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Relation of Diagnostic Accuracy of Viral Respiratory Polymerase Chain Reaction to Specimen Number and Source in Severe Adenovirus Pneumonia: Antimicrobial Stewardship Implications

To the Editor—I read with interest the article by Dr. Schleihauf and colleagues[1] on the number of nasopharyngeal (NP) specimens for diagnosis of respiratory virus by polymerase chain reaction (PCR). Their point is well taken and I agree that the diagnostic yield of respiratory viral PCR testing is not increased beyond 3. In intubated hospitalized adults with undiagnosed viral pneumonia, lower respiratory tract may be preferable to upper respiratory tract sampling. Recently, I had a patient who demonstrated the critical importance of specimen source in accurate diagnosis.

A 64-year-old woman presented with fever, chills, myalgias, dry cough, and shortness of breath. The patient had chronic obstructive pulmonary disease, atrial fibrillation, and recent contact with her sick grandson. She was in respiratory distress, her temperature was 38.7°C, her pulse was 127 beats/min (irregularly irregular), and her respiratory rate was 22 breaths/min. Physical examination was unremarkable except for bilateral conjunctival injection and expiratory wheezes. Laboratory studies included a white blood cell count of 11.5 K/mm^3 (neutrophils = 88%, lymphocytes = 4%, and monocytes = 7%), with a creatinine level of 1.1 mg/dL. Serum transaminases were unremarkable. Chest radiograph was clear with a questionable left lower lobe infiltrate. Procalcitonin (PCT) was 0.72 ng/mL. NP rapid influenza test was negative. NP PCR respiratory viral panel was negative for respiratory viruses. She was started on azithromycin, her respiratory status improved, but she remained febrile (temperature, 40.4°C). Her respiratory status deteriorated on hospital day (HD) 3, and she was placed on noninvasive positive pressure ventilation and transferred to the respiratory intensive care unit. Repeat NP respiratory viral panel was again negative. Repeat PCT was 2.36 ng/mL and on HD 2 ceftriaxone was added. Repeat chest radiograph showed increased interstitial markings, but no segmental/lobar infiltrates. Chest computed tomography showed diffuse lower lobe air space opacities. Ceftriaxone and azithromycin were discontinued and she was started on vancomycin, piperacillin/tazobactam, and doxycycline. Her creatinine level was now 4.55 mg/dL. She was intubated on HD 6, and bronchoscopy was performed. Bronchoalveolar lavage fluid showed 594 nucleated cells (many "smudge cells") and abundant red blood cells. Direct fluorescent antibody for *Pneumocystis* pneumonia was negative. Gram stain showed few polymorphonuclear leukocytes with no organisms and cultures were negative. Respiratory viral panel PCR performed on bronchoalveolar lavage fluid was positive for adenovirus and antibiotics were discontinued. Adenovirus antibody titer was elevated at 1:256 (normal <1:8) and serum quantitative adenovirus PCR was highly positive with 288,000 copies/mL. She defervesced on HD 6, but on HD 8, she developed loose, watery stools positive for *Clostridium difficile*. She was successfully treated for *C. difficile* diarrhea with metronidazole and vancomycin (Figure 1). Although there were no segmental/lobar infiltrates on chest radiograph to suggest bacterial pneumonia, her PCT was elevated and empirical antibiotics were given. Respiratory viral PCR performed on bronchoalveolar lavage fluid was positive for adenovirus and bronchoalveolar lavage fluid cytology showed adenovirus cytopathologic effects, which are large intranuclear basophilic inclusions resulting in a smudged appearance ("smudge cells ") pathognomic for adenovirus infection.[2,3]

The need to consider the *validity* of a sampling source has been reported previously. During the 2009-2010 influenza pandemic, a middle-aged immunocompetent man was

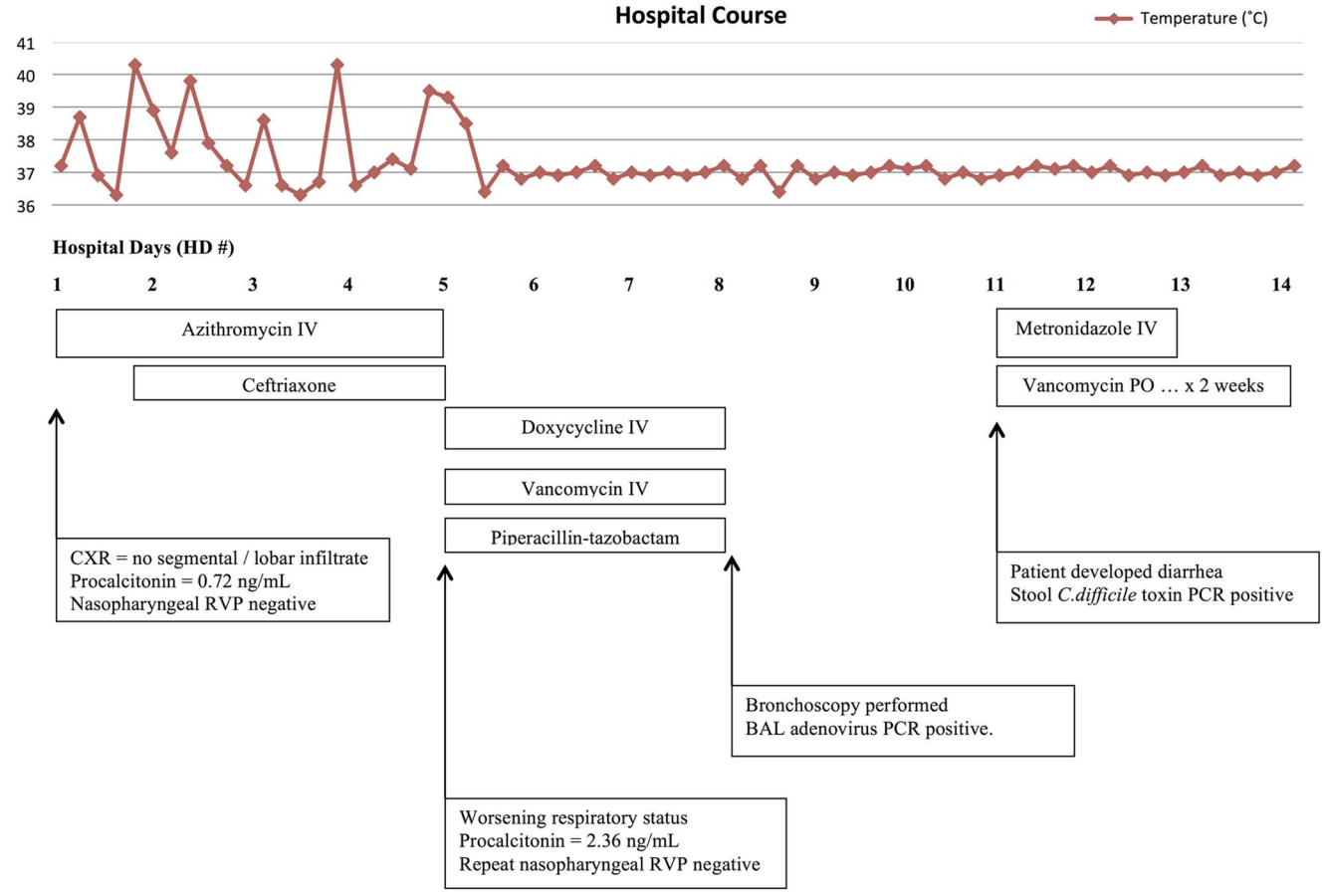

FIGURE 1. Hospital course in case study. BAL, bronchoalveolar lavage; *C. difficile*, *Clostridium difficile*; CXR, chest radiograph; IV, intravenous; PCR, polymerase chain reaction; PO, by mouth; RVP, respiratory viral panel.

hospitalized with a severe viral pneumonia thought to be due to influenza A. Multiple NP specimens were negative for influenza. He rapidly deteriorated and died of severe/prolonged hypoxemia. At autopsy, lung specimens were PCR positive for influenza A (H_1N_1).[4] Although we agree that the optimal number of NP PCR specimens for viral pneumonia diagnosis is 3, there are exceptions. With viral pneumonia of undetermined etiology in intubated patients and repeatedly negative NP PCRs, lower respiratory tract testing may be more reflective of the pulmonary pathogen than an upper airway source.

This case also merits comment from a antibiotic stewardship standpoint since without a definite diagnosis there was no clinical rationale for empirical antibiotics.[5,6] PCT is unhelpful in bacterial pneumonia diagnosis and may be elevated with renal insufficiency, as in this case.[7,8] There were no clinical findings to suggest bacterial coinfection/pneumonia. Unnecessary antibiotic costs aside, from an antibiotic stewardship perspective there is the additional cost of potential antibiotic adverse effects, which should be carefully considered when initiating empirical antibiotic therapy. In this case, *C. difficile* diarrhea may have been avoided.[5]

Antibiotic stewardship lessons from this case are clear. First, accurate diagnosis is needed in order to treat accurately.[5] Second, in hospitalized adults adenovirus pneumonia, when not localized, may mimic influenza pneumonia in radiographic appearance—that is, adenovirus in this patient mimicked influenza pneumonia.[2] Third, when influenza or other viral pneumonias are complicated by bacterial coinfection, the clinical findings of bacterial pneumonia are readily recognizable on chest radiograph—for example, focal segmental/lobar infiltrates superimposed on bilateral patchy interstitial infiltrates of the underlying viral pneumonia.[7,8] In this case, it was assumed she had influenza that may be complicated by bacterial pneumonia, and empirical antibiotic therapy was given on the basis of a potential predisposition of influenza to bacterial coinfection/pneumonia.[9,10] However, this case of adenoviral pneumonia had no clinical findings that suggested bacterial coinfection/pneumonia. Elevated PCT levels are often misleading and are often due to other infectious and noninfectious disorders.[7,8]

Last, from an antibiotic stewardship perspective, empirical antibiotics should be selectively prescribed for the shortest

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possible duration. Unnecessary empirical antibiotic therapy may have adverse pharmacoeconomic and clinical consequences—for example, in this case *C. difficile* diarrhea.[5] In conclusion, it cannot be overstated that accurate diagnosis is essential for accurate therapy. In hospitalized adults with viral pneumonia of unknown etiology, if 3 NP PCR specimens are negative, results should be interpreted in light of the specimen source—that is, is the specimen test result reflective of the infection source?

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Fecal Microbiota Therapy as Rescue Therapy for Life-Threatening *Clostridium difficile* Infection in the Critically Ill: A Small Case Series

To the Editor—A retrospective review of anonymous data obtained from patients treated with fecal microbiota therapy (FMT) was conducted as part of an antibiotic stewardship program in a Bavarian regional medical center that is part of the Network of the German Consulting Center for Infection Control and Prevention. Data handling was perfomed in accordance with German Federal Data Protection Law (Bundesdatenschutzgesetz); the analysis of anonymous routine quality assurance data does not constitute human research requiring institutional review board approval. Table 1 summarizes the descriptions of each case based on point prevalence data from antibiotic stewardship rounds.

All patients were recovering well from their underlying illness at the time of *Clostridium difficile* infection (CDI) onset and deteriorated rapidly in septic shock, so that the attending physicians opted for an emergency FMT as rescue therapy. Our patients met criteria for septic shock with multiple organ failure unresponsive to fluids, specific antibiotics, and increasing vasopressor demand. Informed consent from the patient or guardian was obtained and relatives volunteered as stool donors after an abbreviated medical screen. FMT was performed as soon as possible, at least within 24 hours after the therapeutic decision. One patient died during the preparation period. All treated patients started to respond within 12–24 hours after FMT with clinical improvement including a change of consistency and odor of stools within 12 h, resolution of shock symptoms, significantly reduced vasopressor support after 48 hours, and resolution of inflammatory markers. No immediate procedure-specific complications were observed; however, no long-term follow up was possible owing to the nature of the data source, highlighting the importance of registry projects like the one by the German Society of Gastroenterology and the University of Jena (https://service.zks.med.uni-jena.de/STReg).

Disturbance of the intestinal microbiome by multiple antibiotics, particularly third-generation cephalosporins, fluoroquinolones, and clindamycin[1] and likely proton-pump inhibitors, especially in combination with high-risk antibiotics,[2] plays an important role for the development of symptomatic CDI. Several definitions of CDI severity of illness make comparative studies of treatment difficult. There are increasing positive experiences with FMT in cases of recurrent illness; despite methodological limitations FMT has become a part of the treatment algorithm for recurrent CDI.[3] In a recent meta-analysis the great majority of adverse events of FMT appeared to be mild and self-limiting. In some cases, a credible association was not established owing to the lack of controlled data.[4]