Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Influenza Antiviral Domain

Platform foR European Preparedness Against (Re-)emerging Epidemics
PREPARE

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CCCTG
Canadian Critical Care Trials Group

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Background

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- Seasonal influenza is estimated to cause approximately 300,000 to 650,000 deaths worldwide annually
- Currently, recommended antiviral agents for influenza (**oseltamivir**) have not been studied in placebo controlled randomised trials to demonstrate survival benefit in hospitalized patients with influenza
- Widely used in clinical practice

Background

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- **Baloxavir** is a newly approved antiviral with evidence of benefit in outpatients on time-to-symptom resolution, but no evidence of benefit in inpatients
- Whether it has value by itself, or in combination with oseltamivir, in inpatients is an open question

Influenza Antiviral Interventions

REMAP-CAP

- No antiviral agents active against influenza
- **5-days of oseltamivir***
- 10-days of oseltamivir
- Baloxavir
- Baloxavir + 5 days oseltamivir
- Baloxavir + 10 days oseltamivir

Influenza Antiviral Interventions

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- **5-days of oseltamivir**
- For continuity across regions, important for all sites to participate in this intervention

Eligibility

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Inclusion Criteria

- Influenza infection is confirmed by microbiological testing

(*this has been changed from the previous version to more explicitly target patients with influenza*)

Eligibility

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Exclusion Criteria

- Moderate state: More than 96 hours since hospital admission
- Severe: More than 48 hours since ICU admission
- Already received 2 doses of oseltamivir or a dose of baloxavir
- Clinician does not feel best interests in participating
- Known hypersensitivity to agents
- Pregnancy (baloxavir interventions only)

Influenza Antiviral Interventions

REMAP-CAP

- No antiviral agents active against influenza
- **5-days of oseltamivir***
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No antiviral intervention

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- Do not prescribe any antiviral active against influenza, including oseltamivir
- Withholding of antiviral agents is to continue until the end of study day 28 or hospital discharge, whichever occurs first
- Administration of antiviral agents by ward staff after ICU discharge will not be considered a protocol deviation

Five-day oseltamivir intervention

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- Prescribe a 5-day course of oseltamivir commencing immediately after randomization.
  - 10 doses with BD administration
- Dosing of oseltamivir is determined by the treating clinician
  - The standard dose for adult patients is 75mg enterally BD
- Cease after 5 days or hospital discharge, whichever occurs first

Ten-day oseltamivir intervention

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- Prescribe a 10-day course of oseltamivir commencing immediately after randomization.
  - 20 doses with BD administration
- Dosing of oseltamivir is determined by the treating clinician
  - The standard dose for adult patients is 75mg enterally BD
- Cease after 10 days or hospital discharge, whichever occurs first

Baloxavir

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- Given on Day 1 & 4
- Can give an added dose on day 7 if the treating clinician feels it is clinically indicated

Agent	Weight < 40 kg	Weight 40-80 kg	Weight > 80 kg
Baloxavir	2 mg/kg on days 1 and 4 to max of 40 mg	40 mg on days 1 and 4	80 mg on days 1 and 4

Baloxavir + Oseltamivir

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- Baloxavir + 5 days oseltamivir
- Baloxavir + 10 days oseltamivir

Randomization with delayed reveal

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- In patients with test results pending, can randomize with ‘Delayed Reveal’ when test results are available.

End-point

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Primary endpoint

- As defined in the Core Protocol

Drugs

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- Can use hospital stock of oseltamivir
- Baloxavir to be supplied (supply agreements pending from Roche), or can use hospital stock, if available

Questions?

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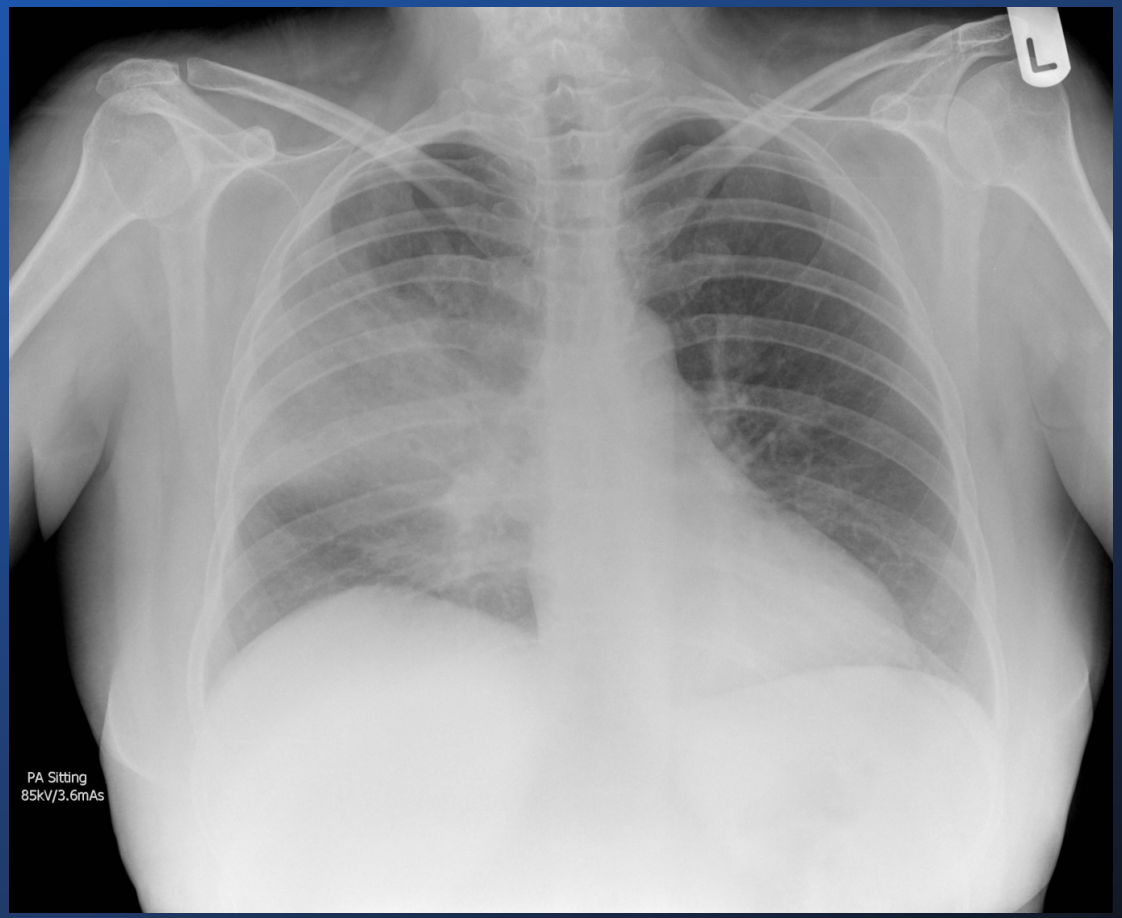

Randomized, **E**mbedded, **M**ultifactorial, **A**daptive **P**latform
For **C**ommunity-**A**cquired **P**neumonia