CORRESPONDENCE

Critical Illness in an Adolescent with Influenza A(H5N1) Virus Infection

TO THE EDITOR: Highly pathogenic avian influenza A(H5N1) viruses are circulating among wild birds and poultry in British Columbia, Canada.[1] These viruses are also recognized to cause illness in humans. Here, we report a case of critical illness caused by influenza A(H5N1) virus infection in British Columbia.

On November 4, 2024, a 13-year-old girl with a history of mild asthma and an elevated body-mass index (the weight in kilograms divided by the square of the height in meters) of greater than 35 presented to an emergency department in British Columbia with a 2-day history of conjunctivitis in both eyes and a 1-day history of fever. She was discharged home without treatment, but cough, vomiting, and diarrhea then developed, and she returned to the emergency department on November 7 in respiratory distress with hemodynamic instability. On November 8, she was transferred, while receiving bilevel positive airway pressure, to the pediatric intensive care unit at British Columbia Children's Hospital with respiratory failure, pneumonia in the left lower lobe, acute kidney injury, thrombocytopenia, and leukopenia (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). A nasopharyngeal swab obtained at admission was positive for influenza A but negative for A(H1) and A(H3) by the BioFire Respiratory Panel 2.1 assay (BioFire Diagnostics). Reflex testing of the specimen with the Xpert Xpress CoV-2/Flu/RSV plus assay (Cepheid) revealed an influenza A cycle threshold (Ct) value of 27.1. This finding indicates a relatively high viral load for which subtyping would be expected; the lack of subtype identification suggested infection with a novel influenza A virus. Oseltamivir treatment was started on November 8 (Table S2), and the use of eye protection, N95 respirators, and other precautions against droplet, contact, and airborne transmission were implemented.

A reverse-transcriptase–polymerase-chain-reaction (RT-PCR) test specific for influenza A(H5)[2] was positive on the day of admission. The patient had signs of respiratory deterioration — chest radiographs were consistent with progression to acute respiratory distress syndrome (Fig. S1) — which prompted tracheal intubation and initiation of venovenous extracorporeal membrane oxygenation (ECMO) on November 9. Continuous renal replacement therapy was initiated on November 10. Combination antiviral treatment with amantadine (initiated on November 9) and baloxavir (initiated on November 11) was added to ongoing treatment with oseltamivir. Bacterial

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Table 1. Results of Virologic Testing of Clinical Specimens from a Patient with Influenza A(H5N1) Virus Infection, November 2024.

Specimen Type (Collection Date)	Influenza A RT-PCR Result*	Influenza A Cycle Threshold	Markers of Reduced Susceptibility†	Susceptibility to Antivirals by NA-Star‡
Blood samples				
Serum (November 9)	Positive	26.3	Not assessed	Not assessed
Serum (November 12)	Indeterminate	35.1	Not assessed	Not assessed
Serum (November 14)	Indeterminate	39.0	Not assessed	Not assessed
Serum (November 16)	Negative		Not assessed	Not assessed
Initial respiratory specimens				
Nasopharyngeal swab (November 7)	Positive		Not assessed	Susceptible
Nasopharyngeal swab (November 8)	Positive	27.1	None	Susceptible
Nasopharyngeal swab (November 8)	Positive	27.3	None	Susceptible
Tracheal aspirate (November 9)	Positive	17.4	None	Susceptible
Serial respiratory specimens				
Tracheal aspirate (November 12)	Positive	17.6	None	Susceptible
Tracheal aspirate (November 14)	Positive	24.5	None	Not assessed
Tracheal aspirate (November 16)	Positive	27.1	Not assessed	Not assessed
Tracheal aspirate (November 18)	Positive	27.8	None	Not assessed
Tracheal aspirate (November 20)	Positive	27.1	Not assessed	Not assessed
Tracheal aspirate (November 22)	Positive	31.5	Not assessed	Not assessed
Tracheal aspirate (November 24)	Positive	33.0	Not assessed	Not assessed
Tracheal aspirate (November 26)	Positive	31.1	Not assessed	Not assessed
Tracheal aspirate (November 28)	Positive	39.9	Not assessed	Not assessed

* Specimens were tested with an influenza A virus–specific reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay.
† Specimens were analyzed for viral sequence markers associated with reduced susceptibility to antiviral agents.
‡ The NA-Star influenza neuraminidase inhibitor resistance detection kit was used to test for susceptibility to oseltamivir and zanamivir.

cultures of blood (samples obtained at admission) and endotracheal aspirate (obtained after intubation) yielded no growth.

Because of concern for cytokine-mediated hemodynamic instability, plasma exchange was performed daily from November 14 through November 16. Serial influenza A–specific RT-PCR tests showed increasing Ct values, which suggested a decline in the viral RNA load in serum and a decline in viral RNA in upper- and lower-respiratory specimens shortly after the initiation of antiviral treatment, with the first negative RT-PCR result for serum obtained on November 16 (Table 1). It is notable that lower-respiratory specimens consistently yielded lower Ct values than upper-respiratory specimens, a finding that suggested higher viral levels in the lower-respiratory tract (Table S3).

Influenza A(H5N1) virus was cultured from respiratory specimens obtained between November 8 and November 12 but not from subsequent respiratory specimens or from any serum specimens (Table 1). No evidence of reduced susceptibility to any of the three antiviral agents used in treatment was observed in serial respiratory specimens by either genomic analysis or pheno-

typic testing with the NA-Star influenza neuraminidase inhibitor resistance detection kit (ThermoFisher Scientific) (Table 1). The patient's respiratory status improved, ECMO was discontinued on November 22, and the patient's trachea was extubated on November 28.

The viral genome sequence obtained from a tracheal-aspirate specimen collected on November 9 (8 days after the onset of symptoms) was reconstructed as described previously.[3] The virus was typed as clade 2.3.4.4b, genotype D1.1,[4] most closely related to viruses detected in wild birds in British Columbia around the same time (Fig. S2). Markers of adaptation to humans were detected in the tracheal-aspirate specimen collected on November 9: the E627K mutation was detected (52% allele frequency) in the polymerase basic 2 (PB2) gene product, and analysis of the H5 hemagglutinin (HA) gene yielded ambiguous calls in the codons for amino acid residues E186 (E190 according to H3 mature HA numbering) — 28% allele frequency for E186D — and Q222 (Q226 according to H3 mature HA numbering) — 35% allele frequency for Q222H. The mutations in the H5 HA gene have previously been shown to increase binding to α2-6–linked sialic acids, which act as receptors that facilitate viral entry into cells in the human respiratory tract and enable viral replication.[5]

Highly pathogenic avian influenza A(H5N1) virus infection acquired in North America can cause severe human illness. Evidence for changes to HA that may increase binding to human airway receptors is worrisome.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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Nationwide, Couple-Based Genetic Carrier Screening

TO THE EDITOR: Kirk et al. (Nov. 21 issue)[1] describe a study of couple-based genetic carrier screening. Cancer-associated genes, such as *BRCA1*, *BRCA2*, and those linked to the Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, and *PMS2*), were excluded from the 1281 genes studied.[2] Biallelic loss-of-function variants in these genes lead to very high rates of cancer in childhood. Biallelic loss of the Lynch syndrome genes results in constitutional mismatch-repair deficiency,[3] whereas biallelic loss of *BRCA1* or *BRCA2* results in Fanconi's anemia.[4] These conditions are associated with aggressive cancers with high mortality, and therefore close surveillance is recommended in childhood.[3,4]