Hantavirus Pulmonary Syndrome, Southern Chile

Raúl Riquelme,* Mauricio Riquelme,* Antoni Torres,† Maria Luisa Rioseco,* José Antonio Vergara,* Luis Scholz,‡ and Andrea Carriel*

We analyzed data from 25 consecutive patients with hantavirus pulmonary syndrome (HPS) admitted to the Puerto Montt and Osorno Regional Hospitals, southern Chile, from 1997 to 2001, emphasizing epidemiologic, clinical, radiographic, treatment, and laboratory aspects. Hemorrhage was frequent (64%), and 48% of patients showed alterations in renal function. Ten patients died (40%). We identified three groups of patients, which included the following: 1) those with the least severe form who had prodromic symptoms without pulmonary involvement; 2) those with moderate illness who had interstitial pulmonary infiltrates, usually needed supplemental nasal oxygen, were hemodynamically stable, and had an APACHE II <12 (none of whom died); and 3) those with the severe form who required mechanical ventilation, frequently had hemodynamic instability (93%), experienced a high mortality rate (77%), and had an APACHE II >12. Mild forms of HPS also exist, which are poorly known; the symptoms could be confounded with those of other viral diseases, leading to underdiagnosis.

Human infection and disease caused by *Hantavirus* spp. were unknown in the Americas until May 1993 (1). Since then, hantavirus infection has been reported in the United States, Brazil, Paraguay, Bolivia, and Chile (2–5). A new species called Andes virus was isolated during an outbreak in Argentina, with a rodent reservoir of *Oligoryzomys longicaudatus* in rural Argentina and Chile (6).

The most well-known clinical presentation of hantavirus pulmonary syndrome (HPS) starts with an influenzalike stage, with high fever, myalgia, asthenia, and after a prodromal period of 2 to 7 days, dyspnea, respiratory failure, and hemodynamic instability. Chest radiography shows rapidly progressing bilateral interstitial infiltrates, with an elevated hematocrit and thrombocytopenia. Other signs and symptoms have been reported, and in some case-patients, the disease may not progress beyond the prodromal stage or clinical symptoms may be completely absent (7).

Asian and European forms of hantavirus disease consist of a group of febrile nephropathies known as hemorrhagic fever with renal syndrome (8), clinical features of which differ from the forms described in the Americas. This study describes some aspects of this emergent disease in a group of 25 patients with confirmed hantavirus infection, emphasizing clinical, radiographic, and laboratory aspects.

Materials and Methods

Patient Population

Clinical chart information was recorded from of all patients with hantavirus pulmonary syndrome (HPS) admitted to the Osorno (n = 7) and Puerto Montt (n = 18) Hospitals from 1997 to 2001. All cases were confirmed by serologic tests performed at the virology laboratories of the Public Health Institute (Santiago) or Universidad Austral (Valdivia), with enzyme-linked immunoassay (ELISA) for immunoglobulin (Ig) M and IgG antibodies using Sin Nombre virus antigens provided by the Centers for Disease Control and Prevention, Atlanta, Georgia, USA. The Student t test was used to compare parametric variables, and chi square and Fisher exact test were used to compare discrete variables when necessary. A p value <0.05 was considered statistically significant.

Data Collection

The following data were recorded: age, sex, work type, residence, probable mechanism of infection, incubation period (only for those case-patients for whom precise information on the time of rodent exposure and onset of symptoms was available), medical history, and differential diagnosis. On admission, dyspnea, fever, anorexia, asthenia, headache, myalgia, chills, cough, abdominal pain, cyanosis, abnormal breathing sounds, hypotension (systolic blood pressure [SBP] <100), pulse rate, temperature, and respiratory frequency were recorded. A pseudoinfluenza course was understood to mean that the patients had a high

*Puerto Montt Regional Hospital, Puerto Montt, Chile; †Clinical Institute of Pneumology and Thoracic Surgery Hospital Cliníc, Barcelona, Spain; and ‡Osorno Regional Hospital, Osorno, Chile

fever, myalgia, headache, asthenia, and usually no rhinorrhea.

Clinical records noted any bleeding, alterations in renal or hepatic functions, alteration in consciousness, intensive care unit (ICU) admission, oxygen support, arterial oxygen tension (PaO_2)/inspiratory oxygen fraction (FiO_2) (PAFI), administration of antibiotic drugs or corticosteroids, and mechanical ventilation (duration and time of connection). We defined a renal function abnormality according to American Thoracic Society (ATS) criteria with plasma creatinine values at the onset or during the course of the disease >1.2 mg/dL or blood urea nitrogen [BUN] >20 mg/dL (9), which are considered specific risk factors for death or a complicated course of community-acquired pneumonia.

Chest x-rays were analyzed, and the results were classified as an alveolar, interstitial, or mixed pattern, and the distribution of radiographic infiltrates as unilobar or multilobar, and unilateral or bilateral. The presence of pleural effusion was noted. In addition, we looked for an increase in the size of the opacity by ≥50% within 48 hours of admission because a rapid spreading of infiltrates shown by radiograph (which usually cannot be determined at the time of admission) indicates severe community-acquired pneumonia (9).

Laboratory tests at admission and during the course of the illness were recorded.

Methylprednisolone was administered (to 10 patients) according to a published protocol (10): 1,000 mg IV per day for 3 days, followed by 16 mg orally per day for 3 days, 8 mg per day for 3 days, and finally, 4 mg per day for 3 days.

An APACHE II severity score was calculated for every patient (11). For those admitted to the ICU, the score was calculated by using the data recorded at that time. For those patients not admitted to ICU, we used the worst parameters during hospitalization to find the worst APACHE.

Shock was defined as having a systolic blood pressure of <90 (which was not changed by fluid administration or required the use of vasoactive drugs), or as abnormalities in tissue perfusion shown by state of consciousness, oliguria, lactate acidosis, or both (12). Refractory shock was defined as shock lasting >1 hour with no response to volume resuscitation or pharmacologic therapy (13). We considered hemodynamic instability to have occurred when hypotension (SBP <100), fitting or not fitting the shock criteria, took place at any time during the clinical course. The length of hospital stay and the mortality rate were also evaluated.

Results

The data of 25 patients with confirmed cases of HPS were analyzed (17 men, 8 women, mean age 33.4 years, range 15-63 years). The infection was most commonly acquired through farm or timber work (40%), and 76% of the patients were rural residents. The incubation period, estimated in 14 cases, was 9.8 ± 7.5 days (range 3-28 days). Symptom duration before admission was 5 ± 1.8 days (range 2-10 days); 12 (48%) of 25 patients had requested previous medical care on one to four occasions before admission; and in 20 (80%) of 25 case-patients, a diagnosis other than HPS was initially suggested.

The differential diagnoses before HPS was considered were community-acquired pneumonia or pneumonitis (including viral, interstitial, atypical, *P. carinii* pneumonia) (9 patients), sepsis (with/without shock or acute respiratory distress syndrome) (5 patients), fever syndrome (4 patients), influenza (3 patients), acute abdominal condition (1 patient), acute pyelonephritis (1 patient), acute tonsillitis (1 patient), bacterial meningitis (1 patient), typhoid fever (1 patient), acute diarrhea (1 patient), and myeloproliferative syndrome (1 patient). The main clinical signs and symptoms at admission were fever in 24 (96%) of 25 patients, myalgia in 24 (96%), asthenia in 19 (76%), headache in 15 (60%), abnormal breathing sounds on auscultation in 15 (60%), abdominal pain in 13 (56%), anorexia in 12 (48%), dry cough in 10 (40%), chills in 8 (32%), vomiting or nausea in 6 (24%), cyanosis in 5 (20%), diarrhea in 2 (8%), hemoptoic sputum in 2 (8%), and epistaxis, metrorrhagia, generalized maculopapular rash, consciousness alteration, lumbar pain, and odynophagia, each in 1 patient. Pseudoinfluenza syndrome was found in 17 (68%) patients. Bleeding was documented in 16 (64%) of 25 patients, and 3 (12%) patients required medical care for this reason. Tables 1 and 2 show the type and severity of bleeding manifestations and their relationship to platelet count.

The results of laboratory tests at admission can be seen in Table 3; thrombocytopenia was indicated by a platelet count of <100,000 in 23 (92%) case-patients. The mean hematocrit values were 49.8 ± 6.4, and three patients showed a value <45%. Twelve (48%) patients showed alterations in renal function, six (24%) exhibited a creatinine level >2.0, and one patient required hemodialysis. In 18 (72%) patients, liver function tests showed alterations, but only one patient had liver failure.

Hypotension at admission was observed in 12 (48%) of 25 patients, and 16 (60%) had hemodynamic instability (reaching 93% in the most severe group). Eight patients experienced refractory shock. In one patient, a Swan-Ganz catheter was used in a late stage of the infection, and the hemodynamic profile was consistent with septic shock, with low systemic venous resistence and high cardiac output. These conditions were also consistent with a case of nosocomial gram-negative sepsis; this was later demonstrated by blood culture. This case was the only one in

Table 1. Bleeding in patients with hantavirus pulmonary syndrome

Area of bleeding	n = 16 (%)
Pulmonary	8 (32)
Hematuria	6 (24)
Puncture sites	5 (20)
Skin (petechiae)	3 (12)
Hematemesis	2 (8)
Gingivorrhagia	2 (8)
Metrorrhagia	2 (8)
Subarachnoid hemorrhage	1 (4)
Peridural (lumbar puncture)	1 (4)
Epistaxis	1 (4)
Subungual	1 (4)
Visceral (necropsy)	1 (4)

which a bacterial overinfection was suspected and confirmed.

Radiographic changes exhibited at admission consisted of bilateral interstitial infiltrates in 14 patients (56%), alveolar infiltrates in 4 (16%), and mixed infiltrates in 5 (20%) patients. In two (8%) patients, the disease progressed without pulmonary infiltrates. The pulmonary infiltrates, when present, were bilateral and extended, involving 4 or 5 lobules in all cases. In seven (28%) patients, radiographic infiltrates were found to progress after 48 hours. Two patients showed pleural effusion. Samples from two patients with no pulmonary involvement underwent serologic tests because the patients lived in a rural region where previous cases had been found and because they had a clinical history of fever, myalgia, and malaise. One patient had thrombocytopenia (platelet count 53,000), and both had raised hematocrit values (50% and 46 %).

The mean PAFI at admission was 160 $\pm$ 121 (range 40-508). Eight (32%) patients received oxygen either nasally or by mask, and in three (12%), supplemental oxygen was not required. Fifteen (60%) patients were admitted to the ICU, and 14 (56%) received mechanical ventilation early, 9 (64%) of 14 during the first 24 hours after admission, 4 before 48 hours, and 1 patient on day 3. The mean period of mechanical ventilation was 4 days (range 1-13 days). Ten (40%) patients died, seven before completing 1 day in the hospital, and one patient died later of septicemia caused by gram-negative bacteria. All patients who died showed diffuse and rapidly progressive interstitial pulmonary infiltrates, compatible with massive pulmonary edema, severe respiratory failure and refractory shock. Finally, electromechanical dissociation and asystolia were noted.

For the 15 patients admitted to the ICU, the mean APACHE II score was 18.3$\pm$8.7. No patient with APACHE II <12 died, and the mortality rate for the patients with APACHE II >12 was 77% (10/13) ($p = 0.000$). In the group of 10 case-patients who received methylprednisolone, 2 (20%) died, which contrasts with 8 (53%) deaths of 15 who did not receive this drug ($p = 0.21$).

We administered prednisolone to 10 patients; the decision to use it was made on admission for half of the case-patients and 2 to 4 days later for the remaining case-patients. One patient had hyperglycemia associated with the use of methylprednisolone. Nineteen (76 %) patients received antibiotic drugs, which were usually discontinued

Table 2. Hemorrhage in patients with hantavirus pulmonary syndrome

Case no.	Bleeding sites	Platelet count 10^3/UL	Bleeding severity[a]	Prothrombin (%)	Outcome
1	Hemoptysis, hematemesis, hematuria	15.6	Moderate	NA[b]	Survived
3	Hematuria, gingivorrhagia	74.0	Mild	100	Survived
4	Hematuria, subungueal, hemoptysis	33.0	Moderate	NA	Died
5	Puncture sites, skin, hemoptysis	19.0	Mild	74	Survived
6	Hematuria	7.1	Moderate	NA	Survived
7	Skin, hematuria, hemoptysis, puncture sites, gingivorrhagia	28.0	Severe	100	Died
9	Skin, hematemesis, hemoptysis, hematuria, subarachnoid	25.0	Severe	13	Died
10	Metrorrhagia	73.0	Severe	NA	Died
11	Hemoptysis	23.0	Moderate	NA	Died
12	Hemoptysis	46.0	Mild	100	Survived
13	Puncture sites	45.0	Mild	100	Survived
14	Puncture sites	11.2	Mild	100	Survived
15	Hemoptysis, epistaxis	20.0	Mild	100	Survived
16	Puncture sites, dura mater	52.0	Severe	100	Survived
20	Metrorrhagia	31.0	Severe	57	Died
21	Viscera	154.0	Mild	NA	Died

[a]Mild, <200 mL (self limited); moderate, 200–500 mL (no transfusion needed); severe $\geq$500 mL (transfusion necessary).
[b]NA, not available.

Table 3. Laboratory results at admission of 25 patients with hantavirus pulmonary syndrome

	N	Media ± SD	Minimum	Maximum
Blood pH	24	7.39 ± 0.09	7.09	7.51
PaO_2 (mm Hg)	24	65.04 ± 24.7	32	131
$PaCO_2$ (mm Hg)	24	27.12 ± 12.1	14	74
Hematocrit (%)	25	49.84 ± 6.4	39	69
Platelets (1,000//µL	24	53,850 ± 40,996	9,900	174,000
Leukocytes (1,000//µL)	25	16,612 ± 14,781	2,800	59,400
Band forms (%)	14	10.8 ± 7.0	2	23
Lymphoblasts (%)	11	22.3 ± 13.9	6	48
HSR (mm/h)	5	5.8 ± 6.9	0	16
Sodium (mEq/L)	23	130.8 ± 5.6	120	143
Potassium (mEq/L)	22	4.0 ± 0.7	3	5.6
Creatinine (mg/dL)	22	1.38 ± 0.5	0.7	3.1
Uremia (mg/dL)	6	76.7 ± 54.2	16	140
Prothrombin (%)	13	80.2 ± 26.9	13	100
Bilirubin (mg/dL)	13	0.69 ± 0.35	0.31	1.44
Alkaline pH (U/L)	9	141.6 ± 56.2	78	233
GOT (U/L)	12	211.8 ± 162.2	24	478
GPT (U/L)	3	43.6 ± 21.8	20	63

[a]SD, standard deviation; HSR, human sedimentation rate; GOT, glutamic-oxaloacetic transminase; GPT, glutamic-pyruvic transminase.

after confirmation of the viral cause. The variables with statistically significant differences between survivors versus nonsurvivors are shown in Table 4. Other variables associated with death were cyanosis (p = 0.005), renal function alteration (p = 0.001), shock (p = 0.000), ICU admission (p = 0.001), and mechanical ventilation (p = 0.001).

Statistically significant differences were not observed for the following variables: hematocrit, platelet count, number of symptomatic days before admission, PaO_2, leukocyte count, plasma sodium and potassium, bilirubin, glutamic-oxaloacetic transaminase (GOT) and glutamic-pyruvic transaminase (GPT), type and number of bleeding episodes, alteration in consciousness, growth of 50% in radiographic images during the first 48 hours, and the use of methylprednisolone.

We identified three groups of case-patients. The first included two case-patients with only prodromic symptoms without pulmonary involvement. The second group (n = 9) consisted of patients who had a self-limited form of the disease, usually with different degrees of interstitial pulmonary infiltrates, who did not require intubation and received oxygen through noninvasive methods (including one case-patient who needed no oxygen), were hemodynamically stable, and had a low APACHE II (<12). The third group (n = 14) had severe forms of the disease with a high mortality rate (APACHE II >12), required intubation and mechanical ventilation, with hemodynamic instability in 13 (93%) and refractory shock in 8 (57%). Pulmonary infiltrates were usually alveolar. The mean hospital stay was 13.6 days ± 24.7, ranging from hours for those patients who died quickly to 120 days in one patient with a peridural hematoma and severe secondary paraparesia as a consequence of a lumbar puncture.

Discussion

Our study confirms the existence of different clinical forms of hantavirus disease (7), including some without pulmonary involvement. A higher mortality rate was clearly associated with the most severe form (APACHE >12) of the disease, and death frequently occurred within the first

Table 4. Variables with statically significant differences in survivors versus no survivors with hantavirus pulmonary syndrome[a]

	Survivors		No survivors		
	Mean ± SD	CI 95%	Mean ± SD	CI 95%	p
APACHE	7.1 ± 1.2	4.4 to 9.8	21 ± 8.3	8.3 to 15.0	0.0000
PAFI	211 ± 127	134 to 288	95 ± 78	39.5 to 151.3	0.0097
Blood pH	7.43 ± 0.04	7.40 to 7.45	7.32 ± 0.12	7.23 to 7.41	0.0043
Creatinine (mg/dL)	1.08 ± 0.23	0.94 to 1.23	1.8 ± 0.59	1.35 to 2.27	0.0003
Prothrombin (%)	90.9 ± 17.8	75.9 to 105.7	63.2 ± 32.0	23.4 to 102.9	0.0340
SBP (mm Hg)	103.7 ± 20.0	92.6 to 114.8	76.6 ± 47.3	42.7 to 110.4	0.0296
Respiratory rate	25.2 ± 10.2	19.5 to 30.8	38.4 ± 7.8	32.4 to 44.4	0.0015
Pulse	104.6 ± 16.5	95.4 to 113.8	117.7 ± 21.9	102 to 133.4	0.0512

[a]SD, standard deviation; CI, confidence interval; PAFI, arterial oxygen tension/inspiratory oxygen fraction; SBP, standard blood pressure.

24 hours of hospital admission (70%). The main variables associated with death were APACHE II score, low PAFI, cyanosis, polypnea and tachycardia at admission, alterations in renal function, shock, and mechanical ventilation.

The incubation period was estimated for 14 cases and ranged from 3 to 28 days ($x = 9.8 \pm 7.5$), which is consistent with other reports (7,14,15). The symptoms at admission were similar to those described in case-patients in the United States (16,17) and Chile (10,14). Fundamentally, the initial clinical presentation is similar to influenza without rhinorrhea, high fever, myalgia, headache, or asthenia, and often accompanied by abdominal symptoms such as pain, nausea, vomiting, and diarrhea. After a prodromal period of 2 to 7 days, respiratory symptoms appear with dyspnea, respiratory failure, and hemodynamic instability. Chest x-rays show bilateral interstitial infiltrates of different degrees of rapid progression.

Nevertheless, the infection can be manifested in other ways, and many cases do not go beyond the prodromal stage or elicit any symptoms. In January 1997, the first hantavirus serologic study was carried out in Chile; of 64 serum samples collected in a rural location, 7 were positive for specific Andes virus nucleoprotein IgG. These 64 samples represented almost the whole population living in the area of the first Chilean case-patient's residence. Thus nearly 10% of this rural population had had contact with the virus, although none of the persons who provided a sample remembered a severe illness (7).

From 1995 to 2000, a total of 10 case-patients with mild forms of hantavirus disease were detected in Chile. The disease progressed in these case-patients without major pulmonary involvement, but the available information does not allow a close analysis of the clinical features of these cases, since most findings were from epidemiologic and serologic investigation (18). We found two case-patients who were admitted to the hospital because of a clinical course of fever, myalgia, and malaise, whose disease progressed with no pulmonary involvement as indicated by serial x-rays during their hospital stay. The diagnosis was suggested after considering the epidemiologic data (they lived in a rural area from which other cases had come) and suggestive laboratory test results: thrombocytopenia indicated by a platelet count of 53,000 in one and raised hematocrit value in both (50% and 46%). In these patients, the symptoms could have been confounded with a viral disease such as influenza and thereby been underdiagnosed because of the nonspecific character of the symptoms. In 80% of our case-patients, the initial diagnosis was incorrect, and 48% had received medical care on one to four occasions before hospital admission. By asking epidemiologically oriented questions in these endemic countries and regions, physicians may be able to make an earlier diagnosis of HPS.

In the series of patients described by Duchin et al. (16) in the United States, the early symptoms were similar to those described in the Asian and European forms of hantavirus disease known as hemorrhagic fever with renal syndrome. Nevertheless, no patient showed hemorrhages, renal involvement was minimal, and neither oliguria nor renal failure was observed in any case. The 1995 outbreak in Argentina was described as similar but details were not given (19). By contrast, the cases described in Chile are different, given the hemorrhagic manifestations observed. In Coyhaique (Chile), Tapia (10) saw petechiae in 38% (9/24), epistaxis in three pediatric patients and microhematuria in 16 patients (66.6%). In Region IX of Chile, Castillo (14,15) described a higher frequency of bleeding events (71% and 81%), including hematemesis, hemoptisis, epistaxis, and puncture site bleeding, similar to what we observed in 64% of the patients (Tables 1 and 2). In three patients of our series, a bleeding event was the reason for seeking healthcare. Thus, hemorrhagic manifestations appear to occur frequently in cases of hantavirus in Chile.

Concerning renal function, Tapia (10) observed raised creatinine of $\geq$1.5 in 7 of 24 cases, which did not correlate with the severity of clinical course. In this study, acute renal failure was considered a terminal phenomenon. Castillo reported two case-patients with acute renal failure; one required hemodialysis, and creatinine values were elevated (1.2-3.3 mg/dL) in 54% of the patients (14,15). In our series, 48% of the patients fulfilled the American Thoracic Society criteria for altered renal function (9), and the difference between the creatinine values of nonsurvivors and survivors measured at admission ($p = 0.0003$) was statistically significant. In 24%, creatinine values were >2.0, and one patient required hemodialysis. We believe that the use of common criteria to define renal failure in larger series can help estimate the changes in renal function, which seem to be more important than previously described and have a prognostic value. With regard to laboratory tests, raised hematocrit values and low platelet counts are exhibited by almost all patients at admission, and thus are important diagnostic elements, although they have no prognostic value.

Corticosteroids have the potential of modulating intrapulmonary inflammatory response by modifying the proinflammatory cytokine levels such as interleukin-1-β and tumor necrosis factor-∝ (TNF-∝), and have been used in the management of severe pulmonary disorders, with both an infective as well as a noninfective etiology such as miliary tuberculosis, *Pneumocystis carinii* pneumonia, vasculitides, and gastric acid aspiration (20).

In our study, 2 of 10 patients who received methylprednisolone (20%) died versus. 8 of 15 (53%) in the group who did not receive this drug, although this difference was

not statistically significant (p = 0.21). In larger series, a significant effect could perhaps be demonstrated. When the first cases were being diagnosed, however, we did not consider the use of corticosteroids; no protocol on how to use them existed, and most severely ill patients died very quickly and thus did not receive corticosteroids; their usage probably would not have changed the fatal course of the disease in this group, however.

The mortality rate in our series was directly related to the type of clinical presentation. In the severe form, with APACHE II >12, the mortality rate reached 77%, in contrast to those with a score <12, among whom no deaths were observed. From 1993 to July 2000, a total of 123 confirmed HPS cases were reported in Chile, 61 (49.6%) of which were fatal. This rate has decreased during the last 2 years, partly because of the improvement in diagnostic capacities and greater knowledge of the disease, which allows quicker identification and more effective treatment (18), but we think that this reduction also may be due to a dilution effect because more mild cases are found.

In our series, we distinguish three groups of patients. The first (n = 2), probably the least known, corresponds to patients with only prodromal symptoms, especially a pseudoinfluenza course with no pulmonary involvement, who are often not admitted to a hospital and are not recognized to have HPS. Correct diagnosis of these cases improves if one makes a good epidemiologic questionnaire. Groups 2 and 3 allow the patients to be classified according to clinical and radiologic criteria, severity, treatment, and prognosis. Use of uniform criteria is required to classify the patients infected by hantavirus with different clinical presentations, to thereby comparatively evaluate the mortality rate and the effectiveness of therapeutic measures.

Dr. Raúl Riquelme is a specialist in internal medicine and respiratory diseases and chief of the Department of Internal Medicine, Puerto Montt Regional Hospital, Puerto Montt, Chile. His main area of research has concerned community-acquired pneumonia.

References

1. Centers for Disease Control and Prevention. Outbreak of acute illness—Southwestern United States, 1993. MMWR Morbid Mortal Wkly Rep 1993;42:421–4.
2. Nichol ST, Spiropoulou CF, Morzunov S, Rollin PE, Ksiazek TG, Feldmann H et al. Genetic identification of a Hantavirus associated with an outbreak of acute respiratory illness. Science 1993;262:914–7.
3. Khan AS, Khabbaz RF, Armstrong LR, Holman RC, Bauer SP, Graber J et al. Hantavirus pulmonary syndrome: the first 100 US cases. J Infect Dis 1996;173:1297–303.
4. Lopez N, Padula P, Rossi C, et al. Genetic identification of a new hantavirus causing severe pulmonary syndrome in Argentina. Virology 1996; 220: 223–6
5. Tapia M. Sindrome pulmonar por Hantavirus (caso clínico). Rev Chil Enf Respir 1997; 13: 103-10
6. Levis S, Morzunov SP, Rowe JE, Enria D, Pini N, Calderon G, et al. Genetic diversity and epidemiology of hantavirus pulmonary syndrome. J Infect Dis 1998;177:529–38.
7 . Baró M, Vergara J, Navarrete M. Hantavirus en Chile: revisión y análisis de casos desde 1975. Rev Méd Chile 1999;127:1513–23.
8. Haemorrhagic fever with renal syndrome: memorandum from a WHO meeting. Bull World Health Organ 1993;61:269–75.
9. American Thoracic Society. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. Am Rev Respir Dis 1993:1418–26.
10. Tapia M, Mansilla C, Vera J. Síndrome pulmonar por hantavirus: Experiencia clínica en diagnóstico y tratamiento. Hospital Coyhaique-Chile. Rev Chil Infect 2000;17:258–69.
11. Knaus WA, Draper EA, Wagner DP, Draper EA, Wagner DP, Zimmerman JE, et al: APACHE II: A severity of disease classification system. Crit Care Med 1985;13:818–28.
12. Fang GD, Fine M, Orloff J, Arisumi D, Yu VL, Kapoor W, et al. New emerging etiologies for community-acquired pneumonia with implications for therapy. Medicine 1990;69:307–16.
13. Shoemaker W, Grenvik A, Ayres S, Holbrook P. Textbook of critical care. Philadelphia: W.B. Saunders; 1996. p. 44.
14. Castillo C, Naranjo J, Ossa G. Síndrome cardiopulmonar por hantavirus en 21 adultos en la IX Región de Chile. Rev Chil Infect 2000;17:241–47.
15. Castillo C, Naranjo J, Sepulveda A, Ossa G, Levi H, et al. Hantavirus pulmonary syndrome due to Andes virus in Temuco, Chile. Chest 2001;120:548–54.
16. Duchin J, Koster F, Peters CJ, Simpson GL, Tempest B, Zaki SR, et al. Hantavirus pulmonary syndrome: a clinical description of 17 patients with a newly recognized disease. N Engl J Med 1994;330:945–55.
17. Hallin G, Simpson S, Crowell R, James DS, Koster FT, Mertz GJ, et al. Cardiopulmonary manifestations of hantavirus pulmonary syndrome. Crit Care Med 1996;24:252–8.
18. Sotomayor V, Aguilera S. Epidemiología de la infección humana por hantavirus en Chile. Rev Chil Infect 2000;17:220–32.
19. Wells R, Sosa S, Yadon Z, Enria D, Padula P, Pini N, et al., and the Hantavirus Pulmonary Syndrome Study Group for Patagonia. An unusual hantavirus outbreak in southern Argentina: person-to-person transmission? Emerg Infect Dis 1997;3:171–4.
20. Mer M, Richards G. Corticosteroids in life-threatening varicella pneumonia. Chest 1998;114:426–31.

Address for correspondence: Raúl Riquelme, Bellavista 123, of 402, Puerto Montt, Chile; fax: 56 65 289409; email: raul@telsur.cl