Diagnostic Testing or Empirical Therapy for Patients Hospitalized with Suspected Influenza: What to Do?

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Accumulating evidence supports the use of specific diagnostic tests and antiviral therapies for seriously ill patients with influenza. Among available diagnostic tests, reverse-transcriptase polymerase chain reaction is faster than culture and more sensitive than commercial antigen assays. Current neuraminidase inhibitors were approved on the basis of their efficacy in ambulatory patients, but seriously ill patients who receive these agents are less likely to die, even when treatment is initiated >48 h after symptom onset. For patients hospitalized with suspected influenza, it is unclear which circumstances warrant diagnostic testing and which warrant the use of empirical therapy. Rapid antigen assays may reduce the unnecessary use of other tests and medications but are relatively insensitive, thus eliminating many patients with influenza as candidates for treatment. Empirical antiviral therapy ensures that all patients receive treatment promptly, at a cost equivalent to that of diagnostic tests alone, but results in the receipt of treatment by many patients without influenza. For patients hospitalized with suspected influenza, clinicians need to combine these approaches in order to optimize patient care.

Current management guidelines for influenza typically emphasize the prevention and treatment of uncomplicated seasonal disease [1]. Nevertheless, even vaccinated patients may become seriously ill from influenza virus infection, and evidence to guide clinical care decisions for these patients is sparse. Data compiled from several recent studies suggest that the time has come to reconsider the approach to influenza treatment for patients who require hospitalization. Two questions must be answered: (1) is there a benefit to antiviral treatment of influenza in seriously ill patients, and (2) how should influenza be diagnosed in hospitalized patients?

IS THERE A BENEFIT TO TREATING INFLUENZA IN SERIOUSLY ILL PATIENTS?

The only large randomized controlled trials that assessed the benefit of the treatment of influenza were trials of early therapy (<48 h after symptom onset) with neuraminidase inhibitors (NAIs) in healthy adults and children. These trials demonstrated that therapy was associated with a significant reduction in the duration and severity of illness and a 40%–60% reduction in the percentage of patients who developed complications or required hospitalization [2–7].

Similar reductions in complications and hospitalization associated with early therapy with oseltamivir have been identified in subsequent observational cohort studies of nursing home residents during influenza outbreaks, in 2 studies in which administrative databases were examined, and in cohort studies of immunocompromised patients [5, 8–10]. However, there is a difference between the early treatment of otherwise-healthy outpatients and the treatment of patients who require hospital admission. The question becomes, what data do we have on the impact of antiviral therapy for the treatment of influenza in patients requiring hospitalization?

There currently are 3 cohort studies that have examined the impact of treatment on patients with community-acquired illness severe enough to warrant hospitalization. In a cohort study by Falsey et al. [11–13],

viral testing was done systematically for patients admitted to Rochester General Hospital with underlying cardiopulmonary disease and respiratory tract infection, congestive heart failure, exacerbation of chronic lung disease, or acute respiratory viral illness during 4 winter seasons, from 1999 to 2003. Of the 193 patients with influenza, 53 received treatment with amantadine or rimantadine, and 15 received treatment with NAIs. In-hospital mortality among these patients was 6%. The investigators were unable to find an effect of treatment with antiviral drugs. However, it is important to recognize that the study was not powered to detect a clinically significant difference: an analysis based on a cohort of 200 patients has <30% power to detect a 50% reduction in mortality. Furthermore, the authors indicated that it appeared that more severely ill patients were more likely to be treated with an antiviral drug, a bias that would decrease the probability of finding a treatment effect.

In a retrospective study of adult patients with influenza who were admitted to the Prince of Wales Hospital in Hong Kong during the 2004–2005 influenza season with fever and respiratory and systemic symptoms, a clinically and statistically significant reduction in length of hospital stay was associated with treatment with oseltamivir [14]. In North America, less severely ill patients would have been screened from this cohort and sent home, but, in Hong Kong, most patients with fever and respiratory and systemic symptoms were admitted to a hospital regardless of disease severity and were screened for severe acute respiratory syndrome coronavirus and other respiratory viruses. Patients who had been symptomatic for ⩽2 days received empirical therapy with oseltamivir; patients who had been symptomatic for ⩾2 days received treatment at the discretion of their physician. In this study, a total of 356 patients were admitted to the hospital, and 257 received treatment with oseltamivir. Of those receiving treatment, 161 received treatment within 2 days of symptom onset. Patients who received treatment experienced a median reduction in their length of hospital stay of 2 days—an ~30% reduction—relative to that of patients who did not receive treatment or who received treatment >2 days after symptom onset ($P < .0001$) [14].

Further support for the use of specific antiviral therapy for hospitalized patients comes from data collected prospectively in a cohort study of patients in Toronto, which showed a surprisingly large reduction in mortality even when therapy was started >48 h after symptom onset [15]. This study correlated mortality with specific antiviral therapy over 2 influenza seasons (2004–2005 and 2005–2006) in Toronto. Of 327 adult patients with laboratory-confirmed influenza who were admitted to a hospital, 106 patients (32%) received treatment with oseltamivir. Overall in-hospital mortality in this cohort was 10.7%. Although the observation of a treatment effect was not anticipated, owing to the small sample size, patients who received treatment with oseltamivir had a risk of death (OR) of 0.21

($P = .03$), corresponding to a point estimate of a 79% reduction in mortality, compared with patients who did not receive treatment. Given the limitations of this study's methodology, it is not possible to state unequivocally that oseltamivir treatment reduces mortality among patients admitted to a hospital with influenza. On the other hand, because of the established treatment effect in healthy outpatients, the apparent magnitude of the treatment effect in compromised and seriously ill patients, and the established safety of oseltamivir, a placebo-controlled trial to determine the efficacy of antiviral therapy for the treatment of severe influenza may no longer be ethically justifiable.

Of note, over the 3 seasons of surveillance in the Toronto Invasive Bacterial Diseases Network (TIBDN) study, about one-third of patients were hospitalized within 48 h of symptom onset. In addition, the treatment effect seen in this cohort was not different for patients treated ⩽48 h or >48 h after symptom onset. These data confirm the findings of Ison et al. [16], who demonstrated that hospitalized patients receiving treatment with rimantadine and zanamivir shed influenza virus for several days after hospital admission. Both the fact that one-third of patients present early and the fact that treatment may be effective when initiated >48 h after symptom onset in hospitalized patients emphasize how important it is to improve our understanding of severe influenza illness. Another interesting finding from the TIBDN study is that, during the 2006–2007 influenza season, 2 of 21 patients admitted to an intensive care unit after out-of-hospital cardiac arrest tested positive for influenza [15]. This raises a concern that influenza may trigger ventricular arrhythmias and sudden death and supports the results of a number of cohort studies suggesting that influenza vaccination is protective against sudden death.

This accumulating evidence for a treatment effect suggests that it is prudent to establish a policy of antiviral treatment for patients who are seriously ill with influenza. Such a policy will have a low risk of adverse events and a low risk of increasing selective pressure for the development of resistant strains of influenza virus. Oseltamivir has no proven serious adverse effects [6, 7, 17]. The neurobehavioral adverse events reported primarily in Japanese adolescents may have been an effect of either influenza or treatment; only further study will resolve this question. Reassuringly, the rate of neurobehavioral adverse events reported to the US Food and Drug Administration by Japan is <1 case per 100,000 prescriptions [18]. For patients within the age range typically admitted to an intensive care unit, that rate is probably low enough to be of very limited clinical relevance. With regard to increasing selective pressure for the development of resistant virus strains, it is important to remember that NAIs are active against only influenza virus. If a patient treated with NAIs does not have influenza, no selective pressure is being applied, and antiviral resistance will

Table 1. Laboratory diagnostic testing for influenza.

Procedure	Acceptable specimen type(s)	Collection time	Time for results
Conventional viral culture	NP or throat swab, nasal or bronchial wash, nasal aspirate, or sputum	Best at ≤72 h after symptom onset and acceptable with symptoms at >72 h after onset	3–10 days
Rapid viral culture (SV + DFA or SV + RT-PCR)	NP or throat swab	Best at ≤72 h after symptom onset	1–4 days (SV + DFA);[a] 2 days (SV + RT-PCR)[b]
Immunofluorescence DFA antibody staining	NP swab, nasal or bronchial wash, nasal aspirate, or sputum	Best at ≤72 h after symptom onset	2–4 h
RT-PCR	NP or throat swab, nasal or bronchial wash, nasal aspirate, or sputum	Best at ≤72 h after symptom onset and acceptable with symptoms at >72 h after onset	<1 day[a]
EIA	NP or throat swab or nasal or bronchial wash	Best at ≤72 h after symptom onset	2 h
Point-of-care diagnostic tests	Varies, per test manufacturer	Best at ≤72 h after symptom onset	<30 min

NOTE. Data are from Centers for Disease Control and Prevention [23] and Petric et al. [24], except where noted otherwise. DFA, direct fluorescence assay; NP, nasopharyngeal; SV, rapid shell-viral assay.

[a] Dwyer et al. [25].
[b] Pérez-Ruiz et al. [26].

not be increased in the patient population. This differs from the effect of empirical antibiotic therapy: every time an antibiotic is used, selective pressure is applied to the host's normal flora, whether or not the antibacterial is active against the pathogen being targeted.

Past influenza-management guidelines have not offered much guidance regarding antiviral treatment for patients admitted to a hospital. Nonetheless, recent guidelines suggest that antiviral therapy should be offered to patients with severe illness and to those who are most likely to develop complications and/or to die. For example, the Association of Medical Microbiology and Infectious Diseases Canada/Canadian Pediatric Society recommends antiviral treatment for individuals with severe illness and for those most likely to develop complications from influenza or to die prematurely as a result [19]. The American Academy of Pediatrics recommends antiviral treatment for high-risk children and for other children with moderate to severe disease [20]. Italian guidelines recommend prioritizing therapy for patients at risk of complications, ensuring that patients take the drug as early as possible, and using antiviral therapy only at the seasonal peak of influenza prevalence [21].

HOW SHOULD INFLUENZA BE DIAGNOSED?

A decision to treat with antiviral therapy requires that physicians either rapidly make a reasonably definitive diagnosis of influenza or choose to treat empirically when the probability of influenza is above a certain threshold. The former is obviously preferable, when possible. Among adults, acute respiratory illness with fever and early cough has a positive predictive value for influenza of >70% during influenza season [22]. However, many adults, particularly those who are elderly or those who have a significant underlying illness, do not mount an adequate febrile response and may not present with early cough.

Thus, clinical features alone cannot be used to diagnose influenza. Commonly available diagnostic tests for influenza are shown in table 1 [23–26]. Of the available laboratory tests, RT-PCR is preferred for its speed, sensitivity, and specificity but is not currently available to a majority of clinicians. In Toronto, most hospital laboratories provide EIA testing. On average, EIA sensitivity is 50%–70%, compared with that for viral culture, and specificity is ~95%, depending on the laboratory and the test. However, the use of viral culture as the gold standard for sensitivity may be outdated. Table 2 compares the sensitivity of viral culture to that of RT-PCR [26–29]. The proportion of virus detected by culture in the different studies ranges from 50% to 90%, or ~70% for purposes of estimation. Thus, actual rapid EIA sensitivity is not 60% but is closer to 60% of 70%, which is ~42%. Other rapid tests with sensitivities ranging from 24% to 90%, relative to that for viral culture, share the same limitation [24]. The lack of a rapid and sensitive clinical diagnostic test for influenza is problematic. Although a number

Table 2. Likelihood of influenza virus detection by culture versus by PCR, with laboratory-confirmed influenza.

	No. (%) of samples		
Study	Total	Positive result by culture	Positive result by RT-PCR
Zambon et al. [27][a]	791	579 (73)	730 (92)
Pérez-Ruiz et al. [26][b]	152	119 (78)	131 (86)
Jennings et al. [28][a]	27	25 (93)	27 (100)
McGeer et al. [29][c]	34	21 (62)	34 (100)

[a] Positive samples identified by culture, PCR, or serology.
[b] Positive samples identified by PCR, culture, or direct fluorescent antigen assay.
[c] Positive samples identified by direct antigen testing (EIA or direct fluorescent antigen assay), culture, or PCR.

Table 3. Prevalence of influenza in case series of patients admitted to a hospital.

Hospitalized population, years	Prevalence of influenza, %	Diagnostic method(s)
Adults aged >65 years with respiratory infection, COPD, asthma, CHF, or viral illness[a,b]		
1999–2000	20	Culture, RT-PCR, and serology
2000–2001	2	Culture, RT-PCR, and serology
2001–2002	20	Culture, RT-PCR, and serology
2002–2003	6	Culture, RT-PCR, and serology
Adults with CAP, 1999–2000[c]	10	DFA, culture, RT-PCR, and serology
Patients with pneumonia or febrile respiratory illness admitted to an ICU during influenza season[d]		
2006–2007	1.2	DFA or EIA
2006–2007	2.8	Culture
2006–2007	6.0	PCR

NOTE. CAP, community-acquired pneumonia; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DFA, direct fluorescent antigen assay; ICU, intensive care unit.

[a] Falsey et al. [11].
[b] For the period November through April.
[c] Jennings et al. [28].
[d] McGeer et al. [15, 29].

of new and sensitive molecular techniques are being investigated, such tests will not become available for several years [30].

WEIGHING THE BENEFITS AND LIMITATIONS OF DIAGNOSTIC TESTING VERSUS EMPIRICAL THERAPY

Given the limitations of currently available diagnostic tests, empirical therapy is an option worth considering. Empirical therapy has the advantage of offering earlier treatment, which is likely to be more effective. It also may be the most cost-effective option, because laboratory testing actually may be more expensive than therapy (which costs ~$60 for a 5-day course). However, empirical therapy has the disadvantage of resulting in many more patients receiving treatment than actually have influenza. The prevalence of influenza in some recent patient cohorts is shown in table 3 [11, 15, 28, 29]. These studies looked at data from different groups of patients, in different years and at different times of year. Seasonal and year-to-year variations in the underlying incidence of influenza explain much of the difference observed. Overall, these studies suggest that, during most influenza seasons, 10%–15% of adult patients with pneumonia and/or febrile respiratory illness are likely to have influenza virus infection [29]. Thus, empirical therapy will result in 5–15 patients without influenza receiving treatment for every patient with influenza. This ratio is similar to that reported in recommendations for the use of empirical therapy for atypical bacterial infection in pneumonia and, thus, is worthy of consideration [31, 32].

On the other hand, the testing of patients provides information to clinicians that enables more-directed therapy. Evidence from both pediatric and adult studies indicates that testing for influenza results in reduced use of antibiotics and possibly reduced use of some other diagnostic tests [12, 33, 34]. Such observations suggest that the information is immediately useful to clinicians. However, false-positive test results occur and may mislead clinicians. The benefits and limitations of laboratory diagnostic testing versus empirical antiviral therapy for influenza are summarized in table 4.

CONCLUSION

As a practical matter, each infectious disease specialist must weigh the uncertainties of diagnosis and the effects of treatment to determine the best option for each patient under his or her care. The accumulating evidence suggests that, for patients with

Table 4. Benefits and limitations of diagnostic testing versus empirical antiviral therapy.

Diagnostic testing
Reduces antibiotic use
Reduces hospital admissions
Misses 30%–65% of cases if PCR is not used
Results in later treatment, which may not be as effective
Empirical therapy
Ensures timely treatment for patients with influenza
Cost approximately the same as the cost of culture or RT-PCR
Results in treatment for 5–15 patients without influenza for each patient with influenza

NOTE. Statements are supported by Falsey et al. [12], Bonner et al. [33], and Democratis et al. [34].

acute cardiorespiratory illness requiring hospital admission during influenza season, consideration should be given to either prompt laboratory diagnostic testing and treatment for influenza virus–infected patients or empirical antiviral therapy for influenza. The best choice is made on a case-by-case basis and depends on the severity of illness in the patient being admitted (since earlier therapy for pneumonia is more effective), the probability of influenza virus infection in the individual patient, and the sensitivity of the rapid diagnostic tests available. It is hoped that the introduction of RT-PCR testing into hospital laboratories and the accumulating information from cohort studies and trials of antiviral therapy among severely ill patients with influenza will soon result in a better understanding of effective diagnosis and therapy and in improved outcomes for severely ill patients.

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