

## Severe Adult Chickenpox Infection Requiring Intensive Care

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### Abstract

**Introduction:** Chickenpox (varicella) in adults can be severe with increased mortality. This study investigated the clinical presentation and outcome of 12 adult chickenpox patients requiring intensive care. **Materials and Methods:** A retrospective, observational study was performed in an adult medical intensive care unit of a university-affiliated hospital involving consecutive patients with varicella admitted over 4 years (1997-2000). **Results:** The 12 patients had a mean  $\pm$ SD age of  $40 \pm 20$  (range, 15 to 86) years. Two patients were above 65 years old (aged 73 and 86 years). All but 1 were male. None had previous varicella vaccination. Six patients had direct exposure to persons with chickenpox infection. Four patients had underlying pulmonary pathology: past pulmonary tuberculosis (2), emphysema (1) and recurrent right pleural effusion from autoimmune serositis (1). The mean APACHE II score was 14.2 (range, 6 to 26). Ten patients had varicella pneumonia (of whom 2 had acute respiratory distress syndrome and 5 had acute lung injury), 1 had chickenpox encephalitis and 1 patient presented concomitantly with diabetic ketoacidosis. The median duration of stay in the intensive care unit (ICU) was 11 days (range, less than 1 day to 76 days). Nine patients (75%) required mechanical ventilation (median duration, 14 days; range, less than 1 day to 79 days). All patients were treated with acyclovir. There were 3 deaths (25%); 2 were above 65 years old and 1 was 37 years old with acute myeloid leukaemia on chemotherapy. **Conclusion:** Patients with varicella infection requiring intensive care carry significant mortality. In our series, old age appears to be associated with increased mortality ( $P = 0.045$ ).

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**Key words:** Mortality, Pneumonia, Ventilation

### Introduction

Chickenpox (varicella) in adults can be severe. It is frequently associated with pneumonia and immunosuppression as well as increased mortality rates.

In the US, the mortality rate from chickenpox in adults has been increasing from 0.17 per million population during 1970-1974 to 0.31 per million population during 1990-1994.<sup>1</sup> The proportion of adult (aged 20 years and above) deaths to total chickenpox deaths also showed an increase from 20% during 1970-1974 to 54.3% during 1990-1994. Compared to children aged 1 to 4 years, adults had a 25 times greater risk of dying from varicella.<sup>1</sup> Similarly, data from England and Wales reported that deaths in adults (aged 15 years and above) had increased relative to the total number of chickenpox deaths, from 48% for the period 1965-1977 to 64% for the period 1978-1985.<sup>2</sup>

The most frequent serious complication of chickenpox in adults is pneumonia. It occurs insidiously, about 1 to 6 days after onset of typical varicella rash, with tachypnoea and cough. Amongst adults who had chickenpox, there was a reported incidence of 0.25% to 10% who developed pneumonia.<sup>3,4</sup> The mortality rate for varicella pneumonia is about 5% to 23%.<sup>5,6</sup> The data from England and Wales showed that the proportion of adult chickenpox deaths that was associated with pneumonia was 42.3% (88 out of 208 deaths).<sup>2</sup>

Other common complications among patients who died from chickenpox include central nervous system (CNS) complications, secondary infections and haemorrhagic conditions.<sup>1</sup>

This study reviews the clinical presentation, treatment and outcome of adult patients with severe chickenpox infections that required intensive care.

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## Materials and Methods

This is a retrospective case series of all adult patients diagnosed with chickenpox who were admitted from 1997 to 2000 to the adult medical intensive care unit (MICU) of the second largest university-affiliated acute care general hospital in Singapore. It also houses the Communicable Diseases Centre, which is a tertiary referral centre for infectious diseases.

The data collected consisted of patient demographics, clinical presentation, laboratory investigations, complications of chickenpox, length of hospital and ICU stay, and mortality.

Varicella was diagnosed based on clinical features of an acute febrile illness with a generalised varicelliform eruption. History of exposure was not used as a diagnostic feature as patients are usually unaware of their exposure. Patients were diagnosed to have pneumonia if they had a chest radiograph with diffuse interstitial or nodular pulmonary infiltrates. Acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) were defined according to the American-European Consensus Conference on ARDS.<sup>7</sup>

The severity of illness was calculated using the Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system.<sup>8</sup>

Data were compiled and analysed using Microsoft Excel 97.

## Results

Twelve patients were admitted to the MICU during the 4-year period. A summary of these cases is shown in Table I.

The patients were all male except for 1. The mean  $\pm$  SD age was  $40 \pm 20$  (range, 15 to 86) years. Two of them were above 65 years (aged 73 and 86 years). Three patients were of Indian origin and the rest were Chinese. Almost half were foreign males working in Singapore (2 Malaysians, 1 Indonesian, 1 Indian national and 1 Bangladeshi).

### Clinical Features

No patient had a history of previous varicella infection or varicella vaccination. Six patients had direct exposure to persons with chickenpox infection. The contacts of 5 of these patients were children.

There were 4 cigarette smokers, 2 ex-smokers, 3 non-smokers and 3 did not have their smoking history documented. Four patients had previous pulmonary pathology: 2 had past pulmonary tuberculosis, 1 had emphysematous lungs and 1 had recurrent right pleural effusion from autoimmune serositis.

Three patients had a background history of immunocompromised states. The first patient has acute myeloid leukaemia and was being treated with mercaptopurine and methotrexate. The second was a newly diagnosed type 1 diabetic who was concurrently admitted for diabetic ketoacidosis. The third had systemic lupus erythematosus and was on systemic steroids at the time of his infection.

The mean APACHE II score was  $14.2 \pm 6.7$  (range, 6 to 26).

Ten patients had varicella pneumonia. Their mean respiratory rate on admission to MICU was  $30 \pm 8$  breaths per minute (range, 18 to 42) and mean ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen was  $261 \pm 60$  (range, 171 to 351). Of these, 2 had ARDS and 5 had ALI.

### Therapy

Eleven patients were admitted to the MICU from the general ward and 1 was admitted through the Emergency Department. The median duration of stay in the MICU was 11 days (range, less than 1 day to 76 days). The median hospital stay was 17 days (range, less than 1 day to 83 days).

For the 9 patients who required mechanical ventilation via the endotracheal tube, the median duration of ventilation was 14 days (range, less than 1 day to 79 days). No patients were placed on non-invasive positive pressure ventilation. Four patients subsequently developed ventilator associated pneumonia.

All the patients were started on a course of intravenous acyclovir at 10 mg/kg every 8 hours for 10 to 21 days depending on the patient's condition. All completed the course (3 were converted to oral formulation subsequently) except 1 patient who died before completion of the course of acyclovir. All patients were empirically treated with cloxacillin (intravenous or oral) and intravenous ceftriaxone.

### Mortality

Of these 12 cases, there were 3 deaths. In this series, age above 65 years old appears to be associated with increased mortality (Fisher's exact test,  $P = 0.045$ ).

The first patient, the only female in this series, was an 86-year-old who had a contact history of chickenpox from her granddaughter. She required mechanical ventilation for 7 days. She developed acute renal failure 2 days after admission (serum creatinine rose from 96 to 252  $\mu\text{mol/L}$ ). The possible causes of her acute renal failure include septic shock and acyclovir. She died 8 days after her admission from multiorgan failure secondary to varicella pneumonia.

The second patient who died was a 73-year-old male who had contact history of chickenpox from his granddaughter. He had symptoms for 3 days before being admitted and was treated in the general ward for 5 days before being transferred to the MICU. On the day of admission to the MICU, he developed an acute non-ST elevation myocardial infarction. His creatinine level progressively rose from 94  $\mu\text{mol/L}$  on admission to a peak of 280  $\mu\text{mol/L}$  about 1 week later. This was suspected to be due to acyclovir and the use of gentamicin when he was first admitted to the MICU. He had a prolonged stay (76 days) in the MICU and was mechanically ventilated throughout his stay in the MICU. He was transferred to the high dependency unit where he finally passed away 3 days later from recurrent pneumonia.

Table 1. Summary Data of 12 Patients with Severe Varicella Requiring Intensive Care

Patient	Sex	Age (y)	Race	Contact history	Smoker	APACHE II score	Respiratory rate (breaths/min)	PaO <sub>2</sub> /FiO <sub>2</sub>	ARDS or ALI	Days on mechanical ventilation	Days in ICU	Days in hospital	Remarks	Final outcome
1	F	86	C	Yes	?	21	28	242	ALI	7	7	9	Complicated by acute renal failure	D
2	M	73	C	Yes	Ex	26	25	248	ALI	79	76	83	Past tuberculosis with scarred lung apices. Complicated by acute renal failure and acute non-ST elevation myocardial infarct	D
3	M	37	C	Yes	No	16	36	250	ALI	1	1	1	Acute myeloid leukaemia on mercaptopurine and methotrexate	D
4	M	31	C	Yes	No	21	40	258	ALI	14	20	45	Systemic lupus erythematosus on steroid with autoimmune serositis with recurrent right pleural effusion	R
5	M	36	C	Yes	Ex	20	42	200	ARDS	39	26	73	Past tuberculosis with left fibrothorax. Complicated by bilateral pneumothorax and right empyema	R
6	M	52	C	?	Yes	14	22	328	No	19	16	37	Chronic emphysema with small right apical and large left upper bullae	R
7	M	32	C	No	Yes	12	18	171	ARDS	0	7	9	-	R
8	M	32	C	No	Yes	12	24	220	ALI	19	22	25	-	R
9	M	26	I	No	Yes	8	38	339	No	0	6	8	-	R
10	M	29	I	?	?	7	28	351	No	7	14	23	-	R
11	M	15	C	?	No	7	22	676	No pneumonia	0	3	11	Recently diagnosed Type 1 diabetes mellitus Admitted with concurrent diabetic ketoacidosis	R
12	M	33	I	Yes	?	6	19	829	No pneumonia	4	5	24	Complicated by seizures	R

ARDS: acute respiratory distress syndrome; ALI: acute lung injury; C: Chinese; D: died; I: Indian; R: recovered

The third patient died within 24 hours of admission to the hospital. He had previously been diagnosed to have acute myeloid leukaemia and was on mercaptopurine and methotrexate. His chickenpox contacts were his 2 children.

## Discussion

In the 4 years from 1997 to 2000, an average of 27,910 reported cases of chickenpox were reported annually in Singapore.<sup>9,10</sup> The data for 1999 showed that 14,015 (44.4%) of a total of 31,592 reported chickenpox cases occurred in persons aged 15 and above.<sup>11</sup> This is similar to other studies done in the tropics,<sup>12,13</sup> where the age distribution of cases and varicella zoster virus (VZV) seroprevalence data have indicated a higher proportion of cases occurring among adults compared to temperate regions.

A previous study on 10 adult patients with varicella pneumonia was done in Singapore from 1 April 1993 to 31 March 1994.<sup>14</sup> The only death in that series was from 1 of the 4 patients who required mechanical ventilation. Risk factor of smoking was present in 7 of the 10 patients. There were no data on the number that required intensive care.

One case series from a hospital in South Africa looked at adult varicella pneumonia that required intensive care over a 10-year period (1983 to 1993).<sup>15</sup> There were no deaths out of the 15 patients admitted to their ICU. The patients in this series appeared to have less severe disease compared to those in our study. The APACHE II scores, which were available only for 10 patients, ranged from 1 to 15 with a mean of 7.9. In that study, only 4 patients required mechanical ventilation, while the rest were managed either by face mask oxygen or continuous positive airway pressure (CPAP) by face mask.

Our study comprised almost entirely of males with foreign males forming almost half of the study group (41.6%). Similarly in Oh and Chew's series,<sup>14</sup> 8 out of 10 patients were male. This gender difference in adults was also noted in hospital admissions for chickenpox in a North London series where male-to-female admission ratio was 2:1 with a trend to more severe disease in males.<sup>16</sup> It has been suggested that men may be more predisposed to more severe disease because they are more likely to be smokers.<sup>16</sup>

Cigarette smoking is a major risk factor for development of pneumonia in adults with chickenpox. This was first reported in a study of 29 patients with varicella infection; 7 out of 19 smokers developed pneumonia while none of the 10 non-smokers developed pneumonia.<sup>17</sup> In another study of 67 adults with chickenpox, 16 out of 34 smokers and only 1 of 33 non-smokers developed pneumonia; the relative risk of developing pneumonia was 15 times higher in smokers than in non-smokers.<sup>18</sup>

Three of our patients had some form of immunosuppression; 1 of whom died. Immunosuppression is a known risk factor for mortality in cases of adult varicella. In England and Wales during 1967-1985, 71 (34%) out of 208 deaths in adults aged 15 and above were associated with immunosuppression.<sup>2</sup>

During this time, the numbers and proportion of deaths from chickenpox with associated immunosuppression increased in this group of adults.

All patients in this study were started on a course of acyclovir, although the benefit of acyclovir in established varicella pneumonia is minimal and the evidence is limited. There has been several case series on the use of acyclovir in adult varicella pneumonia.<sup>6,19,20</sup> They generally recommend the early administration of acyclovir. One retrospective controlled study of 38 patients with varicella pneumonia showed that 11 patients, who had a course of intravenous acyclovir initiated within 36 hours of hospitalisation, showed improvement with decreased tachypnoea and improved oxygenation but only from sixth day of hospitalisation onwards.<sup>5</sup> There has been no randomised prospective study to date because of the low incidence of varicella pneumonia.

Although treatment with acyclovir is relatively safe, there is a small risk of acute renal failure. Acyclovir is eliminated by both glomerular filtration and tubular secretion. Crystallisation of acyclovir in the renal tubules causing obstructive nephropathy has been most commonly suggested as a mechanism of nephrotoxicity.<sup>21</sup> Other mechanisms proven from biopsies are acute tubular necrosis<sup>22</sup> and acute hypersensitivity interstitial nephritis.<sup>23</sup>

The acute renal failure in the 2 patients in our study could have been contributed by acyclovir. In one case, another contributory factor was hypotension (with ischaemic nephropathy) and in the other case, there was concomitant use of gentamicin.

Live, attenuated varicella virus vaccine has been licensed for healthy persons  $\geq 2$  months of age since March 1995 in the USA and since September 1996 in Singapore. The vaccine provides 70% to 90% protection against varicella and 95% protection against severe varicella for 7 to 10 years after vaccination.<sup>24</sup>

The Advisory Committee on Immunisation Practices (ACIP) in United States recommends varicella vaccination for susceptible persons in several high-risk groups including adolescents and adults living in households with children.<sup>24</sup> Additionally, the ACIP recommends post-exposure varicella vaccination for use in susceptible persons within 3 days, and possibly up to 5 days, of exposure.<sup>25</sup> This follows data from the USA and Japan that have shown that post-exposure varicella vaccine is effective in preventing illness or modifying disease.<sup>26-28</sup>

All 3 patients who died had contact with children who had chickenpox. Their deaths may have been prevented if the children they were exposed to had been vaccinated or if they, as susceptible adults, were vaccinated. Two of them were eligible for post-exposure varicella vaccination.

In summary, our study is a reminder that varicella carries a high risk of morbidity and mortality in adults. With the availability of an effective varicella vaccine, the move should be towards prevention of chickenpox. It is important for physicians to offer post-exposure varicella vaccination to susceptible adult contacts of varicella patients. Similarly for

immunocompromised patients, it is important to vaccinate their potential susceptible contacts. In the event of development of varicella, acyclovir should be used early in the disease (within 24 hours of onset of rash) before the potential development of pneumonia or other complications. This is especially so for patients at high risks for complications, i.e. smokers, the immunocompromised, and those with significant premorbid conditions. It is also important to watch out for the development of acute renal failure especially in the elderly when acyclovir is instituted.

## REFERENCES

- Meyer PA, Seward JF, Jumaan AO, Wharton M. Varicella mortality: trends before vaccine licensure in United States, 1970-1994. *J Infect Dis* 2000;182:383-90.
- Joseph CA, Noah ND. Epidemiology of chickenpox in England and Wales, 1967-85. *BMJ* 1988;296:673-6.
- Guess HA, Broughton DD, Melton LJ, Kurland LT. Population-based studies of varicella. *Pediatrics* 1986;78(Suppl):723-7.
- Baren JM, Henneman PL, Lewis RJ. Primary varicella in adults: pneumonia, pregnancy, and hospital admission. *Ann Emerg Med* 1996; 28:165-9.
- Haake DA, Zakowski PC, Haake DL, Bryson YJ. Early treatment with acyclovir for varicella pneumonia in otherwise healthy adults: retrospective controlled study and review. *Rev Infect Dis* 1990;12:788-98.
- Davidson RN, Lynn W, Savage P, Wansbrough-Jones MH. Chickenpox pneumonia: experience with antiviral treatment. *Thorax* 1988;43: 627-30.
- Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818-24.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. *Crit Care Med* 1985;13: 818-29.
- Committee on epidemic diseases. Cases of specified notifiable diseases, Republic of Singapore, December 1998. *Epidemiological News Bulletin (Singapore)* 1999;25:6.
- Committee on epidemic diseases. Cases of specified notifiable diseases, Republic of Singapore, December 2000. *Epidemiological News Bulletin (Singapore)* 2001;27:8.
- Committee on epidemic diseases. Seroprevalence of varicella-zoster virus infection in Singapore. *Epidemiological News Bulletin* 2000; 26:1-4.
- Longfield JN, Winn RE, Gibson RL, Juchau SV, Hoffman PV. Varicella outbreaks in army recruits from Puerto Rico. *Arch Intern Med* 1990; 150:970-4.
- Garnett GP, Cox MJ, Bundy DA, Didier JM, St. Catherine J. The age of infection with varicella-zoster virus in St Lucia, West Indies. *Epidemiol Infect* 1993;110:361-72.
- Oh HM, Chew SK. Varicella pneumonia in adults – clinical spectrum. *Ann Acad Med Singapore* 1996;25:816-9.
- Potgieter PD, Hammond MJ. Intensive care management of varicella pneumonia. *Resp Med* 1997;91:207-12.
- Bovill B, Bannister B. Review of 26 years' hospital admissions for chickenpox in North London. *J Infect* 1998;36(Suppl 1):17-23.
- Ellis ME, Neal KR, Webb AK. Is smoking a risk factor for pneumonia in adults with chickenpox? *BMJ* 1987;294:1002.
- Grayson ML, Newton-John H. Smoking and varicella pneumonia [letter]. *J Infect* 1988;16:312.
- Schlossberg D, Littman M. Varicella pneumonia. *Arch Intern Med* 1988; 148:1630-2.
- El-Daher N, Magnussen R, Betts RF. Varicella pneumonitis: clinical presentation and experience with acyclovir treatment in immunocompetent adults. *Int J Infect Dis* 1998;2:147-51.
- Sawyer MH, Webb DE, Balow JE, Straus SE. Acyclovir-induced renal failure. Clinical course and histology. *Am J Med* 1988;84:1067-71.
- Becker BN, Fall P, Hall C, Milam D, Leonard J, Glick A, et al. Rapidly progressive acute renal failure due to acyclovir: case report and review of literature. *Am J Kidney Dis* 1993;22:611-5.
- Rashed A, Azadeh B, Abu Romeh SH. Acyclovir-induced acute tubulo-interstitial nephritis. *Nephron* 1990;56:436-8.
- Centers for Disease Control and Prevention. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 1996;45(No. RR-11):1-36.
- Centers for Disease Control and Prevention. Prevention of varicella: updated recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 1999;48(No. RR-6):1-5.
- Asano Y, Nakayama H, Yazaki T, Kato R, Hirose S. Protection against varicella in family contacts by immediate inoculation with live varicella vaccine. *Pediatrics* 1977;59:3-7.
- Arbeter AM, Starr SE, Plotkin SA. Varicella vaccine studies in healthy children and adults. *Pediatrics* 1986;78(suppl):748-56.
- Salzman MB, Garcia C. Postexposure varicella vaccination in siblings of children with active varicella. *Pediatr Infect Dis J* 1998;17:256-7.