Research Article

Severe Varicella Pneumonia in Adults: Seven Years' Single-center Experience from India

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Abstract

Context: Varicella pneumonia is a rare but a serious complication of chickenpox in adults. There is paucity of data on varicella pneumonia from India. **Aims:** The aim of this study is to describe the clinical manifestations, hospital course, treatment, and outcome of adult patients with severe varicella pneumonia. **Settings and Design:** This was a retrospective, observational study of patients with severe varicella pneumonia attending a tertiary care teaching hospital. **Subjects and Methods:** The cases of varicella were identified by a computerized search of the medical record for the period between January 2010 and December 2016. During this period, 137 patients got admitted with varicella of which 22 had severe varicella pneumonia. **Statistical Analysis:** Mean and standard deviation were computed. Fisher's Z-test of proportions and analysis of variance were applied. **Results:** There were 17 (77.3%) men and 5 (22.7%) women. The mean age of the patients was 33.4 ± 10.8 years. History of contact with an infected person followed by high-grade fever and typical rash was present in all patients. Forty-five percent (10/22) of patients were immunosuppressed. All the patients received intravenous acyclovir. Forty-five percent (10/22) of patients received invasive mechanical ventilation. The various factors associated with the need for mechanical ventilation were partial pressure of oxygen:fraction of inspired oxygen ratio <150, quick sequential (sepsis-related) organ failure assessment (qSOFA) >2, and early bacterial coinfection. The mean Intensive Care Unit and hospital stay were 7 days (range; 1–16) and 9 days (range; 4–21), respectively. The overall mortality was 22.7% and reached 50% in those requiring invasive ventilation. The mortality was higher among patients with qSOFA >3, mean arterial blood pressure <60 mmHg, and severe acute respiratory distress syndrome at presentation. **Conclusions:** Patients with severe varicella pneumonia are at an increased risk of respiratory failure and death.

Keywords: Mechanical ventilation, respiratory failure, varicella pneumonia

Introduction

Varicella (chickenpox) is an exanthematous, highly communicable airborne viral disease of childhood which usually has a benign course. However, severe infection, serious complication, and mortality can develop, especially in newborn babies, adolescents, adults, pregnant women, and immunosuppressed individuals of any age.[1]

The mortality for varicella ranges 0.29–0.46 per 1 million. Following the introduction of the varicella vaccine in 1995, there has been a significant decline in the incidence, hospitalizations, and deaths, especially in the developed countries.[2,3]

Pneumonia, though rare, is the most serious complication of chickenpox infection in healthy adults.[3] The respiratory complications of varicella are almost 25-fold more common in adults than in children. Varicella pneumonia is estimated to occur in 1 in 400 cases of infection.[4,5] According to another analysis, the incidence of pneumonia in varicella is <1.5/100,000 per year.[6]

Various established risk factors for developing varicella pneumonia include history of contact with a patient having chickenpox, previous or current smokers, chronic lung diseases, impaired immune status, severity of the skin rash, and third trimester of pregnancy.[3,5] The estimated mortality for varicella pneumonia varies between 10% and 33%.[7] The

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mortality approaches 50% in patients requiring mechanical ventilation.[8]

Data on severe varicella pneumonia from India are limited to case reports and small case series, so the present study was intended to describe the clinical manifestations, hospital course, treatment, and outcome in adult patients with severe varicella pneumonia.

Subjects and Methods

This retrospective study was carried out at an 1100-bed tertiary care teaching hospital in Northwest India. The cases of varicella pneumonia were identified by a computerized search of the available medical record database for the past 7 years (January 2010 and December 2016).

During this period, 137 patients with varicella were admitted and 22 had severe varicella pneumonia. Thereafter, the data pertaining to demographic characteristics; risk factor (smoking history, contact with chickenpox patient, varicella vaccine, HIV status, immunosuppressive treatment, and chronic lung disease); clinical manifestations; radiological features; and laboratory investigations were collected on a predesigned structured pro forma.

The diagnosis of varicella was clinical based on fever and characteristic widespread pleomorphic rash.[5] The cases of varicella pneumonia were identified based on the presence of new onset of respiratory symptoms with radiological findings within 10 days following the onset of clinically evident varicella infection.[5]

Patients already diagnosed with bronchiectasis, chronic obstructive pulmonary disease, allergic bronchopulmonary aspergillosis, or interstitial lung disease were classified to have chronic lung disease. Patients were defined as immunosuppressed if they met any one of the following criteria: solid organ transplantation, malignancy, and steroid treatment for more than 1 month or were on any other immunosuppressive drugs or HIV seropositive. Hypoxemia severity was assessed using the partial pressure of oxygen (PaO_2):fraction of inspired oxygen (FiO_2) ratio. Acute respiratory distress syndrome (ARDS) was defined in accordance with the Berlin definition.[9] Disease severity was assessed using the quick sequential (sepsis-related) organ failure assessment (qSOFA) score at the time of admission.[10] All the patients were isolated in the closed rooms adjoining the Intensive Care Unit (ICU) as negative airflow rooms were not available, and these patients were looked after by the staff with varicella immunity. Therapeutic regimens (acyclovir, antibiotics, steroids, and varicella-zoster virus immunoglobulins) including the type of respiratory support provided (oxygen supplementation, noninvasive mechanical ventilation [NIV], and invasive mechanical ventilation) were recorded. ICU-acquired infections were recorded. The diagnosis of infection was confirmed if patients met both the microbiological detection of a pathogen and the intention to treat it with the related antibiotics. Length of stay in ICU and hospital and status of patient at ICU and hospital discharge were noted.

The statistical analyses were performed using SPSS software, version 20.0 (SPSS, Inc., Chicago, IL, USA). The percentages of patients in each category were calculated for categorical variables. The mean and standard deviation were computed. The Fisher's Z-test of proportions and analysis of variance were applied to compare the two groups. $P < 0.05$ was considered statistically significant.

Results

During the 7-year study period, 137 patients with varicella were admitted of these 22 (16%) patients who had severe varicella pneumonia.

Demographic and underlying risk factors

There were 17 (77.3%) men and 5 (22.7%) women. Majority of the patients were relatively young (20–43 years), except two patients who were more than 50 years (mean age 33.4 ± 10.8 years). History of exposure/contact with a person infected with varicella was evident in all patients [Table 1]. Information regarding immunization with varicella vaccine was not available.

Nearly 45.4% (10/22) patients were immunosuppressed. Among the immunosuppressed state, corticosteroid use (6/10) was the most common.

Clinical features

All the patients had an acute presentation with a mean duration of symptom of 4 days (range, 2–7 days) before hospitalization. All the patients had the typical extensive pleomorphic rash and respiratory symptoms. Dyspnea (21/22), fever (18/22), and cough (14/22) were the most common symptoms [Table 2] The comparison between the characteristics of patients requiring invasive mechanical ventilation (ventilated group) during the hospital stay to those who did not require mechanical ventilation (spontaneously breathing group) revealed no difference in the presenting symptoms among the two groups. However, the mean duration from the onset of symptom to hospitalization was significantly ($P = 0.001$) more in the ventilated group (5.1 ± 1.5 days) than the spontaneously breathing group (3.2 ± 0.6 days).

Laboratory investigations

Laboratory findings indicated thrombocytopenia in 9 (40.9%), elevated transaminases in 7 (31.8%), and leukopenia in 3 (13.6%) patients. Thrombocytopenia, elevated transaminases, and hypoalbuminemia were significantly more in the mechanically ventilated group as compared to the spontaneously breathing group [Table 3].

All the patients had an abnormal chest radiograph. Nodular (19/22) and interstitial opacities (11/22) were the most common radiographic abnormality. However, airspace disease was significantly ($P = 0.001$) more in the mechanically ventilated

Table 1: Demographic characteristics and risk factors for severe varicella pneumonia

Variables	Overall (*n*=22)	Spontaneous breathing group (*n*=12)	Intubated group (*n*=10)	*P*
Demographics				
Age (years), mean±SD	33.4±10.8	31.58±11.4	35.6±10.2	0.400
Male gender	17 (77.3)	8 (66.7)	9 (90.0)	0.193
Contact with chickenpox case	22 (100)	12 (100)	10 (100)	0.000
Underlying immunosuppression	10 (45.4)	3 (25.0)	7 (70.0)	-
Steroid treatment	6 (27.2)	1 (8.3)	5 (50.0)	0.028
Any immunosuppressant	3 (13.6)	1 (8.3)	2 (20.0)	0.429
Solid organ transplantation	2 (9.1)	1 (8.3)	1 (10.0)	0.888
Malignancy	1 (4.5)	-	1 (10.0)	-
HIV	1 (4.5)	-	1 (10.0)	-
Tobacco smokers	4 (18.1)	1 (8.3)	3 (30.0)	0.190
Chronic respiratory disease	2 (9.1)	-	2 (20.0)	-
Pregnancy	1 (4.5)	1 (8.3)	-	-
Comorbidities	3 (13.6)	1 (8.3)	2 (20.0)	0.429
Diabetes mellitus	1 (4.5)	-	1 (10.0)	-
Hypertension	1 (4.5)	1 (8.3)	0	-
Chronic liver disease	1 (4.5)	-	1 (10.0)	-

Figures in parentheses indicate percentages. SD: Standard deviation

Table 2: Clinical characteristics of patients with severe varicella pneumonia

Variables	Overall (*n*=22)	Spontaneous breathing group (*n*=12)	Intubated group (*n*=10)	*P*
Fever	18 (81.1)	10 (83.3)	8 (80)	0.841
Dyspnea	21 (95.4)	11 (91.6)	10 (100)	0.352
Cough	14 (68.2)	7 (58.3)	7 (70)	0.568
Hemoptysis	3 (13.6)	-	3 (30)	-
Chest pain	3 (13.6)	2 (16.6)	1 (10)	0.652
Mean duration of illness (days)*	3.8±1.8	2.9±1.4	4.9±1.5	0.020
Temperature (°C), mean±SD	101.9±1.4	101.7±1.4	102.1±1.5	0.522
BP systolic (mmHg), mean±SD	123.2±20.5	134.3±6.9	109.8±23.6	0.003
BP diastolic (mmHg), mean±SD	73.4±13.5	80.3±7.7	64.4±13.8	0.002
BP mean (mmHg), mean±SD	89.9±14.8	98.7±6.2	79.5±15.5	0.001
Respiratory rate (bpm), mean±SD	29.1±5.5	26.00±3.0	32.70±5.5	0.001
Heart rate (bpm), mean±SD	121.8±13.1	112.5±6.8	133.0±9.5	0.001
Saturation (%), mean±SD	76.55±9.9	83.2±6.5	68.6±6.9	-

Figures in parentheses indicate percentages. *Mean duration of illness before hospitalization. BP: Blood pressure; SD: Standard deviation

group (70%) compared to the spontaneously breathing group (16.7%).

Treatment and outcome

All the patients received intravenous acyclovir in the dose of 10 mg/kg/8 hourly for a mean duration of 8 days. None of our patients received treatment with varicella-zoster immune globulin or adjunctive high-dose steroid therapy [Table 4].

At the very outset, 12 patients were managed with supplemental oxygen alone, 7 with NIV and supplemental oxygen, and 3 with invasive mechanical ventilation. NIV failed in 4 and nonrebreather mask in 3 patients who were subsequently intubated and mechanically ventilated. Ten (45.4%) patients required invasive mechanical ventilation during the hospital stay. Most of the patients were intubated on day 1 after admission. The mean duration from the time of hospitalization to mechanical ventilation was 1.6 days (range; 1–3). All the patients who required mechanical ventilation received empirical antibiotics.

Seven patients had severe ARDS according to the Berlin definition, and all of these patients had underlying immunosuppression. The various factors associated with the need for mechanical ventilation in the present study were PaO_2:FiO_2 ratio <150 (9/9), chronic lung disease (2/2), qSOFA score >2 (7/8), early bacterial coinfection (6/7), airspace disease on chest radiograph (7/9), history of smoking (3/4), and immunosuppressed state (7/10) [Table 5]. Vasopressors were required in 7 (31.8%) and renal replacement therapy in 3 (13.6%) patients.

Bacterial coinfection was documented in 10 (45.4%) patients, of these 5 (50%) had early coinfections, within 72 h after admission. The major sites of coinfections were the lungs (60%), bloodstream (20%), skin (10%), and urinary tract

Table 3: Laboratory investigations of patients with severe varicella pneumonia

Variables	Overall (*n*=22)	Spontaneous breathing group (*n*=12)	Intubated group (*n*=10)	*P*
Hemoglobin (g/dl), mean±SD	11.2±2.5	10.3±2.5	11.5±2.1	0.038
WBCs/μL, mean±SD	11.9±3.9	10.4±3.8	13.7±3.6	0.050
Platelet cells/μL, mean±SD	135.5±72.3	160.8±17.1	86.7±25.5	0.002
Total bilirubin (mg/dl), mean±SD	0.9±0.4	0.7±0.3	1.08±0.5	0.025
SGOT (U/L), mean±SD	113.5±68.1	75.9±36.6	158.6±70.9	0.002
SGPT (U/L), mean±SD	77.9±52.9	48.4±21.8	113.4±58.1	0.002
ALP (U/L), mean±SD	112.4±27.6	108.6±32.4	122.2±37.9	0.489
Albumin (g/dl), mean±SD	3.3±0.8	3.6±0.7	2.9±0.8	0.049
Urea (mg/dl), mean±SD	55.6±27.4	46.1±18.4	67.1±32.7	0.070
Creatinine (mg/dl), mean±SD	1.3±0.5	1.0±0.3	1.6±0.6	0.003
Sodium (mmol/L), mean±SD	131.7±8.7	133.8±8.7	129.1±9.3	0.212
PaO_2:FiO_2 ratio (mmHg)	166.1±72.3	221.3±36.5	99.8±40.3	0.0001
Chest X-ray at admission				
Nodular opacities	19 (86.4)	10 (83.3)	9 (90.0)	0.652
Interstitial opacities	11 (50)	8 (66.7)	3 (30.0)	0.087
Airspace disease	9 (40.9)	2 (16.7)	7 (70.0)	0.001
ARDS	7 (31.8)	-	7 (70.0)	-

Figures in parentheses indicate percentages. SGOT: Serum glutamic-oxaloacetic transaminase; SGPT: Serum glutamic-pyruvic transaminase; ALP: Alkaline phosphatase; ARDS: Acute respiratory distress syndrome; SD: Standard deviation; WBC: White blood cells; FiO_2: Fraction of inspired oxygen

Table 4: Management and outcome of patients with severe varicella pneumonia

Variables	Overall (*n*=22)	Spontaneous breathing group (*n*=12)	Intubated group (*n*=10)	*P*
qSOFA score	1.6±0.9	1.1±0.3	2.2±0.9	0.0001
Acyclovir duration	8.4±3.6	6.4±0.7	10.7±4.2	0.002
Empirical antibiotics at admission	17 (77.2)	7 (58.3)	10 (100)	0.020
Early bacterial coinfection	5 (22.7)	1 (8.3)	4 (40)	0.078
Late bacterial coinfection	5 (22.7)	-	5 (50)	-
Vasopressors	7 (31.8)	-	7 (70)	-
Renal replacement therapy	3 (13.6)	-	3 (13.6)	-
Outcome data				
Duration of ICU stay (days)	5.8±1.7	4.8±0.8	8.0±1.0	0.001
Length of hospital stay (days)	8.7±2.9	6.9±0.7	12.8±1.3	0.001
Hospital mortality	5 (22.7)	-	5 (50)	-

Figures in parentheses indicate percentages. qSOFA: Quick sequential (sepsis-related) organ failure assessment; ICU: Intensive Care Unit

Table 5: Need for mechanical ventilation in patients with severe varicella pneumonia

Risk factor	Number of patients	Need for mechanical ventilation
PaO_2:FiO_2 ratio <150	9	9 (100)
Chronic lung disease	2	2 (100)
qSOFA score >2	8	7 (87.5)
Early bacterial coinfection	7	6 (85.7)
Airspace disease	9	7 (77.8)
Smoking	4	3 (75.0)
Underlying immunosuppressed state	10	7 (70.0)
Age >40 years	7	4 (57.1)

Figures in parentheses indicate percentages. qSOFA: Quick sequential (sepsis-related) organ failure assessment; FiO_2: Fraction of inspired oxygen

infection (10%). *Staphylococcus aureus* (30%), *Klebsiella pneumoniae* (20%), and *Acinetobacter baumannii* (20%) were the most often recovered pathogen.

The mean ICU and hospital stay of the entire cohort were 7 days (range; 1–16) and 9 days (range; 4–21), respectively. The mortality in the study period was 22.7%. The main causes of death were as follows: septic shock in 3 (60%) and refractory ARDS in 2 (40%) patients. Septic shock in these 3 patients was attributed to superadded ventilator-associated pneumonia. The mortality was higher among patients with qSOFA score >3 (5/5), mean arterial blood pressure <60 mmHg (2/2), chronic lung disease (2/2), early bacterial coinfection (4/5), severe ARDS at presentation (5/7), immunosuppressed state (5/10), and need for mechanical ventilation (5/10) [Table 6].

Discussion

In the present study of 7 years, 22 patients were identified to have severe varicella pneumonia among the 137 admitted patients with varicella. Majority of the patients were young males. There was male preponderance of varicella pneumonia cases in our study which has also been reported in various

Table 6: Risk factors for mortality in patients with severe varicella pneumonia

Risk factor	Number of patients	Mortality
qSOFA score >3	5	5 (100)
MABP <60 mmHg	2	2 (100.0)
Chronic lung disease	2	2 (100)
Early bacterial coinfection	5	4 (80.0)
Severe ARDS at presentation	7	5 (71.4)
Need for vasopressors	7	5 (71.4)
Underlying immunosuppressed state	10	5 (50.0)
Age >35 years	10	5 (50)
Smoking	4	2 (50)
Need for mechanical ventilation	10	5 (50)

Figures in parentheses indicate percentages. qSOFA: Quick sequential (sepsis-related) organ failure assessment; ARDS: Acute respiratory distress syndrome; MABP: Mean arterial blood pressure

other studies.[11,12] The reason for this male predilection is unclear.

A history of exposure to varicella within a month of onset of illness was observed in all the patients, reinforcing the fact that primary varicella is highly contagious disease.

The data on varicella immunization in our cohort was not available, but it is unlikely that our patients had received such vaccination as it is not included in the Indian national immunization schedule. In countries where varicella is included in their vaccination programs, data support its significant role in reducing mortality and preventing complications in all age groups.[13]

Underlying immunosuppressed state is a well-known risk factor for varicella pneumonia and was seen in 45.4% patients. It was mainly related to impaired cellular immune response (immunosuppressive drugs and/or steroid exposure and malignancy). However, we identified 5 (22.7%) patients with severe varicella pneumonia in apparently young healthy controls, thus reinforcing the fact that varicella pneumonia can occur in an immunocompetent host without any risk factors.

Smoking is a major risk factor for the development of varicella pneumonia in adults;[14] however, only 4 (18.1%) patients in the present study were smokers. The lower number of smokers in the present study reflects the smoking trends for the state of Punjab. Tobacco prevalence is the lowest for Punjab in India as majority of its population (58%) practice Sikh religion, which prohibits tobacco consumption.[15]

The mean duration of illness prior ICU admission was 4 days (2–7), which is similar to other causes of viral pneumonia.[16,17] The course of illness was quite dramatic in about 45% of cases characterized by rapid respiratory deterioration, requiring invasive mechanical ventilation, soon after ICU admission. Seventy percent of the patients requiring mechanical ventilation had severe ARDS.

The mean duration from the onset of symptom to hospitalization was significantly (P = 0.001) more in the ventilated group (5.1 ± 1.5 days) than the spontaneously breathing group (3.2 ± 0.6 days) and may indicate that a delay in seeking medical advice/treatment may increases the risk for respiratory failure and mortality.

All the patients received intravenous acyclovir which is the standard of care for patients with varicella pneumonia. Published data based on 46 retrospective series comprising of 272 patients suggested a 3.6-fold higher mortality in patients who did not receive acyclovir.[2] The use of corticosteroids for severe varicella pneumonia is controversial. None of our patients was treated with systemic steroids. Retrospective series on steroid use in adults with varicella pneumonia have shown a trend toward shorter ICU and hospital stay with no mortality.[18]

Bacterial coinfection occurred in 10 (45.3%), mainly in those who required intubation and invasive mechanical ventilation. A higher number of patients with varicella pneumonia developing bacterial coinfection in the present study may be related to breach in innate immune system due to extensive of skin and mucosal involvement, need for intubation, and presence of coexisting underlying immunosuppressed states which predispose them to a wide range of infections. The reported rate of viral-bacterial coinfection in patients with viral pneumonia varies between 27.6% and 70.0%.[19,20]

The overall mortality in our cohort was 22.7% and reached 50% in patients who received invasive mechanical ventilation. Viruses have now been increasingly recognized as pathogens responsible for severe community-acquired pneumonia. In a prospective study in the ICU setting, the mortality rate of patients with viral pneumonia was similar to that of patients with bacterial pneumonia (25.5% and 26.5%; P = 0.82).[21]

Limitations of the study

Ours is a retrospective study over a long period, during which the supportive practices may have changed and influenced the results. We did not have the serological confirmation of varicella. The clinical and laboratory diagnosis of varicella is restricted to unusual cases. Due to the limited number of patients, we could not identify independent predictors of mortality.

Conclusions

Severe varicella pneumonia in adults is an acute respiratory illness that may require mechanical ventilation in significant number of the cases. Although the underlying medical conditions or immunosuppression is an important risk factor, it can occur in apparently healthy young adults. Delay in seeking medical advice may increase the risk for respiratory failure and mortality. The mortality is high, especially in those requiring invasive mechanical ventilation.

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Conflicts of interest

There are no conflicts of interest.

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