Published in final edited form as:
Lancet Infect Dis. 2010 August ; 10(8): 521–526. doi:10.1016/S1473-3099(10)70133-X.

Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: a multicentre cohort study

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Summary

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Contributors DK, MGM, MG, and AH conceived and designed the study. DK and AH analysed and interpreted the data. All authors were involved in the acquisition of data and critical revision of the paper.

Funding None.

The remaining authors declare that they have no conflicts of interest.

Background—There are few data on the epidemiology and outcomes of influenza infection in recipients of solid-organ transplants. We aimed to establish the outcomes of pandemic influenza A H1N1 and factors leading to severe disease in a cohort of patients who had received transplants.

Methods—We did a multicentre cohort study of adults and children who had received organ transplants with microbiological confirmation of influenza A infection from April to December, 2009. Centres were identified through the American Society of Transplantation Influenza Collaborative Study Group. Demographics, clinical presentation, treatment, and outcomes were assessed. Severity of disease was measured by admission to hospital and intensive care units (ICUs). The data were analysed with descriptive statistics. Proportions were compared by use of χ^2 tests. We used univariate analysis to identify factors leading to pneumonia, admission to hospital, and admission to an ICU. Multivariate analysis was done by use of a stepwise logistic regression model. We analysed deaths with Kaplan-Meier survival analysis.

Findings—We assessed 237 cases of medically attended influenza A H1N1 reported from 26 transplant centres during the study period. Transplant types included kidney, liver, heart, lung, and others. Both adults (154 patients; median age 47 years) and children (83; 9 years) were assessed. Median time from transplant was 3.6 years. 167 (71%) of 237 patients were admitted to hospital. Data on complications were available for 230 patients; 73 (32%) had pneumonia, 37 (16%) were admitted to ICUs, and ten (4%) died. Antiviral treatment was used in 223 (94%) patients (primarily oseltamivir monotherapy). Seven (8%) patients given antiviral drugs within 48 h of symptom onset were admitted to an ICU compared with 28 (22.4%) given antivirals later (p=0.007). Children who received transplants were less likely to present with pneumonia than adults, but rates of admission to hospital and ICU were similar.

Interpretation—Influenza A H1N1 caused substantial morbidity in recipients of solid-organ transplants during the 2009–10 pandemic. Starting antiviral therapy early is associated with clinical benefit as measured by need for ICU admission and mechanical ventilation.

Introduction

A new strain of influenza A H1N1 was first recognised in early 2009 and resulted in a worldwide pandemic.[1] Severe disease has been noted in children, pregnant women, and people with comorbid disorders including chronic lung or heart disease and diabetes.[2,3] Pandemic H1N1 has been characterised as a reassortant virus with genes from swine, avian, and human influenza viruses.[4]

Recipients of solid-organ transplants are thought to be at greater risk for complications from seasonal influenza than are the general population. So annual trivalent inactivated vaccine is recommended for patients after transplantation by the guidelines of the American Society of Transplantation.[5] Influenza is estimated to cause lower respiratory tract disease in up to 17% of transplant recipients.[6] Additionally, respiratory viruses have been associated with acute rejection and the development of bronchiolitis obliterans syndrome in recipients of lung transplants.[7] Compared with the immunocompetent population, patients who had received transplants might have a greater viral burden and shed virus for longer.[8]

Pandemic H1N1, as with influenza in general, may be more likely to cause severe disease in patients who have received organ transplants than in the general population. However, large, multicentre epidemiological studies assessing influenza, including pandemic H1N1, have not been done in transplant recipients. Neuraminidase inhibitors, such as oseltamivir, remain the mainstay of therapy. High doses and long duration of antiviral treatment have been suggested for patients who have received transplants and are immunocompromised.9 Data from immunocompetent people suggest that antiviral drugs reduce the duration of symptoms when started within 48 h of symptom onset.[10] However, several major transplant societies

(American Society of Transplantation, Canadian Society of Transplantation, and The Transplantation Society) recommended that recipients of organ transplants with pandemic H1N1 should be started on treatment irrespective of symptom duration.[9]

Although the initial H1N1 pandemic has abated, another wave of infection might happen during the next influenza season. For this reason, pandemic influenza A H1N1 was recommended by WHO for inclusion in the 2010 trivalent influenza vaccine. However, the response to this vaccine might be suboptimum in transplant recipients, a population that might remain uniquely susceptible to further outbreaks of this disease. We did a multicentre epidemiological study of pandemic influenza A H1N1 among recipients of solid-organ transplants to further characterise the illness and establish factors leading to admission to hospital and intensive care unit and other complications.

Methods

Identification of patients

Participating transplant centres were identified through the American Society of Transplantation Infectious Diseases Community of Practice. This is a multicentre collaborative network of transplant infectious diseases and organ transplant experts. Patients were included in the study if they were recipients of solid-organ transplants actively receiving at least one immunosuppressive drug and had a diagnosis of microbiologically confirmed, community acquired, influenza A infection between April and December, 2009. During the peak of the pandemic (October–December, 2009), microbiological confirmation of influenza A was required but specific confirmation of pandemic H1N1 was not. Both adult and child (age <18 years) inpatient and outpatient groups were included. Patients were excluded if influenza was nosocomially acquired, or if the patient developed influenza while receiving oseltamivir or zanamivir prophylaxis, to allow for analysis of risk factors for outcomes such as admission to hospital and intensive care units (ICUs). A new radiographic abnormality was required for diagnosis of pneumonia (on chest radiograph or CT scan).

Data collection and analysis

A standard data collection form was used for each site. Site investigators were primarily transplant infectious diseases physicians closely involved with the organ transplant programme at their centre. They were asked to submit all cases that had been noted in their transplant population irrespective of severity, need for hospital admission, and intensive care stay or outcome. Data were securely transmitted and stored at a central site (University of Alberta, AB, Canada). Demographic details, type of transplant, immunosuppression, symptoms, diagnosis, and treatment of influenza were collected by chart review. Data were analysed with descriptive statistics. Proportions were compared by use of χ^2 test. We used univariate analysis to identify factors leading to pneumonia, admission to hospital, and admission to an intensive care unit. Multivariate analysis was done by use of a stepwise logistic regression model. We analysed deaths with Kaplan-Meier survival analysis. All data were analysed by use of SPSS Statistics 18 (IBM SPSS, Chicago, IL). Institutional review board approval was obtained at each participating site.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We assessed 242 adults and children who received solidorgan transplants in 26 transplant centres (21 from the USA, four from Canada, and one from the Netherlands). Five patients did not meet study entry criteria and were excluded from analysis (four had nosocomially acquired infection and one had received antiviral prophylaxis), leaving 237 patients in the study. The figure shows the date of symptom onset, with a peak during the first week of November, 2009. The median time of symptom onset after transplant was 3.6 years (range 14 days–21.9 years). Table 1 shows demographic data including type of transplant and immunosuppression. The most common transplant types were kidney and liver. Immunosuppressive treatment varied but included a calcineurin inhibitor (tacrolimus or ciclosporin) in most patients.

The most common presenting symptoms were cough in 199 (91%) of 218 patients, then fever in 193 (85%) of 226, myalgias in 91 (51%) of 178, rhinorrhoea in 82 (43%) of 193, sore throat in 80 (43%) of 185, and headache in 59 (32%) of 186. Children were not always able to report certain symptoms. In a comparison of presenting symptoms in adult versus paediatric transplant recipients, children were substantially more likely to present with fever, rhinorrhoea, sore throat, and headache than were adult patients (table 2). 62 (31%) of 201 patients had ill household contacts.

Imaging (chest radiograph or CT) data were available for 230 (97%) of 237 patients. Imaging was normal or unchanged in 157 (68%) patients. The remaining 73 (32%) patients had imaging findings consistent with pneumonia. The types of imaging abnormalities varied but were predominantly reported as either air space consolidation or interstitial infiltrate. Bacterial pathogens were identified from sputum or bronchoalveolar lavage fluid in 13 (6%) of 237 patients and included five patients with *Staphylococcus aureus*, five with *Pseudomonas aeruginosa*, and three with other organisms. Two patients also had fungal infections. Respiratory virus co-infections were rare and included respiratory syncytial virus (two patients) and rhinovirus (two patients). Concomitant cytomegalovirus viraemia was detected in eight (3%) of 237 patients. Other complications included four cases of otitis media, two of sinusitis, and one of encephalitis. 116 (61%) of 190 patients had lymphopenia (lymphocyte count <1000 cells per μL) at diagnosis. Serum IgG concentration before onset of illness was available for 40 patients: 19 (48%) had hypogammaglobulinaemia (IgG <7 g/L). Before symptom onset, 55 (40%) of 139 patients had received the 2009–10 seasonal influenza vaccination and 20 (11%) of 177 patients had been immunised with pandemic H1N1 vaccine. Vaccination status in the remaining patients was unknown.

To be included in the study all patients were required to have confirmed influenza A. Influenza A was subtyped as pandemic H1N1 in 162 (68%) of 237 patients. The primary method of microbiological sampling was nasopharyngeal swab in 191 (89%) of 214 patients. Influenza PCR was the main method of diagnosis in 142 (70%) of 204 patients. Other methods of diagnosis used were culture in 25 of (12%) 204 patients, direct fluorescent antibody in 29 (14%), and rapid antigen in eight (4%).

223 (94%) of 237 patients received antiviral treatment—221 (99%) were given oseltamivir. One patient was given inhaled zanamivir alone and six were given zanamivir with oseltamivir. One patient received intravenous peramivir. The 14 patients who did not receive antiviral therapy had mild illness and symptoms resolved before diagnosis. The time from symptom onset to the start of antiviral treatment was within 48 h of symptom onset in 90 (42%) of 215 patients, between 48 h and 96 h in 63 (29%), and greater than 96 h in 62 (29%). 97 (76%) of 127 adult patients received oseltamivir at the equivalent of 75 mg twice daily adjusted for renal function. 25 (20%) adult patients received the equivalent of 150 mg

twice daily adjusted for renal function. 49 (96%) of 51 children received standard oseltamivir dosing according to weight. Median duration of treatment was 5 days (range 1–60). Adjunctive therapy included a reduction in immunosuppression in 52 (22%) of 232 patients. 20 (56%) of 36 patients admitted to ICU had immunosuppression reduced compared with 32 (16.3%) of 196 not admitted to ICU ($p<0.001$).

167 (70%) of 237 patients were admitted to hospital at a median of 2 days after symptom onset (range 1–17). The incidence of admission to the ICU was 16% (37 of 237) at a median of 5 days after symptom onset (range 1–37). Of these patients, 21 needed mechanical ventilation for a median duration of 12 days (range 2–42). Two adults and one child received extracorporeal membrane oxygenation. Table 3 shows a univariate analysis of factors associated with admission to the ICU. Early antiviral treatment was associated with a lower likelihood of ICU admission (ICU admission in seven [8%] of 90 patients treated within 48 h *vs* 28 [22%] of 125 patients treated after 48 h; $p=0.007$). Early treatment with antiviral drugs was also associated with a lower incidence of admission to hospital ($p=0.049$; data not shown) and need for mechanical ventilation ($p=0.019$; data not shown).

The multivariate analysis model for ICU admission consisted of early versus late antiviral treatment, use of antilymphocyte globulin, diabetes, and children versus adults. This model included 214 of 237 patients because 14 patients were not treated with antiviral drugs and nine patients had missing data. In this model, delayed antiviral treatment was independently associated with increased risk of admission to ICU (odds ratio [OR] 3.03, 95% CI 1.24–7.39, $p=0.015$). The presence of diabetes was also associated with an increased risk of ICU admission (OR 2.18, 95% CI 1.03–4.64, $p=0.043$).

Ten (4%) of 237 patients died at a median of 15 days after symptom onset (range 4–88). Eight (6%) of 125 patients in the group that received delayed antiviral treatment died compared with one (1%) of 90 in the group that received antiviral drugs early ($p=0.059$ by Kaplan-Meier analysis and log-rank statistic). The single death in this group was due to an unrelated procedural complication after the patient had recovered from influenza. Other factors associated with adverse outcome included diabetes mellitus (again associated with ICU admission and mechanical ventilation). Except for the recent use of antilymphocyte globulin, no other specific immunosuppressive drug or regimen was associated with poor outcomes.

The specific type of transplant did not seem to affect the outcomes. The 33 recipients of lung transplants, generally thought to be prone to more severe influenza, had rates of complications similar to those in receipt of other transplant types. In patients for whom information was available, seasonal influenza vaccination for 2008–09 did not have any protective effect in terms of adverse outcome: ten (14%) of 72 vaccinated patients and four (13%) of 31 unvaccinated patients were admitted to ICUs ($p=1.000$).

60 (40%) of 149 adults had pneumonia compared with 13 (16.0%) of 81 children ($p<0.001$). No other risk factor for pneumonia was identified. 47 (61.0%) of 77 children and 43 (31.2%) of 138 adults ($p<0.001$) received early antiviral treatment. No deaths were reported among the children.

Discussion

Pandemic influenza A H1N1 resulted in a spectrum of illness ranging from mild and self-limiting to severe disease in recipients of solid-organ transplants. Morbidity and mortality in this cohort of patients were substantial (admission to hospital in 71%, admission to ICU in 16%, and death in 4%). Almost a third of patients had pneumonia (either bacterial or presumed viral). The most important finding was that starting antiviral treatment within 48 h

of symptom onset was associated with a decrease in admission to hospital and ICU, need for mechanical ventilation, and death. This finding was consistent across many related outcome measures and reinforces the importance of early treatment with antiviral drugs in this susceptible population.

Although the importance of influenza infection in organ transplantation, including diagnosis, prevention, and treatment recommendations, is well recognised in a number of guidelines, data on the clinical epidemiology of this infection are lacking. Previous studies of influenza infection in recipients of solid-organ transplants were either single-centre case series or assessed infection with multiple respiratory viruses.[6,7,11–14] Conflicting outcomes have been reported. Ljungman and colleagues13 reported 12 renal transplant patients with influenza A infection. Only one was characterised as having severe illness with viral pneumonitis. By contrast, Vilchez and colleagues[6] described 22 organ transplant patients with influenza A infection and eight with influenza B infection. Secondary bacterial pneumonia was noted in five (17%) of 30 patients (22 with influenza A and eight with influenza B) and concurrent allograft rejection was prominent in the subset of patients who had received a lung transplant. Allograft dysfunction (either acute or chronic) seems to be most commonly reported in recipients of lung transplants, with several studies showing an epidemiological link between respiratory virus infections and the development of bronchiolitis obliterans syndrome. Our study included 33 patients that received lung transplants. The incidence of complications including pneumonia, ICU admission, and death were not higher in the lung transplant population compared with the other transplant recipients. We did not look at allograft rejection after influenza infection because of difficulties in interpretation of rejection rates without a control population.

There are few data on the use of antiviral treatment in recipients of organ transplants. In a review of nine patients who received lung transplants and were treated with oseltamivir for influenza,14 antiviral treatment was well tolerated and overall outcomes were good. Data from patients receiving haemopoietic stem-cell transplants also suggest a benefit for neuraminidase inhibitors. In a study of influenza in patients that received haemopoietic stem-cell transplants, six (18%) of 34 untreated patients progressed from upper-tract to lower-tract infection compared with none of nine patients treated with oseltamivir.[8] In our study, several patients received higher doses of oseltamivir (150 mg twice a day) or prolonged treatment with antiviral drugs beyond the standard 5-day course. This finding is consistent with recent transplant guidelines suggesting that critically ill patients receive twice the standard dose of oseltamivir. We did not note a difference in outcomes in those who received higher doses. However, on the basis of our study design, the relative efficacy of different doses or durations of treatment cannot be established. Very few patients received zanamivir, although it is a suggested alternative. There are fewer safety and efficacy data for zanamivir in the organ-transplant population and the lack of systemic exposure of the inhaled formulation of the drug might be a disadvantage. No patient was given intravenous zanamivir, and only one received intravenous peramivir, although both drugs were available through special access during the peak of the pandemic. The guidelines of the American Society of Transplantation suggest starting antiviral treatment irrespective of symptom duration. However, some patients in our cohort were not treated with antiviral drugs. In general, these were patients in whom symptoms resolved before diagnosis was confirmed.

Comorbid illness and pregnancy have been recognised as risk factors for severe H1N1 disease in the recent pandemic. In one study,3 pregnancy was associated with a 3.4 relative risk of admission to the ICU. In a US study of 272 patients admitted to hospital,15 underlying medical disorders were common including asthma, diabetes, and heart, lung, and neurological disease. Data from that study suggested the use of antiviral drugs was

beneficial in patients admitted to hospital especially when given early.[15] The most common comorbidity in our cohort was diabetes (31.9%), which was associated with an increase in ICU admission and death. Diabetes is common among patients that have received transplants, either as a cause of end-stage organ disease necessitating transplant or as a complication of transplant immunosuppressive therapy (steroids, calcineurin inhibitors). Lymphopenia is also common in transplant patients, usually as a result of immunosuppressive drugs or antimicrobial prophylaxis (valganciclovir, co-trimoxazole). Viral infection might have led to further lymphopenia. A large proportion of our population was lymphopenic at the onset of illness.

Our study had several limitations. Although all cases were confirmed influenza A, not all were subtyped as pandemic H1N1 especially during the peak phase of the pandemic. Some cases might have been seasonal influenza A; however, surveillance data show that more than 99% of circulating influenza in the USA during the peak of the epidemic was pandemic H1N1.[16] For example, data from the US Centers for Disease Control and Prevention show that only five (0.02%) of 20 409 specimens that tested positive for influenza A from Oct 14 to Nov 17, 2009, were subtyped as seasonal H3 or H1.[16] Although the number of admissions to hospital and ICU, and death was high in our study, this might reflect reporting bias since patients that are likely to come to medical attention are those with more severe illness. Patients with milder illness might not have contacted their transplant centre or could have been cared for by their local physicians. Similarly, case ascertainment and data capture was probably more difficult for outpatients. The measures we took to collect data from outpatients included frequent reminders to participating sites that we were enrolling both inpatients and outpatients. Additionally, we recommended methods specifically aimed at collecting data from outpatients; these included liaison with outpatient transplant coordinators and the outpatient laboratory.

Although our study was primarily of North America, we believe the criteria for ICU admission are similar to those used elsewhere. For example, only very ill people are admitted to ICU, such as those in need of mechanical ventilation or inotropic support. This is particularly true at tertiary-care centres such as those in our study. Of the 37 patients admitted to ICU in this study, 21 needed mechanical ventilation. Additionally, we believe the results can be generalised to organ transplant populations outside North America because immunosuppression strategies are similar, with calcineurin-inhibitor-based immunosuppression being the most common along with prednisone. Transplant programmes in Asia also use calcineurin-based immunosuppression. Mycophenolate mofetil is commonly used as adjunctive immunosuppression in both North America and Europe. Our analyses considered children and adults as one cohort of patients that had received solid-organ transplants. This was done because both groups were similar with respect to several factors including recent use of antilymphocyte globulin, maintenance immunosuppressive regimens (calcineurin-inhibitor-based regimen most common), and time after transplant.

In conclusion, this study shows the overall potential for severe illness from pandemic H1N1 in transplant patients. Starting treatment with antiviral drugs early is important for reduction of morbidity and mortality in this highly susceptible population. For example, during periods of transmission, transplant patients presenting with signs or symptoms that are compatible with influenza should probably start empirical treatment with antiviral drugs before it is confirmed. Additionally, almost a third of the patients in our cohort reported contact with an ill household member before their own illness. In this setting, postexposure chemoprophylaxis might be an option. Alternatively, a prescription could be given and treatment started immediately with the onset of symptoms.[9] Vaccination of both transplant patients and their household contacts is probably an important preventive measure since vaccine responses might be suboptimum after transplantation.

Acknowledgments

We thank the American Society of Transplantation. We are grateful to our colleagues who made this work possible: Emily Blumberg (University of Pennsylvania, Philadelphia, PA, USA); Bart van Hoek (Leiden University Medical Centre, Leiden, Netherlands); Steve Miller and Charles Chiu (University of California, San Francisco, San Francisco, CA, USA); Alexandra Valsamakis (Johns Hopkins University, Baltimore, MD, USA); Sherif Mossad and Maria Budev (Cleveland Clinic Foundation, Cleveland, OH, USA); Dat Tran (Hospital for Sick Children, Toronto, ON, Canada); Leticia Ely, Bernadette Dodd, and Kathy Jackson (University of Alberta, Edmonton, AB, Canada); Marti Sears (Emory University, Atlanta, GA, USA); Ella Ariza-Heredia, Lilian Abbo, and Gabriel Blaschke (Miller School of Medicine, University of Miami, Miami, FL, USA); Angela Burns and Debbie Harmidy (McGill University, Montreal, QC, Canada); and Mary Ellen Carey and Traci McGaha (University of Pittsburgh Medical Center, Pittsburgh, PA, USA). This work was presented in part as a plenary oral at the American Transplant Congress; San Diego, CA, USA; May 1–5, 2010.

Conflicts of interest DK has received research grants from Roche and Adamas. MIM, AH, UDA, and FPS have each received research grants from Roche. SS has received a research grant from BioCryst. MG has been a consultant for Bristol-Myers Squibb.

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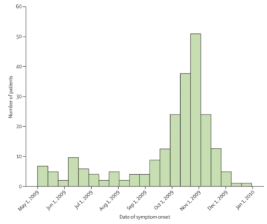

Figure.
Date of symptom onset during pandemic

Table 1

Demographics of recipients of solid-organ transplants with influenza A

	Findings (n=237)*
Median (range) age	
All patients	32 years (range 1–95)
Children	9 years (range 1–17)
Adults	47 years (range 18–95)
Sex	129 men and boys
	108 women and girls
Time from transplant	Mean 5·0 years (SD 4·9)
	Median 3·6 years (range 14 days–21·9 years)
Type of transplant	
Kidney	87 (37%)
Liver	47 (20%)
Lung	33 (14%)
Heart	45 (19%)
Intestinal	5 (2%)
Other combinations	20 (8%)
Immunosuppression	
Prednisone	140 (59%)
Mycophenolate mofetil	134 (57%)
Calcineurin inhibitor	202 (85%)
Sirolimus	44 (19%)
Azathioprine	17 (7%)
Biopsy proven rejection in preceding 3 months	23/234 (10%)
Antilymphocyte globulin in preceding 6 months	18/237 (8%)
Interleukin-2 receptor antagonists in preceding 6 months	11 (5%)
Monoclonal antibody (rituximab or alemtuzumab) in preceding 6 months	10 (4%)
Comorbidity	
Diabetes	75/236 (32%)
Obesity (body mass index >40)	21/233 (9%)
Chronic renal failure	34 (14%)
Chronic lung disease	14/219 (6%)
Smoking	2/229 (1%)
Seasonal influenza vaccination in 2008–09	72/103 (70%)

* Data not available for all patients; unless otherwise stated denominator is 237.

Table 2

Clinical presentation and complications of influenza A in adult and paediatric recipients of solid-organ transplants

	Adults	Children	p value*
Fever >38°C	115/144 (80%)	78/82 (95%)	0·003
Cough	132/145 (91%)	67/73 (92%)	1·000
Sore throat	50/134 (37%)	30/51 (59%)	0·013
Rhinorrhoea	40/134 (30%)	42/59 (71%)	<0·001
Headache	33/136 (24%)	26/50 (52%)	0·001
Myalgias	70/135 (52%)	21/43 (49%)	0·866
Gastrointestinal symptoms	66/154 (43%)	39/83 (47%)	0·636
Pneumonia on chest radiograph or CT scan	60/149 (40%)	13/81 (16%)	<0·001
Admission to hospital	112/154 (73%)	55/83 (66%)	0·373
Admission to the intensive care unit	27/154 (17·5%)	10/83 (12·0%)	0·357
Mechanical ventilation	18/153 (12%)	3/83 (4%)	0·063
Antiviral treatment within 48 h	43/138 (31%)	47/77 (61%)	<0·001
Antiviral treatment after 48 h	95/138 (69%)	30/77 (39%)	<0·001
Death	10/154 (7%)	0/83 (0%)	0·016

*Statistical differences are by χ^2 test.

Table 3

Univariate analysis of factors associated with admission to the intensive care unit (ICU)

	Not admitted to the ICU	Admitted to the ICU	p value*
Early antiviral therapy (within 48 h)	83/180 (46%)	7/35 (20%)	0·007
Delayed antiviral therapy (after 48 h)	97/180 (54%)	28/35 (80%)	0·007
Diabetes mellitus	56/199 (28%)	19/37 (52%)	0·01
Antilymphocyte globulin use in the previous 6 months	12/200 (6%)	6/37 (16%)	0·043
Abnormal chest imaging at presentation	46/193 (24%)	27/37 (73%)	<0·001
Lymphopenia at time of presentation	94/162 (58%)	22/28 (79%)	0·064

*Statistical differences are by χ^2 test.