Molecular point-of-care testing for influenza to improve early neuraminidase inhibitor treatment and outcomes in hospitalised adults

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TO THE EDITOR -

We read with great interest the findings by Katzen *et al.* suggesting that neuraminidase inhibitor (NAI) treatment of influenza infection in hospitalised adults, administered early (<6 hours) after admission, is associated with reduced length of hospital stay and mortality [1]. This is the first study to evaluate the effect of timing of NAI use from admission rather than from onset of symptoms and is highly relevant to clinical practice as most patient with seasonal influenza present after 48 hours of symptoms duration - the time period during which NAI use is thought to be most effective. The effect of timing, from admission to administration, on NAI effects is scientifically credible and mirrors the finding in antibiotic treatment of severe bacterial infection which has led to widespread use of early antibiotic therapy for suspected sepsis. The authors suggest that in line with national guidelines [2,3] promoting the early liberal use of empirical NAI (i.e. used presumptively prior to the results of laboratory testing) in patients with suspected influenza, can achieve this goal.

However, as their study demonstrates, adherence to guidelines advocating empirical NAI use is sub-optimal and NAIs are often withheld in patients with suspected influenza. In addition, clinician judgement has been shown to be poor at discriminating which patients have influenza and which patients do not (even during periods of peak transmission) thereby missing treatment opportunities in patients with influenza, and causing unintended NAI exposure in those without [4]. Concerns have been raised about unnecessary patient exposure to NAI treatment in patients who do not have influenza virus infection because of adverse events including nausea and vomiting [5]. Therefore a strategy enabling early pathogen-directed therapy, rather than relying on undirected empirical treatment, is clearly desirable.

New molecular test platforms that generate rapid results, are easy to use, have accuracy comparable to laboratory PCR, and can be deployed as point-of-care tests (POCT) for influenza in hospitals, could achieve this aim [6]. In our pragmatic, randomised controlled trial of routine molecular POCT for respiratory viruses, versus standard care, in adults presenting to hospital with acute respiratory illness [7] we showed a median turnaround time for result of 1.6 hours with POCT compared to around 30 hours for laboratory RT-PCR ($p<0.0001$). In the POCT group 82% of all NAI use occurred in influenza positive patient versus 47% in the control group ($p=0.0001$) and the median number of doses of oseltamivir in those patients who received an NAI but did not have influenza was 1 doses in the POCT group compared with 5 doses (2.5 days) in the control group ($p=0.0003$) [7]. In addition 91% of influenza-positive patients in the POCT group received a NAI compared with only 65% in the control group ($p=0.0026$). POCT was also associated with higher rates of early hospital discharge and

early discontinuation of antibiotics and *post hoc* analysis demonstrated that this was optimized with a turnaround time of <1.6 hours, compared with longer turnaround times. [8]

The study by Katzen *et al*. reinforces the importance of early NAI use in hospitalised adults with influenza to improve patient outcomes. Our work shows that this can be achieved with a routine molecular POCT strategy, which unlike the current paradigm of empirical NAI use, use allows early pathogen-directed therapy and avoids unnecessary drug exposure in influenza negative patients. If further studies confirm these clinical benefits and demonstrate the cost effectiveness of this strategy, molecular POC testing for influenza should replace empirical NAI use in hospitals.

Disclaimers

The views expressed in the submitted article are the authors' own and not an official position of the institutions to which they belong.

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Potential conflicts of interest

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References

1. Katzen J, Kohn R, Houk JL, Ison MG. Early oseltamivir after hospital admission is associated with shortened hospitalization: A five-year analysis of oseltamivir timing and clinical outcomes. Clin Infect Dis **2018**. [Epub ahead of print].
2. Centers for Disease Control and Prevention. Influenza guidelines. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. [Last accessed 24th October 2018].
3. Public Health England. PHE guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza. Version 8.0, September **2017**. https://www.gov.uk/government/publications/influenza-treatment-and-prophylaxis-using-anti-viral-agents. [Last accessed 24th October 2018].
4. Dugas AF, Valsamakis A, Atreya MR, et al. Am J Emerg Med **2015**;33(6):770-5.
5. Kelly H, Cowling BJ. Influenza: the rational use of oseltamivir. Lancet **2015**;385(9979):1700-1702.
6. Brendish NJ, Schiff HF, Clark TW. Point-of-care testing for respiratory viruses in adults: The current landscape and future potential. J Infect **2015**;71(5):501-10.
7. Brendish NJ, Malachira AK, Armstrong L, et al. Routine molecular point-of-care testing for respiratory viruses in adults presenting to hospital with acute respiratory illness (ResPOC): a pragmatic, open-label, randomised controlled trial. Lancet Respir Med **2017**;5(5):401-411.
8. Brendish NJ, Malachira AK, Beard KR, et al. Impact of turnaround time on outcome with point-of-care testing for respiratory viruses: a post hoc analysis from a randomised controlled trial. Eur Respir J **2018**;52(2). pii: 1800555.