Influenza Virus Shedding in the Upper and Lower Respiratory Tract of Invasively Ventilated Critically Ill Patients

Frank van Someren Gréve[1,2], Nicole P. Juffermans[1], Jan M. Binnekade[1], Annemarije Braber[3], Olaf L. Cremer[4], Evert de Jonge[6], Richard Molenkamp[2], David S.Y. Ong[4,5], Sjoerd P.H. Rebers[2], Angelique M.E. Spoelstra–de Man[7], Koenraad F. van der Sluijs[1], Peter E. Spronk[3], Kirsten D. Verheul[2], Monique C. de Waard[7], Rob B.P. de Wilde[6], Tineke Winters[1], Marcus J. Schultz[1], Menno D. de Jong[2]

Academic Medical Center, Amsterdam, The Netherlands, Departments of [1]Intensive Care and [2]Medical Microbiology; Gelre Hospitals, Apeldoorn, [3]Department of Intensive Care; University Medical Center Utrecht, Utrecht, Departments of [4]Intensive Care and [5]Medical Microbiology; Leiden University Medical Center, Leiden, [6]Department of Intensive Care; VU Medical Center, Amsterdam, [7]Department of Intensive Care

Rationale

Knowledge of influenza virus shedding dynamics during infection is essential for rational decision-making regarding antiviral treatment and isolation measures. However the exact patterns in critically ill patients are poorly understood, especially in the lower airways.

Aim

We assessed influenza virus shedding patterns during invasive ventilation in patients admitted to the intensive care unit (ICU) in both upper and lower respiratory tract.

Methods

Prospective observational study in 5 ICUs in the Netherlands from March to April 2013 and September 2013 to April 2014. Included were acutely admitted patients requiring invasive ventilation, with an influenza-positive nasopharyngeal (NP) swab or tracheobronchial aspirate (TA), confirmed by real–time polymerase chain reaction (RT–PCR). Daily NP swabs and TAs were collected during the period that patients were on invasive ventilation, and tested for influenza using RT-PCR. Kaplan Meier analysis was performed to determine the probability of remaining influenza positive over time. The number of shedding–free days and invasively ventilated was defined as the number of ventilated days minus the number of days a patient had influenza detected in NP swabs or TA.

Results

Patient characteristics

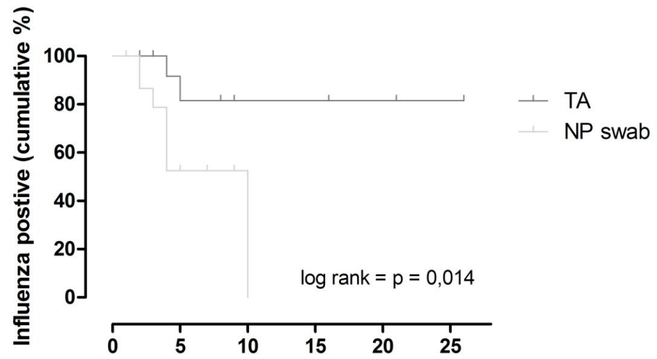
	Patients with influenza infection n = 23
Age (median, IQR)	64 (61-73)
Male (n)	11 (50%)
History of COPD (n)	6 (26%)
APACHE II score (median, IQR)	25 (18-30)
Reported respiratory symptoms prior to intubation (n)	7 (39%)
Clinical parameters at intubation (median, IQR)	
Temperature (ºC)	36,6 (35,4-37,4)
Leucocytes (x10^9/L)	10,2 (7,2-12,9)
CRP (mg/L)	37 (11-80)
Alveolar consolidations on chest X-ray at intubation (n)	10 (48%)
Antivirals used during ICU stay (n)	7 (33%)
Clinical outcomes	
Duration of mechanical ventilation (days, IQR)	4,5 (3-6)
Duration of ICU stay (days, IQR)	5 (3-10)
In-hospital mortality (n)	10 (45%)

Site and duration of shedding

	Patients with influenza infection n = 23
Site of positive PCR on inclusion (n)	
Only in NP swab	2 (9%)
Only in TA	7 (30%)
Both	14 (61%)
Proportion of patients still positive in their last obtained sample (n)	
NP swab	10/16 (63%)
TA	19/21 (90%)
Any sample	21/23 (91%)
Minimal duration of shedding (median days; IQR)	
NP swab	3 (1-5)
TA	4 (2-8)
Any sample	3 (1-7)

In total, 23 patients were included, of whom 9 had an infection with influenza A (H1N1), 8 with influenza A (H3N2) and 6 with influenza B. The longest observed duration of shedding was 9 days in NP swabs and 26 days in TA.

Shedding over time and shedding-free days



No of patients at risk

Days	0	1	2	3	4	5	7	8	9	10	16	21	26
TA	21	21	18	15	12	9	6	6	4	3	3	2	1
NP swab	16	16	15	11	9	5	3	2	2	1	0	0	0

Kaplan Meier analysis showed a significantly higher cumulative percentage of patients remaining influenza positive in TA compared to NP swabs, while on invasive ventilation. The number on shedding-free days while on invasive ventilation was significantly lower in TA compared to NP swabs (1 [0-1] vs. 2 [0-3] days, p = 0.029).

Conclusions

- Almost all critically ill patients with an influenza infection shed virus for as long as they are invasively ventilated, particularly in lower respiratory tract specimens. These findings may be relevant for isolation measures.
- In a substantial proportion of patients, influenza virus was only detected in lower respiratory tract specimens. These findings indicate that influenza infections will be missed when solely relying on NP swabs for detection.

Correspondence: *Frank van Someren Gréve; frankvsg@gmail.com; +31 20 56 66345*
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