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ORIGINAL ARTICLE

Characteristics of critically ill influenza patients in an intensive care unit in the Netherlands

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Abstract

Background: From December 2015 until March 2016, an influenza epidemic occurred in the Netherlands. There was a remarkably high admission rate of young patients without comorbidities to our ICU. The severity of their symptoms and the admission rate in our ICU seemed even higher than during the influenza pandemic in 2009.

Methods: A retrospective observational study was conducted for all patients with a proven influenza infection in the ICU.

Results: Twenty patients were included in the study, of whom 90% were infected with the influenza A(H1N1)pdm09 strain. Patients were dominantly male and younger than 65 years. A high incidence of multi-organ failure (80%) and a high mortality rate (30%) was noticed in this atypical patient group. In contrast to the 2009 influenza A (H1N1)pdm09 outbreak, ileus and lung bleeding were observed.

Conclusion: Facing a new influenza pandemic each year, this article illustrates the possible fulminant outcome of influenza, even in young and relatively healthy patients. It raises awareness for certain symptoms and underlines the need for adequate preventive measures.

Introduction

Seasonal influenza is an acute viral respiratory infection caused by different types of the influenza viruses, which have a strong antigenic drift.[1] Symptoms are usually mild, but the virus can cause severe illness or even death in high-risk patient groups, such as young children, the elderly, certain chronic or metabolic diseases and immunocompromised patients.[2]

From December 2015 until March 2016, an annual influenza epidemic was present in the Netherlands which lasted for 11 weeks.[3] In our intensive care unit (ICU) in The Hague, the Netherlands, we saw a remarkably high admission rate of young patients without comorbidities during this period. This atypical patient group developed severe symptoms as multi-organ failure secondary to influenza infection. The severity of these symptoms and the admission rate to our ICU seemed even higher than during the influenza pandemic in 2009. We also noticed symptoms that had not or not often been described in other articles on influenza.

One of the isolated influenza strains, the influenza A(H1N1)pdm09, was similar to the strain that caused the worldwide epidemic in the spring of 2009 and has genetically not changed. The other strains isolated in this epidemic were influenza A(H3N2) and influenza B/Victoria/2/87 and B/Yamagata/16/88.[4]

The abnormal behaviour pattern of the influenza infections and the atypical patient group made us wonder why this patient group was at risk and if there were clinical similarities to the pandemic in 2009, which was caused by the same strain of influenza virus. Therefore, we analysed the patient characteristics and outcome of the influenza patients admitted to our ICU in the influenza season of 2015-2016. The aim of this article is to obtain a better insight into this patient group and the severe complications and high mortality in the ICU. Additional information about the clinical course of different influenza pandemics in especially young patient groups can lead to improved awareness of severe symptoms and might lead to the adjustment of any preventive measures against influenza infections.

Materials and methods

A retrospective observational study was conducted in patients admitted to the ICU of the Haga Hospital in the Netherlands, a top clinical hospital with approximately 600 beds and a level III ICU. All patients admitted in the ICU between December 2015 and February 2016 with a positive nasopharyngeal swab for influenza were included in the study. Patient demographic characteristics, clinical features, laboratory findings, vaccination status and the treatment given were retrospectively collected from the clinical patient files using our electronic patient file system. Medical ethics committee approval was obtained.

In case of a positive influenza A, a subtype analysis was performed in the microbiology laboratory of the hospital. If the initial test was performed in another hospital, subtype analysis could not be performed.

Additionally, the Acute Physiology and Chronic Health Evaluation (APACHE) IV score was calculated, using data from the first four hours of admission. If a patient was re-admitted, the data of the first admission were used. One patient was admitted for one day, transferred to an academic hospital and relocated after five days. For this patient, we used the data of the second admission.

Acute respiratory distress syndrome (ARDS)[5] was defined according to the Berlin definition and acute kidney injury according to the RIFLE criteria.[6] The International Society of Thrombosis and Haemostasis- disseminated intravascular coagulation (ISTH-DIC) score was used to calculate possible DIC[7] and rhabdomyolysis was defined as a more than tenfold increase in creatine kinase.[8] An abnormal liver blood test was defined as a more than twofold increase of the reference value for alanine aminotransferase (ALAT >90 U/l) in combination with a twofold increase in bilirubin (>34 µmol/l).

Results

Microbiological findings

Twenty-two positive nasopharyngeal influenza samples were collected. Two patients were excluded for being transferred to another hospital because of logistic reasons within eight hours of admission.

Of the 20 remaining included samples, 18 (90%) tested positive for influenza A and two (10%) tested positive for influenza B. In one patient, polymerase chain reaction was negative, but a later performed RNA was positive for influenza A. Twelve influenza A patients were infected with the (H1N1)pdm09 subtype and three had the H3N2 subtype. For three patients, the subtype was unknown since the initial test was performed in another centre.

Clinical features

The baseline characteristics are shown in *table 1*. As far as known, all patients were immune competent. The majority of patients (70%) were male, with a median age of 56 years (IQR 48 – 64). Half of the patient group had a history of pulmonary disease. One patient was diagnosed with sarcoidosis and one other patient with asthma. The other eight patients suffered from chronic obstructive pulmonary disease. Fourteen patients (70%) were overweight, defined as a body mass index (BMI) above 25 kg/m² and five patients (25%) had obesity with a BMI above 30 kg/m². One patient was pregnant.

The median APACHE score was 59 (IQR 50-91). The median duration of admission was six days (IQR 2-11), varying from 0 days (for instance when a patient died in less than 24 hours of admission) to a maximum of 78 days.

Table 1. Baseline characteristics of patients with confirmed influenza admitted to the ICU

n=20 (100%)

Male sex	14 (70%)
Median age (years) [IQR*]	56 [48 - 64]
Pulmonary History	10 (50%)
Obesity (BMI** > 25 kg/m²)	14 (70%)
Pregnancy	1 (5%)
Influenza vaccination	5 (25%)
Median duration of admission (days) [IQR]	6 [2-11]
Median APACHE score at admission [IQR]	59 [50 - 91]
Influenza A	18 (90%)
Influenza A(H1N1)pdm09	12 (67%)
Influenza A(H3N2)	3 (15%)
Unknown subtype	2 (11%)
Influenza B	2 (10%)

*IQR = interquartile range, **BMI = Body Mass Index

Vaccination status

Five patients (25%) were vaccinated against influenza. For one patient, the vaccination status could not be retrieved. The other 14 patients were not vaccinated, although four of them required an influenza vaccine according to the guidelines of our national vaccination program.[9]

Outcome

Ventilation

All but one of the patients (95%) required ventilation. One of those patients received non-invasive ventilation and the other 18 patients required invasive ventilation *(table 2)*. The mean time of intubation was five days, but there was a large variation between patients, varying from one day of intubation to a maximum of 39 days. Overall, it was noticed that high oxygen requirements and high positive end-expiratory pressure settings were necessary, especially in the young patients. Seven patients (35%) were ventilated in the prone position. Most of them required one or two sessions of prone ventilation in the first days. Two patients were turned three times in the prone position and one patient was turned eight times. This patient was eventually transferred for extracorporeal membrane oxygenation (ECMO)[10] to an academic centre. Another patient, who initially qualified for ECMO, was also transferred but returned after five days with an evolved clinical state after more ventilation in the prone position and without the use of ECMO. More than half of the subjects had ARDS. Two patients (10%) died of a lung bleeding.

Non-respiratory organ failure

Creatine kinase was elevated in all patients; varying from a maximum of 127 to 240,360 U/l (IQR 550-3333 U/l) *(table 2)* and 40% of the patients had rhabdomyolysis. Eight patients (40%) developed novel renal failure, of which five required renal

Table 2. Organ failure during ICU admission for influenza
n=20 (100%)

Mechanical ventilation	19 (95%)
Invasive ventilation	18 (90%)
Non-invasion ventilation	1 (5%)
Median days of intubation [IQR]	5 [2-11]
Prone ventilation	7 (35%)
Acute Respiratory Distress Syndrome (ARDS)	11 (55%)
Lung bleeding	2 (10%)
Sepsis	15 (75%)
Acute Kidney Injury (AKI) (failure)	8 (40%)
Renal Replacement Therapy	5 (25%)
Rhabdomyolysis	8 (40%)
Ileus	7 (35%)
Anormal liver function test	7 (35%)
Median Creatine Kinase (CK) [IQR] (U/L)	1563 [550 - 3333]
Diffuse Intravasal Coagulation (DIC)	1 (5%)
Bacterial Superinfection	12 (60%)
Multi Organ Failure (MOF)	16 (80%)
Mortality	6 (30%)

replacement therapy.
The majority of patients (80%) developed multi-organ failure. One patient (5%) had DIC. Abnormal liver function tests were present in seven of our patients (35%) and ileus occurred in seven patients (35%).

Superinfections
All patients had a bacterial superinfection. In the sputum cultures, Staphylococcus aureus was isolated most frequently, followed by *Escherichia coli, Streptococcus pneumoniae* and *Enterobacter aerogenes. Moraxella catarrhalis, Pseudomonas aerunginosa, Serratia marcescens* and *Klebsiella pneumoniae* were isolated less frequently.
Aspergillus was cultured from respiratory samples in four patients (20%). The infection was proven in one patient after a postmortem biopsy showed fungal hyphae in the lungs. All four of these patients had the influenza A subtype and had all received corticosteroids during their admission as part of treatment of a refractory shock. Table 3 shows how many days after admission a positive culture for aspergillus was grown. It is also shown that three out of four patients (75%) had no comorbidities that made them more susceptible for an aspergillus infection, such as pulmonary disease or a compromised immune system.

Treatment
All patients were treated with antibiotics for a suspected bacterial superinfection, as well as the standard protocolled treatment with selective oropharyngeal decontamination for all patients in our ICU. The antibiotics most frequently given were ciprofloxacin (90%), flucloxacillin (55%), cefuroxime (40%) and amoxicillin (20%). Twelve patients had a proven bacterial superinfection with one or more bacteria isolated in the culture. Eight patients (40%) received oseltamivir and ten patients (50%) received corticosteroids as part of a treatment for refractory shock. Voriconazole was given to two patients with an aspergillus infection *(table 3)*. For patient Y, this was started five days after the first positive culture and for patient Z after 15 days. For patient Z, the minimum inhibitory concentration (MIC) was determined. This patient was infected with both *Aspergillus fugimatus* and *Aspergillus terreus*. The MIC for the *Aspergillus fugimatus* was 1, which indicates a susceptible microorganism. For the *Aspergillus terreus* however, there is insufficient evidence that the species is a good target for voriconazole.[11]

Mortality
The mortality rate among all patients was 40%. All the patients who died had an influenza A infection and in six patients the influenza A (H1N1) subtype was confirmed. In the other two patients, subtype analysis could not be performed. Three of the deceased patients received oseltamivir and six received corticosteroids. Three out of four patients with an aspergillus infection died *(table 3)*.

Table 3. Characteristics of influenza patients with an aspergillus infection

Patient	W	X	Y	Z
Aspergillus subtype	fugimatus	fugimatus	fugimatus	fugimatus & terreus
First diagnosis (days after admission)	12 days	51 days	3 days	1 day
Diagnostic method	RS*	RS	RS	RS + lung biopsy
Relevant comorbidities	None	None	COPD	None
Corticosteroids	Yes	Yes	Yes	Yes
Influenza	A **	A (H1N1)	A (H1N1)	A (H1N1)
Oseltamivir	Yes	No	No	No
Voriconazole	No	No	Yes	Yes
Mortality	No	Yes	Yes	Yes

* RS: Respiratory Sample
** the influenza subtype was unknown

Discussion
This article describes the influenza patients in the ICU of the Haga Hospital during a seasonal epidemic in the Netherlands. Unlike during other seasonal influenza epidemics, affected patients were predominately male adults, younger than 65 years of age. The age distribution and the isolation of influenza subtypes correspond to the national data of the Netherlands.[1,4]

The influenza A(H1N1)pdm09 type is dominant, which is the same strain as during the 2009 pandemic.[12] The high mortality rate was solely due to the A(H1N1)pdm09 strain and not to influenza B. Moreover, publications on the H1N1 pandemic in

2009 highlighted that young patients were more affected by viral pneumonia and had more complications than to be expected during other seasonal epidemics,[13-19] which is comparable with our findings.

The majority of our patient group had no indication for vaccination, mainly because of their young age and lack of comorbidities. However, one-fourth of the study group had a severe infection despite vaccination. The vaccine used in the season 2015-2016 included A(H1N1)pdm09, A(H3N2) and B(Victoria lineage) and all isolated strains were susceptible to the vaccine.[1] The vaccine effectiveness was estimated on 42% for the A(H1N1)pdm09 strain and 53% for the B(Victoria lineage) strain by the influenza surveillance group of the Netherlands. This research group established a protective effect in patients above 60 years of age with chronic diseases for this vaccine, but the same effect could not be objectified in the age group under 60 years with comorbidities.[1]
The vaccine composition for the 2016-2017 influenza epidemic in the Netherlands consisted of a influenza A(H1N1)pdm09, A(H3N2) and influenza B (Brisbane and Phuket) strain.[20] Even if there was a sufficient protective effect of the vaccine, severe infections might be expected if the incidence of influenza A(H1N1)pdm09 in younger patients is as high as in the 2015-2016 season.

Sepsis and ARDS were the most common symptoms of organ failure. Compared with other studies, the rate of ARDS and DIC was similar.[15] A high incidence of prone-position ventilation was observed and one patient required ECMO. Another frequent symptom of organ damage was rhabdomyolysis, with some extremely high values of creatine kinase. The cause of the noteworthy high CK of 240,360 U/l in one patient was a viral myositis, confirmed by a tissue biopsy. High CK levels are described often after H1N1 infections[13] and it is considered a biomarker of severity in influenza infections.[21]

Ileus was a common symptom in our research group, despite ICU protocols which dictate low dosages of opiates and sedation and the early use of prokinetics and laxatives. This is a remarkable finding, given that ileus as a symptom of severe influenza infections has not been described in other articles on influenza. This could be because of a lack of awareness of the possible combination of ileus and influenza infections. However, any relationship between the symptoms and an influenza infection cannot be proven due to the small research group.

Co-infections with both bacteria and fungi were frequently objectified in our patient group. This underlines the importance of early antibiotic treatment[22] for severe influenza infections and underscores the importance of the diagnostics towards fungal co-infections infections in patients who fail to respond initial treatment.

Remarkably, two patients died because of acute lung bleeding. Both patients had a positive respiratory sample for aspergillus and a tracheostomy. Autopsy in the first patient showed blood in the lungs and diffuse inflammatory pulmonary changes. It confirmed the aspergillus infection by showing local invasive fungal hyphae in the lungs. There were no signs of a trachea-aortic fistula. Unfortunately, there was no consent for autopsy in the other patient. The cause of the haemoptysis might be due to a fistula or to late inflammatory effects of the influenza and/or aspergillus infection. It has been described that influenza virus infections can cause diffuse alveolar haemorrhage.[23] In performed autopsies after influenza A(H1N1) infections, a 66% incidence of alveolar haemorrhage has been established.[24] However, based on the design of this study it was not possible to test or confirm this hypothesis.

Strength and limitations
This retrospective report is based on ICU admission in a large city in the Netherlands and it provides valuable descriptive information. It illustrates the possible severe outcome of influenza and raises awareness for certain symptoms and patient groups in future pandemics. However, the research group is too small to provide standardised statistical analyses. Also, the results do not reflect on clinical features in less severe cases not admitted in the ICU. Another limitation is that the inclusion of patients was retrospectively performed by collecting positive nasopharyngeal swabs, which means that theoretically there could be an underestimation if not all patients with influenza were tested. However, the awareness of a possible influenza infection in the Haga Hospital each year is high and swabs are frequently taken in the process of preventive measurements.
The study population in our hospital might differ from the influenza patients that have been described in research in ICUs in academic centres in the Netherlands, where one might expect older patients with more comorbidities in the first place, given the tertiary function of these centres. Therefore, research conducted in these centres might give a misleading higher percentage of patients with comorbidities and influenza.

Conclusion

Since we face new influenza pandemics each year, awareness of the fulminant course of disease that the influenza virus can cause is extremely important, especially for the influenza A(H1N1)pdm09 strain. This study provides useful information about the clinical course of the influenza pandemic in the ICU in 2015-2016. It was noticed that a large group of young and relatively healthy people were admitted to the ICU with a severe influenza infection and a high incidence of multi-organ failure and a high mortality rate. In contrast to the 2009 influenza A

(H1N1)pdm09 outbreak, ileus and lung bleeding were observed. Since the reason for this is yet unknown, we should be aware of these symptoms during the next outbreak and more research is recommended in patients in and outside the ICU.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

References

1. Teirlinck AC, van Asten L, Brandsema PS, et al. Surveillance of influenza and other respiratory infections in the Netherlands: winter 2014/2015, (accessed October 26, 2016 at: http://www.rivm.nl/dsresource?objectid=rivmp:290866&type=org&disposition=inline&ns_nc=1)
2. Fact sheet on seasonal influenza, World Health Organisation (WHO). (Accessed October 11, 2016 at: http://www.who.int/mediacentre/factsheets/fs211/en/)
3. Nieuwsbrief influenza-surveillance 2015-2016, Nationaal Influenza Centrum (NIC): Rotterdam (Erasmus MC), Bilthoven (RIVM); Nederlands instituut voor onderzoek van de gezondheidszorg (NIVEL); Inspectie voor de Gezondheidszorg (IGZ). (Accessed October 11, 2016 at: http://www.nivel.nl/sites/default/files/nb_2015_16_no_31.pdf)
4. Influenza nieuwsbrieven 2015-2016, Nederlands instituut voor onderzoek van de gezondheidszorg (NIVEL). (Accessed October 26, 2016 at: http://www.nivel.nl/nl/dossier/influenza-nieuwsbrieven-0)
5. Ranieri VM, Rubenfeld GD, Thompson BT, et al., for the ARDS Definition Task Force,. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307:2526-33.
6. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8:R204-12
7. Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. J Intensive Care. 2014;2:15
8. Zutt R, van der Kooi AJ, Linthorst GE, Wanders RJA, de Visser M. Rhabdomyolysis: Review of the literature; Neuromuscul Disord. 2014;8:651-9.
9. Nationaal Programma Griepppreventie. Rijksinstituur voor Volksgezondheid en Milieu, 2016. (Accessed October 26, 2016 at: http://www.rivm.nl/Onderwerpen/G/Griep/Griepprik/Nationaal_Programma_Griepppreventie
10. Mitchell MD, Mikkelsen ME, Umscheid CA, Lee I, Fuchs BD, Halpern SD. A Systematic Review to Inform Institutional Decisions About the Use of Extracorporeal Membrane Oxygenation During the H1N1 Influenza Pandemic, Crit Care Med. 2010 ; 38:1398-404.
11. EUCAST Clinical breakpoints - fungi (version 8.0) (2015-11-16), (Accessed 13 Dec at: http://www.eucast.org/clinical_breakpoints/)
12. Nieuwsbrief influenza-surveillance 2015-2015, 04-02-2016, jaargang 24, no 3. (Accessed October 26, 2016 at: http://www.nivel.nl/sites/default/files/nb_2015_16_no_31.pdf)
13. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, et al. Pneumonia and Respiratory Failure from Swine-Origin Influenza A (H1N1) in Mexico. N Engl J Med. 2009; 361:680-9.
14. ANZIC Influenza Investigators, Webb SA, Pettilä V, Seppelt I, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med. 2009;361:1925-34.
15. Lee EH, Wu C, Lee EU, et al. Fatalities Associated with the 2009 H1N1 Influenza A Virus in New York City, Clin Infect Dis. 2010;50:1498-504
16. Domínguez-Cherit G, Lapinsky SE, Macias AE, et al. Critically Ill patients with 2009 influenza A(H1N1) in Mexico. JAMA. 2009;302:1880-7
17. Rello J, Rodríguez A, Ibañez P, et al. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. Crit Care. 2009;13(5):R148
18. Belongia EA, Irving SA, Waring SC, et al. Clinical Characteristics and 30-Day Outcomes for Influenza A 2009 (H1N1), 2008-2009 (H1N1), and 2007-2008 (H3N2) Infections, JAMA. 2010;304:1091-8
19. Centers for Disease Control and Prevention (CDC) Hospitalized patients with novel influenza A (H1N1) virus infection - California, April-May, 2009. Morb Mortal Wkly Rep. 2009;58:536.
20. Samenstelling griepvaccins 2016-2017, donderdag 23 juni 2016. (Accessed October 26, 2016 at: https://www.klav.be/klavinfo/nl/samenstelling-griepvaccins-2016-2017)
21. Borgatta B1, Pérez M, Rello J, et al. Elevation of creatine kinase is associated with worse outcomes in 2009 pH1N1 influenza A infection. Intensive Care Med. 2012;38:1152-61.
22. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J Infect Dis. 2008;14:1193-9.
23. Von Ranke FM, Zanetti G, Hochhegger B, Marchiori E. Infectious Diseases Causing Diffuse Alveolar Hemorrhage in Immunocompetent Patients: A State-of-the-Art Review. Lung. 2013;191:9.
24. Rivera J, Sarmiento L, Parra E, et al. Morphological changes in lung tissue of victims associated with the 2009 A H1N1/v09 influenza pandemic in Colombia. Biomedica. 2011;31:372-80.