 as compared with patients under 50 years of age.

The faculty considers that evaluation for cancer or HIV infection is not justified in the case of zoster affecting elderly patients.

Immunocompromised patients

Immunosuppression promotes the development of zoster and increases the risk of dissemination of VZV. The course is often longer than in immunocompetent persons.

Immunocompromised patients with an increased risk for severe zoster include those suffering from acute leukaemia, lymphoma under treatment, lupus erythematosus, organ-allograft recipients, patients receiving cytotoxic or immunosuppressive treatments (longstanding steroid treatment) and HIV-infected patients, mainly when CD4 counts fall below 350/nIM3. The risk for disseminated disease is lower in cancer patients in periods of non-treatment and in HIV infected patients with a moderate level of immunodeficiency.

QUESTION 2. WHAT SHOULD THE MANAGEMENT OF VARICELLA BE (INCLUDING SOCIAL ASPECTS, SYMPTOMATIC TREATMENTS AND MEASURES OF ISOLATION)? TO WHICH PATIENTS, WHEN AND HOW SHOULD OTHER TREATMENTS (ANTIVIRAL DRUGS, IMMUNOGLOBULINS ...) BE ADMINISTERED?

Symptomatic treatment

If fever is present, aspirin is contraindicated because of the risk of Reye's syndrome; paracetamol or ibuprofen should be used instead.

In the presence of pruritus only sedating anti-H I antihistamines should be used (hydroxyzine, dexchlorpheniramine) for their antipruritic effect.

Tepid showers and baths once or twice daily using a soap, a soap free cleansing bar or dermatologic cleansing fluid (excluding antiseptics) are recommended for skin care. Chlorhexidine in aqueous solution is useful to prevent superinfection. No other agent (talc, creams, ointments or gels) should be applied to the skin. Local antibiotics, antiviral agents, antipruritic and anaesthetic agents should not be used.

Fingernails should be kept short and clean to minimise the risk of bacterial superinfection.

In the event of cutaneous superinfection an oral anti-staphylococcal and anti-streptococcal antibiotic treatment should be administered.

Antiviral treatment

No indication for the curative treatment of varicella with oral aciclovir exists. Antiviral treatment with intravenous aciclovir is indicated in the following cases:

- immunocompromised host (haemopoietic malignancy, HIV disease, chemotherapy for cancer) (official licensure), - varicella of the newborn (no official licensure),
- newborn whose mother develops varicella 5 days before to 2 days after delivery, even if no cutaneous lesions are present,
- severe forms in infants within the first year of life (no official licensure),
- complicated varicella, namely by pneumonia (no official licensure),
- varicella in pregnant women starting within 8-10 days before delivery (no official licensure).

The recommended dose is 20 mg/kg every 8 hrs in the newborn, 15 mg/kg every 8 hrs in pregnant women, 10 mg/kg every 8 hrs in immunocompetent adults and 1020 mg/kg every 8 hrs (i.e. 250-500 Mg/M2 every 8 hrs) in immunocompromised children. The treatment is usually given for 8- 10 days.

Immunoglobulin treatment

Specific immunoglobulins administered after close exposure can be used to reduce disease severity in immunocompromised patients and newborns. However, VZIG have not been available in France since 1994. Polyvalent immunoglobulins (IVIG) have no proven efficacy and are not indicated.

Measures of isolation

Patient isolation until clinical recovery is statutory, but not mandatory from a medical point of view, unless superinfection exists.

In pregnancy

If varicella manifests before the 24th week of amenorrhea there is a risk of embryo-foetopathy, justifying specialised follow-up in a department of prenatal diagnosis. If the disease manifests near delivery, hospitalisation is recommended for treatment with intravenous aciclovir and for applying measures aimed at delaying delivery. Strict isolation in the department of obstetrics is necessary.

In the absence of relevant data in the literature, the faculty gives no recommendation regarding social management of the disease.

QUESTION 3. HOW SHOULD HERPES ZOSTER BE MANAGED? TO WHOM, HOW AND WHEN SHOULD ANTIVIRAL DRUGS BE ADMINISTERED? WHAT TREATMENTS SHOULD BE ASSOCIATED IN THE ACUTE PHASE? WHAT ARE THE PECULIARITIES OF OPHTHALMIC ZOSTER? HOW SHOULD POST HERPETIC NEURALGIA BE TREATED?

To whom, how and when should antiviral drugs be administered?

In immunocompetent hosts, the treatment should be started before the 72nd hr of the eruptive phase in the following cases:

- ophthalmic zoster, in order to prevent ocular scarring: aciclovir 5 x 800 mg/d, or valaciclovir 3 x 1 g/d for 7 days (official licensure);
- patients older than 50 years of age, in order to prevent post herpetic neuralgia: famciclovir 3 x 500 mg/d or valaciclovir 3 X 1 g/d for 7 days (official licensure).

Even though less than convincing data exist, the faculty considers that treatment with famciclovir or valaciclovir can be given for ophthalmic zoster to patients under 50 years of age, if factors predicting the development of post herpetic neuralgia exist, such as extensive eruption, severe pain at the eruptive phase, pain appearing several days before the eruptive phase (no official licensure).

In immunocompromised hosts, zoster should always be treated with an antiviral drug.

Intravenous aciclovir is recommended at the dose of 10 mg/kg in adults and 500 mg/ml in children every 8 hrs for at least 7 to 10 days. Treatment duration and dosage should be increased in the event of CNS complications.

It is recommended that patients be taught to recognise the first symptoms of zoster so as to allow the treatment to be started as soon as possible.

The usefulness of oral famciclovir and valaciclovir treatment merits evaluation in this setting.

The same treatment as for immunocompetent hosts is proposed for patients with solid tumours receiving no treatment at the time of the infection, and for HIV-infected patients with a moderate immunodeficiency provided the initial lesions are monodermatomal and a close clinical follow-up is possible.

Other treatments at the acute phase

Tepid showers or baths once or twice daily with a soap free cleansing bar or dermatologic cleansing fluid (excluding antiseptics) are recommended for skin care. Chlorhexidine in aqueous solution is useful for preventing superinfections.

The faculty comes out against the use of any other agent (talc, cream, ointment or gel), including local antibiotics and anaesthetics, antiviral and antipruritic medications.

If cutaneous superinfection is present, an oral antistaphylococcal and antistreptococcal antibiotic treatment should be prescribed.

Treatment of ophthalmic zoster

An antiviral treatment should invariably be given for ophthalmic zoster. Orally administered aciclovir and valaciclovir have been proven effective for the prevention of ocular complications. The treatment should be started early

within 48 hrs with aciclovir or 72 hrs with valaciclovir of the onset of the skin eruption.

A specialised ophthalmologic examination is desirable; treatment with aciclovir ointment should be decided on the advice of an ophthalmologist and always combined with a systemic antiviral treatment.

Topical steroids should only be used for the treatment of immunologic keratitis and anterior uveitis. Systemic steroid treatment should only be given for ophthalmic zoster complicated by acute retinal necrosis or ischaemic optic neuropathy.

Treatment of associated pain

The faculty recommends the use of a scale of assessment of pain (visual analogue scale) in order to obtain the best evaluation of the effect of analgesics.

Pain in the acute phase, when moderate, necessitates the use of class 11 analgesics (paracetamol-codeine, paracetamol-dextropropoxyphene) taken over 24 hrs at regular intervals.

In the event of insufficient efficacy, morphine may be necessary as a sulphate salt in adults and as chlorhydrate in the elderly, starting with low doses. The faculty recommends that steroid treatment should not be used for pain in the acute phase.

Post herpetic neuralgia necessitates other treatments. Amitriptyline (75 mg/d) has been proven effective in adults for reducing the unremitting painful background (official licensure). Carbamazepine (400-1,200 mg/d) is effective for the treatment of acute exacerbations of pain (no official licensure).

Techniques of contra-irritation (cryotherapy, acupuncture, transcutaneous neurostimulation) have not been evaluated.

The medico-psychological aspects of zoster necessitate a global management of patients' psychological well-being.

QUESTION 4. WHO SHOULD BENEFIT FROM PREVENTION OF VZV INFECTIONS AND HOW? CURRENT STATUS AND FUTURE PERSPECTIVES

Vaccination

The anti-varicella vaccine is made up of a live attenuated virus.

In children under 12 years of age, the injection of a single dose of the vaccine of 2,000 PFU (plaque-forming units) is well tolerated and confers good protection. Beyond that age two injections are necessary. Even though limited data are available in adults, the level of protection approaches 50%.

The faculty does not recommend generalisation of vaccination because of i) the benign course of varicella in childhood and ii) the risk of shifting varicella towards adulthood, resulting in more severe forms, due to insufficient vaccinal coverage.

The faculty recommends selective vaccination (2 injections at a 3 month-interval) adhering strictly to the officially approved indications, i.e.:

- 1 - children with no past history of VZV infection, suffering from haemopoietic malignancies or solid tumours not receiving chemotherapy, and their siblings,
- 2 - hospital personnel in close contact with immunosuppressed children.

The faculty does not recommend regular VZV serologic examination in adults with no history of infection.

Passive immunotherapy

VZIG (Varicella-Zoster Immunoglobulins) used to reduce the severity of the disease in immunosuppressed patients and newborns after a contaminating contact. Since their withdrawal in 1994, polyvalent intravenous immunoglobulins (IVIG) have been used in high doses but their usefulness has not been proved in man. Therefore the faculty recommends that VZIG again become available for use, after their absolute safety has been proved. Their use must conform to the official recommendations.

Specific antiviral chemoprophylaxis

The use of antiviral drugs for the prevention of VZV infections has not been well studied. Only aciclovir has been used. No primary prophylaxis against VZV infections in HIV-infected patients is available.

Prophylactic chemotherapy can be recommended in the following cases:

- in a newborn whose mother develops varicella 5 days before to 2 days after delivery,
- for bone-marrow graft recipients at the period of maximal immunosuppression.

Isolation measures

The optimal duration of exclusion of a child with varicella from school or day nursery cannot be defined. Since communicability is greatest during the days around the onset of the eruption, the faculty recommends returning to the community even before all crusted lesions have fallen off, provided no new vesicular crops develop.

If hospitalisation of a VZV-infected patient cannot be avoided, the patient should be isolated until his cutaneous lesions become crusted.

The development of zoster in an elderly inpatient does not necessitate isolation.

In every institution the committee responsible for dealing with nosocomial infection should monitor the compliance to these recommendations, and the involved medical and paramedical personnel should receive relevant information.

Perspectives

In the absence of anti-VZV drugs more efficacious than the presently available ones (in terms of antiviral activity, pharmacokinetics and tolerance), it would be useful to evaluate the recent antiviral drugs - famciclovir and valaciclovir - in the fields where this has not yet been done, namely the curative treatment of immunocompromised hosts, prophylaxis after exposure in non-vaccinated hosts at risk, and generally in children. E

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- - the French Society of Dermatology,
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