

# Varicella Pneumonia in Southern Israel: Clinical Characteristics, Diagnosis and Therapeutic Considerations

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**ABSTRACT:** **Background:** The most common and most serious complication of varicella (chickenpox) in adults is pneumonia, which can lead to severe respiratory failure. Varicella pneumonia is associated with considerable morbidity and even death. **Objectives:** To summarize our experience with varicella pneumonia in terms of clinical, laboratory and radiological characteristics as well as risk factors, management and outcome. **Methods:** We conducted a retrospective cohort survey in our facility from 1995 to 2008. **Results:** Our cohort comprised 21 patients with varicella pneumonia, of whom 19 (90%) were men; their mean age was  $35 \pm 10.5$  years. Nineteen patients (90%) were Bedouins and 18 (86%) were smokers. Eleven (52%) were admitted to the Medical Intensive Care Unit; 3 of them required mechanical ventilation and the remaining 10 (48%) were admitted to the general medical ward. Median length of stay was  $6 \pm 7.7$  days. Hypoxemia and elevated lactate dehydrogenase on admission were associated with respiratory failure. Radiological manifestations were variable and nine patients exhibited characteristic findings. All but one patient were treated with acyclovir. All patients fully recovered. **Conclusions:** In southern Israel varicella pneumonia is primarily a disease of young male Bedouins who are smokers. Severity ranges from mild disease to severe, resulting at times in respiratory failure requiring mechanical ventilation. Prognosis is favorable with complete recovery.

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**KEY WORDS:** varicella pneumonia, acyclovir, respiratory failure, mechanical ventilation, Bedouins

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Chickenpox is a highly contagious airborne viral infection that usually occurs during childhood [1]. In contrast to children, where chickenpox is a relatively mild disease associated with a low complication rate, the adult variety is associated with considerable morbidity and even death. Data from the 1980s suggest that the incidence of chickenpox in adults is increasing, with a parallel increase in hospital admissions

[2]. More recent data, however, suggest a decrease in the incidence of varicella in adults [1,3]. The most common and most serious complication of chickenpox is pneumonia, which can lead to severe respiratory failure. The mortality rate in these patients, as reported in various series, ranges from 10% to 30%. In severe cases requiring mechanical ventilation, this rate may reach 50% despite appropriate supportive and antiviral therapy [2,4-6].

Varicella pneumonia is relatively rare, and large-scale clinical studies are unavailable. Hence, most data come from small retrospective series [2] and over the past 30 years fewer than 300 patients have been described [2]. We therefore sought to summarize our experience with this entity in terms of clinical, laboratory and radiological characteristics as well as risk factors, management and outcome.

## PATIENTS AND METHODS

The Soroka University Medical Center is the only tertiary hospital in southern Israel and serves a population of more than half a million people. Searching the hospital archives for the period 1 January 1995 to 31 July 2008, we identified 21 patients admitted to the general medical wards or the MICU with a diagnosis of varicella pneumonia. Varicella pneumonia was defined as the presence of a typical rash associated with bilateral pulmonary infiltrates with no alternative identifiable cause. Serological confirmation was not performed. Mild hypoxemia was defined as the need for oxygen supplementation via nasal prongs. Moderate to severe hypoxemia was defined as the need for 100% oxygen supplementation by face mask or the need for mechanical ventilation.

Charts were reviewed for a history of exposure to a family member (children) infected with varicella; immunization status; and a wide variety of demographic, clinical and laboratory data. Additional extracted data included clinical manifestations, radiology, laboratory tests, management, ICU admission, ICU length of stay, hospital length of stay, and outcome. The chest X-rays were retrieved and reviewed by a senior radiologist who was unaware of the patient's clinical status or outcome. Chest X-rays were interpreted in relation

MICU = Medical Intensive Care Unit

to what is considered characteristic of varicella pneumonia, i.e., multiple ill-defined nodules 5–10 mm in size with a tendency to coalesce. These patchy confluent opacities may appear and disappear in different areas of the lung [7].

## RESULTS

We identified 21 patients; their clinical and demographic characteristics are presented in Table 1. There was a remarkable preponderance of males: 19 men (90%) and only 2 women. Nineteen patients (90%) were Bedouins and 18 (86%) were smokers. With the exception of one patient who was 70 years old, all other patients were rather young (16–49 years) with a mean age  $\pm$  SD of  $35 \pm 10.5$  years. In 12 patients (57%) there was a history of exposure to a family member infected with varicella. In the remaining nine no clear source of infection could be determined. Information regarding immunization status was unavailable.

**Table 1.** Clinical and demographic characteristics of the study group

No. of patients (%)	Mild* N=10 (48%)	Moderate to severe* N=11 (52%)
Male patients	9 (90%)	10 (91%)
Bedouin patients	8 (80%)	11 (100%)
Age (yrs, mean $\pm$ SD)	$37.8 \pm 12.8$	$31.2 \pm 6.4$
Mechanical ventilation	0	3 (27%)
Hospital length of stay (days, mean $\pm$ SD)	$5.8 \pm 2.2$	$11.4 \pm 10.4$
ICU length of stay (days, mean $\pm$ SD)	0	$8 \pm 7.8$
Duration of illness before admission (days, mean $\pm$ SD)	$3.6 \pm 2$	$3.5 \pm 1.4$
Current smokers	8 (80%)	10 (91%)
<b>Complaints</b>		
Fever	9/0 (90%)	7/10 (70%)
Cough	4/10 (40%)	6/11 (55%)
Shortness of breath	5/10 (50%)	9/11 (82%)
Characteristic rash	10/10 (100%)	11/11 (100%)
<b>On admission</b>		
Temperature ( $^{\circ}$ C, mean $\pm$ SD)	$38.1 \pm 1.1$	$38.3 \pm 0.9$
BP systolic (mmHg, mean $\pm$ SD)	$111 \pm 11.7$	$113.5 \pm 14.1$
BP diastolic (mmHg, mean $\pm$ SD)	$64.6 \pm 13.8$	$66.6 \pm 8.3$
Pulse (bpm, mean $\pm$ SD)	$92.5 \pm 13.8$	$113 \pm 21.8$
Respiratory rate (bpm, mean $\pm$ SD)	$22.5 \pm 5.3$	$29.3 \pm 5.1$
Saturation (% , mean $\pm$ SD)	$94.2 \pm 2.9$	$90 \pm 11.2$
pO <sub>2</sub> /FIO <sub>2</sub> ratio (mean $\pm$ SD)	NA	$156.9 \pm 134$

\* Mild hypoxemia was defined as the need for oxygen supplementation via nasal prongs. Moderate to severe hypoxemia was defined as the need for 100% oxygen supplementation by face mask or the need for mechanical ventilation.

## CLINICAL COURSE

We identified two groups of patients [Table 1]: 10 (48%) who had a relatively mild disease without significant hypoxemia and were admitted to the general medical wards and 11 (52%) with moderate to severe disease admitted to the MICU. In the latter group 3 patients (15%) had severe pneumonia with profound hypoxemic failure, clinically consistent with adult respiratory distress syndrome necessitating mechanical ventilation. Fortunately, none of the patients died.

Table 1 further summarizes the clinical manifestations on admission stratified according to the two patient groups. The 11 patients admitted to the MICU had a mean ICU length of stay of 8 days and overall length of stay of 11.4 days, while the mean length of stay in the rest of the cohort was 5.8 days. All patients had the characteristic vesicular rash of chickenpox infection at presentation to the hospital, with a relatively short duration of illness preceding their admission.

## LABORATORY

Table 2 summarizes the main laboratory findings on admission. Two patients had leukopenia (3300 and 3260 cells/ $\mu$ l). In 11 patients (52%) thrombocytopenia was observed either

**Table 2.** Laboratory findings on admission

Variables	Mild	Moderate to severe
pH (mean $\pm$ SD)	$7.45 \pm 0.03$	$7.39 \pm 0.1$
pCO <sub>2</sub> (mmHg, mean $\pm$ SD)	$33.3 \pm 2$	$39 \pm 9.7$
HCO <sub>2</sub> (mmol/L, mean $\pm$ SD)	$23.2 \pm 1.2$	$23.8 \pm 3.4$
Hemoglobin (g/dl, mean $\pm$ SD)	$14.9 \pm 1.9$	$15.1 \pm 2.3$
Hematocrit (% , mean $\pm$ SD)	$43.8 \pm 5.4$	$43.4 \pm 8.2$
WBC cells/ $\mu$ L (mean $\pm$ SD)	$7266 \pm 2009$	$9132.7 \pm 2914$
Polymorph nuclear cells (% , mean $\pm$ SD)	$61.3 \pm 16.6$	$67.6 \pm 15$
Lymphocytes (% , mean $\pm$ SD)	$26.7 \pm 14.2$	$24.8 \pm 15.3$
Platelets cells/ $\mu$ L (mean $\pm$ SD)	$122,700 \pm 39,240$	$113,000 \pm 37,563$
INR (mean $\pm$ SD)	$1.36 \pm 0.35$	$1.23 \pm 0.13$
Urea (mg/dl, mean $\pm$ SD)	$33.4 \pm 21.1$	$41.3 \pm 0.23$
Creatinine (mg/dl, mean $\pm$ SD)	$0.95 \pm 0.32$	$0.96 \pm 0.23$
Sodium (mmol/L, mean $\pm$ SD)	$135.2 \pm 4.4$	$135.4 \pm 3.2$
Albumin (mg/dl, mean $\pm$ SD)	$3.4 \pm 0.6$	$3.4 \pm 0.4$
Aspartate aminotransferase (U/L, mean $\pm$ SD)	$73.3 \pm 34$	$72.7 \pm 72.6$
Alanine aminotransferase (U/L, mean $\pm$ SD)	$58.4 \pm 27.8$	$57 \pm 43.5$
LDH (U/L, mean $\pm$ SD)	$705 \pm 336.7$	$1150 \pm 584.3$

on admission or within the first 2 days of their hospitalization. Thrombocytopenia was somewhat more pronounced among the moderate to severe group. The lowest values were observed among the three requiring mechanical ventilation (25,000–54,000 cells/ $\mu$ l). In two of them there was clinically significant bleeding from the upper gastrointestinal tract, necessitating blood transfusion. In the other patients in the group thrombocytopenia was mild (57,000–99,000 cells/ $\mu$ l), transient and clinically inconsequential.

Mild elevation in transaminases was noted in 10 patients (48%). Upon admission lactate dehydrogenase was elevated (> 1000 U/L) in 7 patients (33%); indeed, in the 3 patients requiring mechanical ventilation LDH levels were substantially higher (1500–3000 U/L).

**RADIOLOGY**

Chest X-rays were available for review in 18 of the 21 patients (85%). For the purpose of this report the chest X-ray with the worst findings is described. Table 3 summarizes the radiological findings while a characteristic chest X-ray is presented in Figure 1. In 10 patients (48%) the initial findings were described as typical of varicella pneumonia. Atypical radiological findings were unilateral nodular opacities in two patients, and left lower lobe consolidation superimposed on the characteristic pattern in one patient. This latter patient, on admission, had a positive blood culture for *Streptococcus pneumoniae*, probably reflecting a bacterial pneumonia complicating the course of his viral illness. In 11 patients there were no follow-up chest X-rays. In only five patients were follow-up chest X-rays available and those were interpreted as normal. In two patients there were bilateral interstitial fibrotic findings within a few years after the initial varicella pneumonia.

**MANAGEMENT**

All but one patient were treated with intravenous acyclovir (10 mg/kg every 8 hours) initiated within a few hours of admission. Two of the severely ill patients also received antibiotics. One of them had a positive blood culture for *Streptococcus viridans*. The single patient who was not treated with acyclovir was a 36 year old Bedouin man who had a very mild disease, presented afebrile with minimal respiratory complaints but with a characteristic chest X-ray and was discharged after 2 days with marked improvement.

One patient on mechanical ventilation was severely hypoxemic (PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 70). He was placed in the prone position and had tracheal gas insufflation during the first days of his ICU stay. On the ninth day his course was further complicated by polymicrobial severe sepsis due to ventilator-associated pneumonia. Blood cultures were positive for *Klebsiella pneumoniae* and *Acinetobacter baumannii*.

**Table 3.** Summary of radiological findings of 18 patients with at least one chest radiogram available for review

	Mild N=8 (44%)	Moderate to severe N=10 (56%)
Bilateral nodular pattern	5 (63%)	8 (80%)
Bilateral patchy consolidations	0	6 (60%)
Focal unilateral patchy consolidations	3 (38%)	2 (20%)
ARDS-like	0	5 (50%)
Interstitial reticular pattern	2 (25%)	5 (50%)
Typical of varicella pneumonia	3 (38%)	7 (70%)

ARDS = acute respiratory distress syndrome

**Figure 1.** Characteristic chest X-ray of varicella pneumonia in a patient with moderate to severe disease, revealing multiple bilateral nodules in the upper lung fields with patchy peri-hilar confluent opacities



He gradually recovered and was eventually discharged after 15 days in the MICU.

The time from admission to temperature normalization was shorter in the mild group (mean 44 hours), but substantially longer in the moderate to severe group (mean 120 hours).

Two patients had positive blood cultures on admission: one with mild disease had *Strep. pneumoniae* and the second, described earlier, with severe respiratory failure necessitating mechanical ventilation had *Strep. viridans*. Infective endocarditis was ruled out by transthoracic echocardiography followed by transesophageal echocardiography. An additional four blood cultures were sterile.

Two patients had mild transient acute renal failure; however, it is difficult to determine though whether renal

LDH = lactate dehydrogenase

dysfunction was related to the primary chickenpox infection. Alternatively, it could be related to medications (i.e., acyclovir) or sepsis-induced organ dysfunction (in one patient).

Transient electrocardiographic changes were observed in one patient in the form of right bundle branch block with inverted T waves in L2-3 and V1-3 that completely resolved within 48 hours. There was no elevation in creatinine phosphokinase and echocardiography was normal.

## DISCUSSION

### EPIDEMIOLOGY

Although data from the 1980s suggest that the incidence of chickenpox in adults is increasing with a parallel increase in hospital admissions, more recent data suggest a decrease in the incidence of varicella in adults [1,2]. While the exact frequency of varicella pneumonia is difficult to determine, it is estimated that one in 400 cases of chickenpox will develop pneumonia [3]. The incidence of adult varicella infection in our region is unknown, but according to data from the Tel Aviv area the risk for hospitalization related to varicella was 1/285 in the early 1990s [8]. Our data reveal that for the study period there was an annual incidence of one to two cases per year and there was no change in this pattern over the years.

An interesting finding of our study was the preponderance of Bedouin males (90%). This predominance is particularly remarkable in view of the fact that Bedouins account for only 23% of the overall population in the region. The reason for this predilection with relative sparing of women is unclear. We speculate that genetic predisposition may have contributed to this distinct predilection. Moreover, a serological study from northern and central Israel suggested that among Arab children, in the first 3 years of life, the prevalence of varicella antibody was double that of children from Jewish families, possibly suggesting a higher burden of exposure among adult Bedouins as well [9]. In another study performed in the early 1990s it was shown that 98% of Jewish army recruits tested positive for chickenpox [10].

Since June 2000 a varicella vaccine has been available in Israel [9]. Data on immunization in our cohort are not available but it seems rather unlikely that our patients received such a vaccination.

Smoking is considered a risk factor for the development of varicella pneumonia [11,12]. Proposed mechanisms include enhanced primary viremia due to the effects of smoking on the nasal mucosa and increased susceptibility of human macrophages to herpes viruses [1]. Thus, the high rate of smoking among Bedouins, as reflected in this series, may be an additional factor accounting for this unusually high incidence of varicella pneumonia.

Our data are in line with previous reports indicating that varicella pneumonia is much more common among males

[13,14]. Additional factors associated with an increased risk for varicella pneumonia include chest symptoms at presentation, more than 10 spots on the skin, contact with a patient with chickenpox, history of one's own child with chickenpox, and pregnancy [2]. Precise data regarding the presence of these risk factors among our cohort were not available.

### CLINICAL MANIFESTATIONS AND MANAGEMENT

In the current study, severity ranged from a relatively mild disease with minimal symptoms and radiological findings, to a more severe disease requiring ICU admission, to the rarer, severe life-threatening hypoxemic respiratory failure mandating mechanical ventilation (15%).

All patients who eventually required ICU admission presented with significant hypoxemia, respiratory distress and substantially elevated LDH levels. Other respiratory tract infections are also associated with elevated LDH levels, such as *Pneumocystis carinii* where a higher serum level of LDH tends to correlate with decreasing PaO<sub>2</sub>/FiO<sub>2</sub> [15]. In our series patients with moderate to severe disease had relatively higher LDH levels. This LDH elevation is attributed primarily to the acute lung injury. Interestingly, this observation was not reported in previous studies [4-6,13,14]. Given the retrospective nature of this report it is difficult to determine the predictive value of admission variables. Nonetheless, it seems prudent to admit patients with varicella pneumonia, who present hypoxemic with elevated LDH levels to an ICU, since respiratory failure may rapidly ensue. Indeed, among the patients previously reported 55% were admitted to a high dependency unit [4-6,13,14].

Acyclovir has become the standard of care for patients with varicella pneumonia even though there are no randomized controlled trials to support this practice. Current practice suggests a 7 to 10 day course, as given to all our patients but one. Published data based on 46 retrospective series encompassing 272 patients suggested a 3.6-fold higher mortality in patients who did not receive acyclovir (odds ratio 3.6, 95% confidence interval 1.63-7.95;  $P = 0.001$ ) [2]. The reported mortality among patients with varicella pneumonia is approximately 25% [3]. However, in recent reports as in this one, there were no fatalities. This improvement is probably related to the widespread use of acyclovir, in addition to marked advances in ICU care in general and mechanical ventilation in particular.

The use of corticosteroids in this setting is controversial. None of our patients was treated with systemic steroids. Two retrospective studies including 34 patients (of whom 16 were treated) showed a trend towards shorter ICU and hospital stay with no mortality [16,17]. Given the favorable outcome of recent reports, the adoption of this practice should probably await further controlled clinical trials.

The complications rate was rather low. Approximately half of our patients had mild transient thrombocytopenia and

increased transaminases. These disturbances were evenly distributed among the two patient groups and did not appear to reflect severity of the respiratory compromise. One patient had transient electrocardiographic changes that resolved within 48 hours with a normal ECG, possibly reflecting myocardial involvement. Two patients had mild transient renal failure of uncertain etiology.

In summary, varicella pneumonia in southern Israel is predominantly a disease of young Bedouin males who are active smokers. The disease is generally confined to the lungs and severity may range from mild brief illness to severe respiratory failure. Management is based on supportive care and intravenous acyclovir, leading to a favorable outcome and complete recovery.

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