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Varicella pneumonia in adults

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ABSTRACT: Varicella is a common contagious infection in childhood with increasing incidence in adults. Pneumonia, although rare, is the most serious complication that commonly affects adults. Over the last two decades there have been major advances in the understanding of Varicella infections, management and prevention. This review discusses the epidemiology, pathogenesis, pulmonary manifestation, morbidity, long-term clinical consequences and current state of management of Varicella pneumonia in adults. Prevention and other disease-modifying therapy are also discussed.
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Varicella (chickenpox) is a common infection of childhood typically affecting children aged 2–8 yrs and usually follows benign outcome. However, data from Europe and North America have shown that the incidence of chickenpox in adults has doubled in recent years and this has been paralleled with an increase in hospital admissions [1–5] and mortality [6]. The reason for this age shift is not known, though it may be the result of less exposure to the Varicella-Zoster virus (VZV), smaller family size or increased virus virulence. Varicella pneumonia is the most common and serious complication of chickenpox infection in adults [7, 8], with a reported incidence in healthy adults that is 25-fold greater than in children [9]. In the USA chickenpox is the leading cause of death among vaccine-preventable diseases [10]. Currently, the proportion of adults in industrial nations susceptible to chickenpox is ~7%, evident from negative Varicella-Zoster antibodies [11, 12]. Varicella pneumonia is so uncommon that large-scale studies are difficult to conduct and most published studies represent either collections of small case series or retrospective analyses over many years.

This article will review aspects relating to Varicella pneumonia and its natural history in adults.

Methods

All relevant published articles relating to the epidemiology, natural history and treatment of Varicella pneumonia since 1964 were identified. The Medline database was first searched using the terms "Varicella pneumonia" and "chickenpox pneumonia". For the treatment section, the terms "acyclovir" and "immunoglobulin" were searched both as single words and in combination. The effect of acyclovir treatment was assessed on the basis of single outcome, with mortality *versus* survival as an end-point. Studies investigating risk factors for the development of pneumonia were also combined according to each factor and the odds ratio was calculated. All studies were included, even case reports.

Incidence

Although most data suggested increasing incidence of Varicella in adults, this was largely in the 1980s and early 1990s and more recent data suggests a decrease in incidence of Varicella in adults [13]. The frequency of Varicella pneumonia in chickenpox has been difficult to determine in most populations. However, it is estimated to occur in one in 400 cases of chickenpox infection [14]. Recent data from the USA has shown an incidence of pneumonia of 2.3 in 400 cases [5]. The incidence of pneumonia in adults has been reported in two studies and varied between 0.32–1.36 cases per 100,000 person years [5, 15]. Adults who develop chickenpox are at much greater risk of developing changes on their chest radiograph, with an incidence of 5–50% [3, 15–19]. A report of 110 chest radiographs from 114 USA army recruits who developed Varicella during basic training showed that 18 (16.3%) had interstitial and/or nodular infiltrates indicative of pneumonia [19]. Pregnant females were also reported to develop this implication in 9% of cases [20]. Patients with impaired immune status and patients with chronic lung disease who develop primary Varicella-Zoster infection have an increased risk of developing pneumonia [21–23].

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Clinical presentation

Varicella pneumonia usually presents 1–6 days after the onset of the rash and is associated with tachypnoea, chest tightness, cough, dyspnoea, fever and occasionally with pleuretic chest pain and haemoptysis. However, chest symptoms may start before the appearance of the skin rash [16, 24, 25]. Physical findings are often minimal and chest radiographs typically reveal nodular or interstitial pneumonitis [16, 19], as shown in figure 1. The presence of new chest symptoms has been shown to be strongly associated with the documentation of radiological pneumonia [16, 26, 27]. With the exception of hypoxia, physical signs are a poor guide of severity [18]. The risk of developing respiratory failure requiring artificial ventilation is difficult to predict early in the disease. Radiographic abnormalities were detected in nearly 16% of enlisted military personnel who developed Varicella in an outpatient setting, yet only one-quarter of these had a cough and only 10% of those with radiographic abnormalities developed evidence of tachypnoea [19]. Therefore, the data indicate that asymptomatic pneumonitis may exist more commonly than might be supposed.

Table 1 summarises factors shown to be associated with the development of pneumonia, from prospective studies only [16, 28–31]. There is a strong correlation between pneumonia and the development of new respiratory symptoms. Previous or current smokers were also at increased risk of developing pneumonia. It is possible that smokers have an enhanced primary viraemia, secondary to the effects of smoking on the nasal mucosa, and this predisposes pneumonia. Furthermore, a previous report has shown that smoking renders human alveolar macrophages more susceptible to infection by herpes viruses [30], which could be relevant pathogenetically, although this requires further study. Increased number of skin spots (>100 spots), *i.e.* severity of rash, was a factor that increased the risk of developing pneumonia, which may be a reflection of enhanced viraemia. A history of contact with an index case was another factor predisposing to the development of pneumonia. This could be a consequence of these patients having closer contact with the index case and therefore receiving a larger "infecting dose" with an enhanced primary viraemia. Previously, it has been demonstrated that children who get chickenpox from siblings usually have a worse disease with more spots [31]. The third trimester of pregnancy was shown in univariate, but not multivariable, analysis to be associated with an increased incidence of pneumonia [28]. This is likely to be the result of both immune tolerance during pregnancy and the increased demand and pressure of the baby on the respiratory system. Duration of fever was shown to be independently associated with the incidence of pneumonia (odds ratio (OR) 5.6, 95% confidence interval (CI) 2.4–13.0) in a retrospective setting [32]. Immunocompromised hosts and patients with chronic lung disease are also at increased risk of developing pneumonia [21–23]. It has been reported that patients with chronic obstructive pulmonary disease develop more severe pulmonary complications in comparison with healthy individuals [33].

Table 1. – Factors associated with increased incidence of pneumonia in chickenpox

Country	[Ref.]	Factor	OR (95% CI)
UK	[16]	Chest symptoms at presentation	28.1 (4.1–19.1)
USA	[26]		
USA	[27, 28]	Ever smoker	8.9 (4.1–10.1)
UK	[16, 29]		
USA	[28]	Spots n >100	17.0 (2.1–134.6)
UK	[16]	Any contact with chicken pox	4.8 (1.04–22.1)
UK	[16]	History of contact with own child	7.8 (1.85–33.2)
USA	[28]	Pregnancy (third trimester)	4.0 (1.4–11.9)

Data from referenced studies were merged to calculate the odds ratio (OR). ref.: reference; CI: confidence interval.

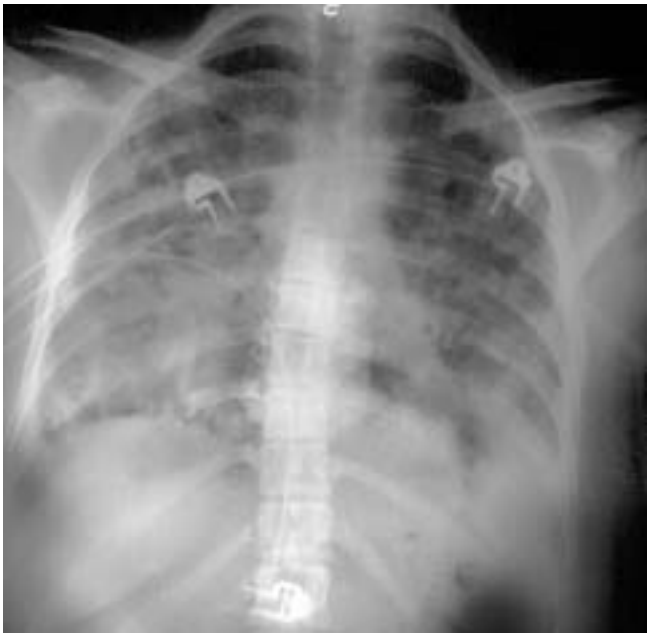

Fig. 1. – Chest radiograph showing bilateral interstitial infiltrates of a patient presenting with severe Varicella pneumonia.

Immunocompromised

The course of Varicella appears to be more aggressive in immunocompromised hosts. In a recent series on human immunodeficiency virus-infected patients from South Africa, seven of 12 patients who were hospitalised with chickenpox developed clinically severe pneumonia and, despite receiving antiviral within 12 h of admission, three (43%) died [21]. A review of 38 cases of adult renal allograft recipients with disseminated Varicella infection, reported in 15 different studies, found that of the 29 patients with primary Varicella, 29% developed Varicella pneumonia and the overall mortality was 34%. However, the mortality from 1981–1990 was 53% and from 1990–2000 was 22% [23]. The improvement in mortality rate was most likely to have been influenced by the availability of specific antiviral therapy, since antiviral therapy was used in 33% of cases before 1990 and 74% of cases after 1990.

Pathogenesis

The data available on the pathogenesis of Varicella is limited. Infection with VZV usually occurs by an airborne route, with high infectivity resulting in a secondary attack rate of >90% in households with susceptible individuals [31]. Airborne spread in hospitals is also well documented [34]. Uncertainty exists as to whether the portal of entry is the conjunctiva, pharynx or lungs. Postinfection primary viraemia starts at ~96 h, probably following replication in the regional lymph nodes; the use of Varicella-Zoster immune

globulin (VZIG) is usually successful in preventing progression to disease if administered before that time [9]. The second stage of viral replication takes place in the lymph nodes, lungs, bone marrow, liver, pancreas and adrenal glands, and this mainly takes place in the macrophages. Two studies showed that among the white blood cells, only the monocyte/macrophage will support VZV replication [35, 36]. The pulmonary lesions caused by acute Varicella consist of endothelial damage in small blood vessels, with focal haemorrhagic necrosis, mononuclear infiltration of alveolar walls and fibrinous exudates with macrophages in the alveoli, which contain eosinophilic intranuclear inclusions [37]. Lung involvement in Varicella infection seems to occur through the bloodstream rather than local extension through the respiratory tree, as shown by the use of monoclonal antibodies [38].

Treatment

Acyclovir has been associated with successful treatment of Varicella pneumonia; the first case was reported in 1980 [39]. It has become standard therapy for patients with or at risk of developing complications of Varicella infection, despite the fact that there have been no randomised controlled trials for its use in the treatment of Varicella pneumonia. However, trials have shown a clear benefit of acyclovir in reducing severity of the skin rash in immunocompetent adults when administered at <24 h of rash onset [40]. Currently, the consensus is to use acyclovir daily for 7–10 days and this use should be tailored to each patient's clinical assessment. Table 2 summarises published cases with chickenpox pneumonia and antiviral therapy use [5, 15–19, 25, 28, 29, 32, 39–75]. This comprised 46 reports, which included 272 patients with Varicella pneumonia. The data is selective; 11 of 179 treated with acyclovir died compared with 17 of 89 patients who received no treatment and none of the other six patients who had other antiviral treatment. There was a significant difference between the groups, with a mortality rate 3.6-fold higher in the group who did not receive acyclovir (OR 3.6, 95% CI 1.63–7.95; p=0.001). There are several limitations to this analysis: 1) only published reports are included; 2) patient selection procedure; 3) lack of randomised controlled trials; 4) no adjustment for the severity of the pneumonia; and 5) no adjustment for ventilatory support. In the most recent series there were no fatalities [16, 28], which may be explained on the basis of having better experience using acyclovir and availability of improved intensive care unit (ICU) support for patients with severe disease. Data from >1,400 pregnant women did not show increased foetal abnormalities as a result of acyclovir treatment [76]. Acyclovir is not currently licensed for use in pregnancy, however, the risks from withholding treatment, particularly in the second half of pregnancy when severe complicated chicken pox are more common, probably outweigh the risks of adverse drug effects on the foetus or mother.

Table 2. – Adults with chickenpox pneumonia; mortality according to chemotherapy intervention

Therapeutic category	Patients n	Died	Mortality rate %	OR (95% CI)
Acyclovir[#]	179	11	6.1	
Others[¶]	6	0	0	
No treatment	89	17	19.1	3.6 (1.63–7.95)***
Total	269[+]	28	10.4	

Data are presented as n unless otherwise stated. OR: odds ratio; CI: confidence interval; [#]: reference group; [¶]: γ-globulin, adenosine arabinoside, idoxuridine, cytosine arabinoside; [+]: 62 patients with Varicella pneumonia were pregnant. In one study [41], pregnancy was not stated; ***: p<0.001.

The antiviral agents licensed for treatment of VZV include aciclovir, valaciclovir and famciclovir. Valaciclovir is the valine ester of aciclovir and improves oral bioavailability from ~15% to ~75%. It is broken down after absorption to valine and aciclovir. Famciclovir is similarly well absorbed. VZV is ~10-times less sensitive to aciclovir compared with the Herpes Simplex virus. With serious illness, such as pneumonia, it is important to appreciate the necessity to use *i.v.* therapy (by slow *i.v.* infusion). However, some clinical response in uncomplicated chickenpox and/or shingles has been demonstrated with oral aciclovir, valaciclovir and famciclovir, the better absorbed preparations probably being preferable. The earlier in the illness the agent is given, the greater the likely benefit.

Corticosteroid use adjunctive to current therapy was assessed in one study that included 15 patients, who were all admitted to ICUs. Six received corticosteroids and showed significantly shorter hospital and ICU stays, and no mortality was recorded [77]. The study was small, mainly retrospective, but may form the basis for a prospective, randomised and controlled trial.

Varicella pneumonia can progress rapidly to fulminant respiratory failure despite maximum conventional support; this type of respiratory failure is potentially refractory. This argues for the use of extracorporeal membrane oxygenation/life support (ECMO/ECLS), which have been shown to be beneficial. Of 20 patients treated using ECMO/ECLS, 16 patients survived (60%) [78, 79]. BUGGE and TANBO [80] reported a case that was successfully treated with nitric oxide as an alternative to ECMO/ECLS. These interventions have not been subjected to prospective trials to show they improve the outcome. However, they should be considered as an option in those patients who develop fulminant respiratory failure as a result of Varicella pneumonia.

The authors suggest that maximum ventilatory support should be offered to patients who progress to respiratory failure. Acyclovir reduces mortality and should be used early in the course of illness in patients with suspected or proven chickenpox pneumonia.

Morbidity and mortality

Very few reports have addressed the long-term morbidity of Varicella pneumonia [16, 29, 81]. Many studies have reported diffused milliary calcifications, which are thought to be clinically insignificant [72]. Three published studies investigated the effect of Varicella pneumonia on respiratory function. They included only 33 patients with chickenpox pneumonia and 41 patients without pneumonia who were assessed prospectively [16, 29, 81]. Two of these studies did not indicate whether the patients studied had any history of previous pneumonia or immunosuppression and the follow-up varied between 2–13 months [29, 81]. However, the remaining study followed 38 immunocompetent patients, with no history of previous pneumonia or lung disease, until recovery or ⩾12 months from hospital discharge [16]. The main abnormality observed in all studies was a defect in the single breath transfer factor of the lung for carbon monoxide (TL,CO) in patients with and without pneumonia, although the reduction was significantly greater in the pneumonia group. MOHSEN *et al.* [16] reported that patients with pneumonia showed no evidence of further improvement in TL,CO >5 months after hospital discharge. BOCLES *et al.* [81] studied four

patients with possible chickenpox pneumonia retrospectively and demonstrated a defect of diffusion $\leqslant 8$ yrs after the acute illness, which raises the possibility that these changes might be permanent.

There were temporary reductions in forced vital capacity (FVC) and forced expiratory volume in one second (FEV1), although FEV1:FVC remained normal in 92% of patients in their initial lung function tests in two studies [16, 81]. However, this was not found in a study by ELLIS *et al.* [29]. These changes are probably the result of diffuse inflammation of lung tissue, affecting patients with and without radiological evidence of pneumonia. The abnormalities indicate that chickenpox may be associated with a restrictive lung disease pattern in the acute and recovery phase. There was no evidence to suggest that chickenpox causes obstructive small airway disease in the recovery period.

Mortality rates from chickenpox pneumonia seem to be improving, with an average of 19% in the 1960s and 1970s compared with 6% in more recent data (table 2). The improvement in mortality is likely to be the result of several factors including better experience and availability of chemotherapy, better respiratory support on ICUs and early diagnosis and institution of aciclovir therapy.

Prevention

There has not yet been a study with sufficient power to address whether antiviral therapy will prevent complications, such as pneumonia. However, the use of acyclovir as prophylaxis/treatment during the incubation period of chickenpox has been shown to prevent or modify illness [82]. Although it is not currently licensed, there is indication that such intervention may be used more in the future.

Three immunoglobulin preparations were studied for the prevention and modification of Varicella infection. Currently, the only formula available is VZIG, which is derived from outdated plasma in blood banks. VZIG has proved to be effective [83], and its use is recommended for susceptible immunosuppressed patients and pregnant women who have been in contact with a proven source of Varicella infection [69]. It should be emphasised that VZIG should be administered <96 h after exposure to be maximally effective.

Recent evidence suggests that Varicella vaccine is effective in preventing or modifying the severity of Varicella infection if used <3 days and possibly even <5 days after exposure and in outbreak control [84–86]. The United States Advisory Committee on Immunization Practices provides a recommendation about administration of Varicella vaccine after exposure, however, it is contraindicated in pregnancy [87].

Immunocompromised hosts are at increased risk of developing severe disease and immunisation of susceptible patients, such as those requiring chemotherapy, prior to profound immunosuppression may be useful (the immunisation available currently uses a live attenuated strain of Varicella). Furthermore, those who have been in contact with a Varicella infection source, and therefore at risk of developing Varicella, should be offered Varicella-Zoster immunoglobulin and monitored closely. The use of acyclovir as prophylaxis post-exposure may be of value but has not yet been formally assessed in this group.

References

1. Miller E, Vurdien J, Farrington P. Shift in age in chickenpox. *Lancet* 1993; 341: 308–309.
2. Joseph C, Noah ND. Epidemiology of chickenpox in England and Wales, 1967–85. *BMJ* 1988; 296: 308–309.
3. Wilkins EG, Leen CL, McKendrick MW, Carrington D. Management of chickenpox in adults. *J Infect* 1998; 1: 49–48.
4. Gray GC, Palinkas LA, Kelley PW. Increasing incidence of varicella hospitalisations in the United States Army and Navy personnel: are today's teenagers becoming more susceptible? Should recruits be vaccinated? *Pediatrics* 1990; 86: 867–873.
5. Choo WP, Donahue GJ, Manson EJ, Platt R. The epidemiology varicella and its complications. *J Infect Dis* 1995; 172: 706–712.
6. Rawson H, Crampian A, Noah N. Death from chickenpox in England and Wales 1995–7: analysis of routine mortality data. *BMJ* 2001; 323: 1091–1093.
7. Guess HA, Broughton DD, Melton LJ, Kurland LT. Chickenpox hospitalisations among residents of Olmsted Country, Minnesota, 1962 through 1981. *Am J Dis Child* 1984; 138: 1055–1057.
8. Poltkin SA. Clinical and pathogenetic aspects of varicella-zoster. *Postgrad Med J* 1985; 61: Suppl. 4, 7–14.
9. Center for Disease Control. Varicella-zoster immune globulin for the prevention of chickenpox. *Morb Mortal Wkly Rep* 1984; 33: 84–90.
10. Center for Disease Control and Prevention. Varicella-related deaths among children-United States, 1997. *Morb Mortal Wkly Rep* 1997; 47: 365–368.
11. Munich R, Nassim C, Niku S, Sullivan-Bolyai JZ. Seroepidemiology of Varicella. *J Infect Dis* 1986; 153: 153–154.
12. Struewing JP, Hyams KC, Tueller JE, Gray GC. The risk of measles, mumps and varicella among young adults: a serosurvey of US navy and marine recruits. *Am J Public Health* 1993; 83: 1717–1720.
13. Brisso M, Edmund JW, Gay JN, Miller E. Deaths from chickenpox in adults are decreasing. *BMJ* 2002; 324: 609.
14. Mandell GL, Douglas GR, Bennett JE. Principal and Practice of Infectious Diseases. 5th Edn. Philadelphia, Churchill Livingston, 2000; p. 1582.
15. Nilsson A, Ortqvist A. Severe varicella pneumonia in adults in Stockholm County 1980–1989. *Scand J Infect Dis* 1996; 28: 121–123.
16. Mohsen AH, Peck RJ, Mason Z, Mattock L, McKendrick MW. Lung function tests and risk factors for pneumonia in adults with chickenpox. *Thorax* 2001; 56: 796–799.
17. Clark GPM, Dobson PM, Thickett A, Turner NM. Chickenpox pneumonia, its complications and management. *Anaesthesia* 1991; 46: 376–380.
18. Hockberger RS, Rothstein RJ. Varicella pneumonia in adults: a spectrum of disease. *Ann Emerg Med* 1986; 15: 931–934.
19. Webber DM, Pellecchia JA. Varicella pneumonia: a study of prevalence in adult men. *JAMA* 1965; 192: 228–229.
20. Paryani SG, Arvin AM. Intrauterine infection with varicella-zoster virus after maternal varicella. *N Engl J Med* 1986; 314: 1542–1546.
21. Popara M, Pendle S, Sacks L, Smego RA, Mer M. Varicella pneumonia in patients with HIV/AIDS. *Int J Infect Dis* 2002; 6: 6–8.
22. Ong ELC, Mulvenna P, Webb AK. Varicella-zoster infection in adults with cystic fibrosis: role for acyclovir. *Scand J Infect Dis* 1991; 23: 283–285.
23. Fehr T, Bossart W, Wahl C, Binswanger U. Disseminated varicella infection in adult renal allograft recipients: four cases and review of the literature. *Transplantation* 2002; 73: 608–611.
24. Weinstein L, Meade RH. Respiratory manifestations of chickenpox. *Arch Intern Med* 1956; 98: 91–99.
25. El-Daher N, Magnussen CR, Betts RF. Varicella pneumonitis: clinical presentation and experience with acyclovir treatment in immunocompromised adults. *Int J Infect Dis* 1998; 2: 147–151.
26. Baren JM, Henneman PL, Lewis RJ. Primary varicella in adults: pneumonia, pregnancy and hospital admission. *Ann Emerg Med* 1996; 28: 165–169.
27. Grayson ML, Newton-John H. Is smoking a risk factor for

pneumonia in adults with chickenpox. *J Infect Dis* 1988; 16: 312.
28. Harger JH, Ernest JM, Thurnau GR, *et al.* Risk factors and outcome of varicella-zoster virus pneumonia in pregnant women. *J Infect Dis* 2002; 185: 422–427.
29. Ellis EM, Neal KR, Webb AK. Is smoking a risk factor for pneumonia in adults with chickenpox? *BMJ* 1987; 294: 1002.
30. Rose RM, Wasserman AS, Weiser WY, Remold HG. Deficient responses of pulmonary macrophages from healthy smokers to antiviral lymphokines in vitro. *J Infect Dis* 1986; 154: 611–618.
31. Ross AH, Lechner E, Reitman G. Modification of chickenpox in family contacts by administration of gamma globulin. *N Engl J Med* 1962; 267: 369–376.
32. Pugh RNH, Omar RI, Hossain MM. Varicella infection and pneumonia among adults. *Int J Infect Dis* 1998; 2: 205–210.
33. Waring JJ, Neuberger K, Geever EF. Severe forms of chickenpox in adults with autopsy observations in a case with associated pneumonia and encephalitis. *Arch Intern Med* 1942; 69: 384–408.
34. Leclair JM, Zaia JA, Levin MJ, Congdon RJ, Goldman DA. Airborne transmission of chickenpox in a hospital. *N Engl J Med* 1980; 302: 450–453.
35. Arabeit RD, Zair JA, Valerio MA, Levin MJ. Infection of human peripheral blood mononuclear cells by varicella-zoster virus. *Intervirology* 1982; 18: 56.
36. Ozaki T, Ichikawa T, Matsui Y, *et al.* Viremic phase in immunocompromised children with varicella. *J Pediatr* 1984; 104: 85–87.
37. Sargent NE, Carson MJ, Reilly ED. Roentgenographic manifestations of varicella pneumonia with postmortem correlation. *Am J Roentgenol Radium Ther Nucl Med* 1966; 98: 305–317.
38. Weigle K, Groce C. Varicella pneumonitis: immunodiagnosis with a monoclonal antidody. *Pediatrics* 1984; 105: 265–268.
39. van der Meer JW, Thompson J, Tan WD, Versteeg J. Treatment of chickenpox pneumonia with acyclovir. *Lancet* 1980; 2: 473–474.
40. Wallace MR, Bowler WA, Murray NB, Brodine SK, Oldfield EC. Treatment of adult varicella with oral acyclovir. *Ann Intern Med* 1992; 117: 358–363.
41. Eder SE, Apuzzio JJ, Weiss G. Varicella pneumonia during pregnancy: treatment of two cases with acyclovir. *Am J Perinatol* 1988; 5: 16–18.
42. Leen CL, Mandal BK, Ellis ME, Brettle RP. Acyclovir and pregnancy. *BMJ* 1987; 294: 308.
43. Pillans P. Chickenpox pneumonia. *S Afr Med J* 1983; 63: 861–862.
44. Boyd K, Walker E. Use of acyclovir to treat chickenpox in pregnancy. *BMJ* 1988; 296: 393–394.
45. Hankins GD, Gillstrap LC, Patterson AR. Acyclovir treatment of varicella pneumonia in pregnancy. *Crit Care Med* 1987; 15: 336–337.
46. Harris RE, Rhoades ER. Varicella pneumonia complicating pregnancy: report of a case and review of the literature. *Obstet Gynecol* 1965; 25: 734–740.
47. Triebwasser JH, Harris RE, Bryant RE, Rhoades ER. Varicella pneumonia in adults: report of seven cases and review of the literature. *Medicine (Baltimore)* 1967; 46: 409–423.
48. Williams MT, Marsland DW. Varicella pneumonia at parturition. A non-fatal case. *J Fam Pract* 1976; 3: 153–154.
49. Winkelmann RK, DeRemee RA, Ritts RE. Treatment of varicella-zoster pneumonia with transfer factor. *Cutis* 1984; 34: 278–281.
50. Scully RE, Galdabini JJ, McNeely BU. Case records of the Massachusetts General Hospital: weekly clinico-pathological exercise: case 9: 1976. *N Engl J Med* 1976; 37: 226–227.
51. MacFarane JT, Smith FD, Finch RG. Vidarabine in fulminating chickenpox pneumonia. *Thorax* 1982; 37: 226–227.
52. Lowthian JT, Gillard LJ. Varicella pneumonia in the gravid patient. *J LA State Med Soc* 1980; 132: 69–70.
53. Duong CM, Munns RE. Varicella pneumonia during pregnancy. *J Fam Pract* 1979; 8: 277–280.
54. Chitkara R, Gordon RE, Khan FA. Acyclovir in the treatment of primary varicella pneumonia in non-immunocompromised adults. *NY State J Med* 1987; 87: 237–238.
55. Munnich D. Nagy kiterjedesu ketoldali tudogulladassal jaro felnottkori varicella progressive esetunk sikeres intravenas Zovirax/acyclovir/kezelese. [Successful intravenous zovirax/acyclovir therapy in a case of adult progressive varicella complicated by extensive bilateral pneumonia]. *Orvosi Hetilap* 1985; 126: 1663–1665.
56. Kuster W, Hofner W, Wicke L, Kuhbock J. Varicellenpneumonie bei Morbus Hodgkin. [Varicella pneumonia in a patient with Hodgkin′s disease]. *Radiologe* 1987; 18: 398–400.
57. Raidt H, Gottschalk D, Krummenerl T, *et al.* Acyclovir bei schwerer Varizellapneumonie und bei Herpes ophthalmicus. [Acyclovir in severe varicella pneumonia and in herpes ophthalmicus]. *Schweiz Rundsch Med Prax* 1983; 72: 1179–1182.
58. Tatti V. La pneumonie a varicella chez l′adulte. [Varicella pneumonia in adults]. *Rev Med Suisse Romande* 1975; 95: 263–267.
59. Landsberger EJ, Hager WD, Grossman JH. Successful management of varicella pneumonia complicating pregnancy: a report of 3 cases. *J Reprod Med* 1986; 31: 311–314.
60. Tear EL, Cohen JA. Treatment of chickenpox pneumonia with adenine arabinoside. *Lancet* 1979; 1: 873.
61. Aizawa H, Ohsaki Y, Sakai E, Ikeda Y, Kuwajima T, Onodera S. Two cases of primary varicella pneumonia. *Nihon Kyobu Shikkan Gakkai Zasshi* 1986; 24: 195–199.
62. Selleger C. Pneumonie varicelleuse mortelle chez l′adulte: rapport de deux cas et revue de la literature. [Fatal varicella pneumonia in adults. Report of two cases and review of literature]. *Rev Fr Mal Respir* 1979; 7: 9–18.
63. Bryer A, Potgeiter PD, Moodie J. Acyclovir and varicella pneumonia. *S Afr Med J* 1984; 66: 515.
64. Myint SS, Lee SK. Chickenpox pneumonia: a case report. *Singapore Med J* 1986; 27: 80–83.
65. Wolters J, Maesen F, Lamers J. Varicellapneumonie (Varicella pneumonia). *Ned Tijdschr Geneeskd* 1979; 123: 1777–1782.
66. Davidson RN, Lynn W, Savage P, Wansbrough-Jones MH. Chickenpox pneumonia: experience with antiviral treatment. *Thorax* 1988; 43: 627–630.
67. Hammershoy O. Primaer varicelpneumoni. [Primary varicella pneumonia]. *Ugeskr Laeger* 1979; 141: 1855.
68. Harper JR, Marshall RD, Parkinson MS. Intermittent positive-pressure ventilation in chickenpox pneumonitis. *BMJ* 1969; 3: 637–638.
69. Glaser JB, Loftus J, Ferragamo V, Mootabar H, Castellano M. Varicella-zoster infection in pregnancy. *N Engl J Med* 1986; 315: 1416.
70. Schlossberg D, Littman M, Littman M. Varicella pneumonia. *Arch Intern Med* 1988; 148: 1630–1632.
71. Jones AM, Thomas N, Wilkins EGL. Outcome of varicella pneumonitis in immunocompetent adults requiring treatment in a high dependency unit. *J Infect* 2001; 43: 135–139.
72. Knyvett AF. The pulmonary lesions of chickenpox. *Q J Med* 1965; 139: 313–323.
73. Broussard RC, Payne K, George RB. Treatment with acyclovir of varicella pneumonia in pregnancy. *Chest* 1991; 99: 1045–1047.
74. Gogos CA, Vagenakis AG. Varicella pneumonia in adults. A review of pulmonary manifestations, risk factors and treatment. *Respiration* 1992; 59: 339–343.
75. Smego RA, Asperilla MO. Use of acyclovir for varicella pneumonia during pregnancy. *Obst Gynecol* 1991; 78: 1112–1116.
76. Lim WS, Macfarlane JT, Colthorpe CL. Pneumonia and pregnancy. *Thorax* 2001; 56: 398–405.

77. Mer M, Richards AG. Corticosteroids in life-threatening varicella pneumonia. *Chest* 1998; 114: 426–431.
78. Roberts N, Peek JG, Jones N, Firmin KR, Elbourne D. Extracorporeal membrane oxygenation has important role. *BMJ* 2002; 324: 609.
79. Lee AW, Kolla S, Schreiner RJ, Hirschl RB, Bartlett RH. Prolonged extracorporeal life support (ECLS) for varicella pneumonia. *Crit Care Med* 1997; 25: 977–982.
80. Bugge JF, Tanbo T. Nitric oxide in the treatment of fulminant pulmonary failure in a young pregnant woman with varicella pneumonia. *Eur J Anaesth* 2000; 17: 269–272.
81. Bocles JS, Ehrenkranz NJ, Marks A. Abnormalities of respiratory function in varicella pneumonia. *Ann Intern Med* 1964; 60: 183–195.
82. Lin TY, Huang YC, Ning HC, Hsueh C. Oral acyclovir prophylaxis of varicella after intimate contact. *Pediatr Infect Dis J* 1997; 16: 1162–1165.
83. Zaia JA, Levin MJ, Preblud SR, *et al.* Evaluation of varicella-zoster immune globulin: protection of immunosupressed children after household exposure to varicella. *J Infect Dis* 1983; 147: 737–743.
84. Watson B, Seward J, Yang A, *et al.* Postexposure effectiveness of varicella vaccine. *Pediatrics* 2000; 105: 84–88.
85. Asano Y, Nakayama H, Yazaki T, Kato R, Hirose S. Protection against varicella in family contacts by immediate inoculation with varicella vaccine. *Pediatrics* 1977; 59: 3–7.
86. Hall S, Galil K, Watson B, Seward J. The use of school-based vaccination clinics to control varicella outbreaks in two schools. *Pediatrics* 2000; 105: 111.
87. Advisory Committee on Immunisation Practices (ACIP). Prevention of varicella: update recommendation of the Advisory Committee on Immunisation Practices (ACIP). *Morb Mortal Wkly Rep* 1999; 48: 2.