



Early View

Research letter

The outcome of severe varicella pneumonia with respiratory failure admitted to the intensive care unit for mechanical ventilation

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The outcome of severe varicella pneumonia with respiratory failure admitted to the intensive care unit for mechanical ventilation

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To the editor

Varicella pneumonia carries a mortality of 10-30%; mortality rate increases to 50% in patients that warrant mechanical ventilation secondary to respiratory failure despite appropriate antiviral and supportive treatment. Risk factors for the development of severe disease include cigarette smoking, pregnancy, immunocompromised states and a more extensive skin involvement.¹ Treatment options for life-threatening varicella consist mainly of cardiorespiratory support, antiviral therapy and steroid use. The benefit of antiviral therapy however, is still controversial.²

Due to the paucity of data pertaining to varicella zoster pneumonia attributed to its rarity, we aimed to describe all cases of varicella pneumonia admitted to an ICU which provides tertiary care to a population with a high HIV and tuberculosis burden. Moreover, we aimed to identify possible predictors of non-survival.

All cases of varicella pneumonia presenting to Tygerberg Academic Hospital adult respiratory intensive care unit between January 2004 and December 2016 were identified from an existing registry. Tygerberg Academic Hospital is a 1380-bed public hospital in South Africa serving approximately three million people in and around the Cape Town metropole. The population served has a HIV prevalence of 5.2% (95% confidence interval (CI) 3.4 - 7.8%)^{3,4} and the incidence of tuberculosis was 100/100,000 in 2016.⁵ Only patients (>18 years) with complete medical and radiological records were included in the final analysis. Ethical approval for the study was provided by the Stellenbosch University Research Ethics Committee (S16/04/082).

Apart from the general epidemiological characteristics, we specifically documented the presence or absence of co-morbid diseases and other potential risk factors, including current or recent pregnancy, HIV infection, active or previous pulmonary TB, COPD, obesity [body mass index (BMI) > 30 kg/m²], known malignancies and the use of immunosuppressive drugs.

The severity of illness was assessed by means of the acute physiology and chronic health evaluation (APACHE) II score,⁶ which was calculated 24 hours after admission to ICU, as well as the PaO₂/FIO₂ (partial pressure of arterial O₂ to the fraction of inspired O₂). We adapted a scoring system described by Opravil et al. to grade the severity and extent of pulmonary infiltrates: each lung was divided into four equal quadrants and each quadrant was scored on a scale of 0–3 (0: normal; 1: subtle increased interstitial markings; 2: prominent interstitial opacities; 3: confluent interstitial and acinar opacities),

giving a maximum score of 24 for both lungs.⁷ Peripheral blood white cell counts and C-reactive protein (CRP) levels were performed on admission

We specifically noted the following complications defined according to accepted criteria: acute respiratory distress syndrome (ARDS),⁸ septic shock,⁹ acute renal failure¹⁰ and ventilator associated pneumonia (VAP).¹¹ In the absence of a post-mortem investigation, we accepted the opinion of the unit's morbidity and mortality committee regarding the cause of death.

The IBM SPSS version 24 (IBM Corp, Armonk, NY, USA) was used to analyse the data. Due to the small sample size, only bivariate analysis was carried out to examine associations between risk factors and mortality. For continuous variables, non-parametric Mann Whitney tests were used and for categorical variables, Fisher's exact tests were used. Where possible, odds ratios (OR) with 95% confidence intervals were calculated for dichotomous risk factors that were found to have a p value <0.05. Unless stated otherwise, data are displayed as medians +/- interquartile range (IQR).

A total of 26 cases with severe varicella pneumonia requiring ventilatory support were identified during the study period. Two were excluded from further analysis due to incomplete medical and radiological records. Of the 24 patients included [median age 30.0 years; IQR (27.0-33.5)], 15 were females (62.5%). Notable risk factors included HIV co-infection (n=10, 41.7%), pregnancy/puerperium (n=8, 33.3%) and underlying TB (n=7, 29.2%). The mean duration of initial onset of symptoms to ICU admission was 3.9 +/- 1.5 days (range 1-7 days). Seven patients died (ICU mortality 29.2%). No risk was associated with non-survival. All patients were treated with intravenous acyclovir (5 mg/kg 8 hourly for 10 days), and 20 were treated with intravenous hydrocortisone. Neither the addition of hydrocortisone to acyclovir (mortality 6/20 vs. 1/4, p=1), nor the dose thereof which varied from 50 mg (n=6) to 100mg (n=12) to 200 mg (n=2) had an impact on survival.

A bilateral nodular appearance on the chest radiograph was the most common radiological finding (n=22, 91.7%), although no specific radiological pattern or radiological score had a significant effect on prognosis. The radiological score for survivors was 19.0 (18.0-22.0) and non-survivors 20.0 (17.0-22.0, p=0.42). The indices of disease severity and common complications are summarised in table 1. Metabolic acidosis (pH=7.11 vs. 7.39, p=0.020 and HCO_3^- =14.3 vs. 24.5, p=0.016) and a higher APACHE II score (22.0 vs. 13.0, p=0.009) were significantly associated with non-survival. Acute renal failure (ARF) on admission (p=0.023) was found to be a risk factor for mortality, with an odds ratio of 14.4 (1.4-152.5).

Other complications (ARDS, septic shock, secondary infections and VAP) were equally distributed between the groups.

In our study population, which to the best of our knowledge included the largest number of cases from a single-centre cohort, we found that varicella pneumonia necessitating ICU admission had a mortality of approximately 30%. Disease severity indicators - metabolic acidosis ($p=0.02$), a higher APACHE II score and acute renal failure on admission were significant predictors of mortality; whereas risk factors, chest radiography, and secondary infections were not.

General risk factors for varicella pneumonia in the adult population include cigarette smoking, pregnancy, immunocompromised states and a greater number of skin lesions.¹² Despite the fact that all our patients had at least one or more risk factor, none were found to predict non-survival. These findings are comparable to previous studies suggesting that the underlying medical context was no longer significantly associated with prognosis after adjustment for the severity of the acute disease.¹³

Treatment options for life-threatening varicella includes cardiorespiratory support, antiviral therapy and corticosteroids. In a retrospective study of 99 patients, no benefit was shown prior to and after the introduction of acyclovir.² Despite its limited efficacy, it is still widely recommended as an early primary therapy.^{14,15} Earlier studies (all with small sample sizes) suggested a mortality benefit, reduced ICU stay and even more rapid radiological improvement.² A large, recent French multicentre retrospective trial failed to confirm these potential benefits. In fact, steroid use was associated with more ICU-acquired infections.¹³ The present study could also not demonstrate any survival benefit from the addition of steroids to acyclovir.

A recent study showed that severity of respiratory disease, early bacterial co-infection and other organ failure on ICU admission were independent risk factors for invasive mechanical ventilation but due to the limited number of deaths, they were unable to identify predictors of hospital mortality.¹³ Apart from acute renal failure, our data failed to show an association between early bacterial co-infection and other organ failure on ICU admission and mortality.

Severe varicella is fortunately relatively rare, which makes large prospective studies very difficult. The major strengths of our study are the relative large sample size, and the fact that data was only missing in two of 26 patients. Potential limitations include the retrospective nature and the fact that the absolute

numbers may compromise efforts to obtain statistical significance. Moreover, it should be noted that acute renal failure, acidosis and the APACHE II score are all related and not independent parameters, which combined with the sample size, precluded a multivariate analysis. Other limitations include the single centre design and the fact that the data collection spanned 13 years during which evidence ICU management constantly evolved.

In conclusion, we found that varicella pneumonia in our population studied still carries a high mortality rate (29.2%). Metabolic acidosis, a higher APACHE II score and the presence of acute renal failure on admission predicted poor outcome. Further prospective, multi-centre studies with larger cohorts may be needed to identify other prognostic factors.

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TABLES

Table 1: Disease severity and complications related to Varicella pneumonia on admission

		<i>All (n=24)</i>	<i>Survivors (n=17)</i>	<i>Non-Survivors (n=7)</i>	<i>p-value</i>
APACHE II Score		16.0 (11.5-21.0)	13.0 (8.0-17.0)	22.0 (17.0-22.0)	0.01
P_aO_2/F_{iO_2}		171.0 (100.3-225.0)	179.0 (111.5-225.0)	157.5 (90.9-184.0)	0.35
ABG	P_aO_2 (kPa)	10.7 (9.7-13.5)	10.7 (9.7-12.0)	13.4 (9.7-17.2)	0.47
	P_aCO_2 (kPa)	6.1 (4.9-7.1)	5.9 (4.9-6.9)	6.7 (6.1-9.9)	0.26
	HCO_3 (mEq/L)	22.4 (16.9-28.1)	24.5 (21.9;28.1)	14.3 (13.7;16.6)	0.02
	pH	7.38 (7.26-7.41)	7.39 (7.35-7.41)	7.11 (6.98-7.26)	0.02
	Lactate (mmol/L)	1.7 (1.2-2.9)	1.5 (1.2-2.2)	3.5 (1.5-6.6)	0.10
Laboratory Data	WCC ($\times 10^9/L$)	10.9 (8.1-14.6)	10.9 (8.1-12.4)	12.7 (10.4-15.3)	0.52
	CRP (mg/dL)	105.0 (66.0-180)	105.0 (67.0-138.0)	101.0 (60.0-180.0)	0.76
	CD_4 count (cells/ mm^3) *	145.0 (67.0-296.0)	204.5 (57.0-296.0)	76.0 (67.0-326.0)	1
Complications	Secondary sepsis	11 (45.8%)	8 (47.1%)	3 (42.9%)	1
	ARDS	14 (58.3%)	8 (47.1%)	6 (85.7%)	0.81
	VAP	8 (33.3%)	6 (35.9%)	2 (28.6%)	0.75
	Septic shock	11 (45.8%)	8 (47.1%)	3 (42.9%)	1
	ARF (on admission)	11 (45.8%)	5 (29.4%)	6 (85.7%)	0.02

Values in brackets represent interquartile range (IQR) for continuous data and percentages for categorical data.

*Available for 9 of 10 patients

APACHE II, Acute physiology and chronic health evaluation; P_aO_2/F_{iO_2} , ratio of arterial oxygen partial pressure to fractional inspired oxygen; ABG, arterial blood gas; P_aO_2 , partial pressure of oxygen; P_aCO_2 , partial pressure of carbon dioxide; WCC, white cell count, CRP, C-reactive protein; ARDS, acute respiratory distress syndrome; VAP, ventilator-associated pneumonia; ARF, acute renal failure