Standard guidelines for the clinical management of severe influenza virus infections
Initial Guideline Development Group (GDG) Meeting
WHO HQ, Geneva, 14-16 November 2017

Conclusions

In response to human infections with avian influenza A(H5N1) and 2009 pandemic influenza A(H1N1)pdm09 viruses, WHO published a series of "rapid advice" (emergency) guidelines for the clinical management of influenza virus infection. Guidelines issued in 2010[1] replaced recommendations published in 2009 and focused on updates in pharmacological treatment of influenza. At the time, attempts were also made to expand the scope of the guidance to seasonal, pandemic, and zoonotic influenza virus infections.

Considerable data have since become available, and new threats of avian influenza A viruses (H7N9), (H5N6) and other subtypes, as well as swine influenza A viruses (variant viruses), have emerged. WHO is therefore developing new consolidated guidelines for the clinical management of severe illness from influenza virus infections and of individuals at high risk of severe illness; the guidelines will apply to seasonal, pandemic, and zoonotic influenza across all resource settings. In October 2017, the WHO Guidelines Review Committee (GRC) approved the proposed plan for guideline development, which will apply the GRADE methodology to ensure preparation of evidence-based recommendations.[2]

WHO convened an initial meeting of the Guideline Development Group (GDG) at WHO headquarters in Geneva on 14-16 November 2017. The GDG co-chairs are clinicians with expertise in guideline methodology; GDG members include specialists in public health, pharmacology, pulmonary medicine, intensive care medicine, internal medicine, paediatric medicine, medical education, virology, and infectious diseases. The multidisciplinary composition of the membership reflects the challenges of developing robust guidelines for the clinical management of influenza that consider viral, host, and epidemiologic factors affecting disease severity and patient outcomes. Effective management of influenza patients also has broad considerations beyond clinical medicine, including public health practice, social and economic policy, and economic development. Consequently, GDG members were selected from a spectrum of high-, middle-, and low-income countries and with representation from all WHO Regions. All members underwent a conflict-of-interest assessment by the WHO legal and ethical teams; individuals with potential conflicts were excluded either from the GDG or from decision-making activities, depending on the nature of the identified conflict. The members' biographies were published for public review prior to the initial meeting.[3]

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[1] WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses see: http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/
2 See http://www.who.int/publications/guidelines/guidelines_review_committee/en/
3 See http://www.who.int/influenza/resources/documents/clinical_management_guidance_group/en/

The GDG's deliberations focused on six main topics: 1) specification of critical and important outcomes of interest, 2) definition of severe illness from influenza virus infection, 3) antiviral medications, 4) adjunctive pharmacologic therapies, 5) supportive therapies, and 6) diagnostic testing. Discussions yielded the following decisions and action steps, which will facilitate subsequent development of recommendations.

- Outcomes of interest -- The GDG defined four outcomes of critical concern: mortality, progression of disease severity to hospitalisation or ICU admission, development of complications requiring medical intervention, and transmission of influenza viruses to others. The GDG defined four outcomes as important but not critical: length of hospital stay, length of mechanical ventilation, development of resistance to antiviral medications, and days off work or school.

- Definition of severe illness from influenza virus infection -- The GDG determined that the need for hospitalisation (when available) characterised severe influenza. To ensure a definition compatible across all settings, however, including those in which hospitalisation may not be an option, the GDG identified sources of prior guidance that they will use to come to consensus on the signs and symptoms characterising a clinical diagnosis of severe influenza (e.g., WHO Integrated Management of Childhood Illness [IMCI][4]).

- Antiviral medications -- A systematic review has been commissioned of observational studies of antiviral medications (i.e., oseltamivir and zanamivir) that are widely available for the treatment of influenza in the populations specified by the GDG. This review of observational studies is underway and will be refined based on GDG discussions. The GDG also prioritised an independent analysis of data from randomised controlled trials of antiviral treatments to address contradictory conclusions from published analyses. The review team will be mandated to interact with the authors of prior reviews with discordant conclusions to ensure a full review of all relevant evidence using rigorous and transparent methods.

- Adjunctive therapies -- The GDG will review evidence of patient-relevant outcomes associated with potential benefits and harms of selected adjunctive pharmacologic therapies (e.g., macrolide antibiotics, corticosteroids, immunoglobulins, and convalescent plasma/serum).

- Supportive therapies -- The GDG reviewed the Surviving Sepsis Guidelines[5] for adult patients with respect to the supportive management of patients with severe influenza. The methodologic quality of the guidelines was formally assessed as high quality based on

[4] See http://apps.who.int/iris/bitstream/handle/10665/81170/9789241548373_eng.pdf?sequence=1
[5] See http://www.survivingsepsis.org/Guidelines/Pages/default.aspx

Institute of Medicine criteria,[6] and the GDG agreed that these guidelines should be used. However, the GDG noted that some Surviving Sepsis Guidelines may not be applicable to influenza and that the Guidelines might not include consideration of all issues specific to patients with influenza virus infection. GDG members will therefore review the guidelines and proceed as necessary if such issues are identified. Pending publication of the paediatric version of the Surviving Sepsis Guidelines, paediatric patients with severe illness due to influenza virus infection may be treated according to existing WHO paediatric Emergency Triage, Assessment and Treatment (ETAT)[7] or IMCI guidance.

- Diagnostic testing -- As part of its mandate to review influenza diagnostic testing strategies, the GDG identified a systematic analysis of best evidence on the accuracy of available tests. The GDG recognised, however, that prior probability of influenza virus infection will vary by circumstance (i.e., off-season, in season, pandemic) and by patient characteristics; optimal testing strategies are therefore likely to differ across these circumstances. The GDG identified alternative strategies such as: not testing for influenza and treating no one for influenza; testing no one and treating all; or testing for influenza and treating on the basis of results from available tests. The GDG noted that, using the GRADE approach, estimates of the impact of alternative testing approaches on patient-important outcomes are required for making recommendations. Since there are no observational studies or randomised trials directly comparing influenza testing strategies, a modelling approach is required. The GDG therefore requested WHO to commission a decision-analytic model that considers the accuracy of available influenza diagnostic tests and that integrates data on the treatment effects of antiviral medications on outcomes important to patients.

The additional work defined by the GDG is expected to be available in 2018, at which time the GDG will reconvene to generate its recommendations. In the interim, the 2010 guidelines continue to be the reference for decision-making.

[6] See http://nationalacademies.org/hmd/~/media/Files/Report%20Files/2011/Clinical-Practice-Guidelines-We-Can-Trust/Clinical%20Practice%20Guidelines%202011%20Insert.pdf
[7] See http://www.who.int/maternal_child_adolescent/documents/paediatric-emergency-triage-update/en/