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

Antibiotic Domain

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

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CCCTG
Canadian Critical Care Trials Group

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anzic research centre

Background: Antibiotic Domain

REMAP-CAP

- In the majority of cases of CAP, no microbiological diagnosis is made.
- Empiric antibiotic therapy is almost always commenced before a microbiological diagnosis is available
- A respiratory quinolone (moxifloxacin or levofloxacin) or combination antimicrobial therapy with a beta-lactam and macrolide are both recommended treatment for CAP in national and international guidelines.
- The use of these therapies is associated with mortality benefit in CAP, however whether one of these options results in lower mortality than the other remains unclear

Antibiotic Domain Interventions

REMAP-CAP

- IV Ceftriaxone plus macrolide
- IV Piperacillin-tazobactam plus macrolide
- IV Amoxicillin-clavulanate plus macrolide
- IV Moxifloxacin (or Levofloxacin)

- IV Ceftaroline plus macrolide (included in approved protocol but not available at launch)

Eligibility

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Exclusion criteria:

- Received >48h of IV antibiotic treatment for this illness
- More than 24h has elapsed since ICU admission
- A specific antibiotic is indicated
  - E.g. suspected or proven concomitant infection, suspected or proven infection with resistant bacteria, febrile neutropenia or immune suppression, melioidosis, or sufficient microbiological information to guide antibacterial therapy

Eligibility

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Exclusion criteria:

- Treating clinician believes that participation is not in the patient's best interest

Intervention exclusion criteria:

- Known hypersensitivity to an intervention at the site
- Patients must be eligible for at least two interventions to be randomised into the domain

Interventions

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- Antibiotic dose and frequency is at the discretion of the treating clinician
  - What you or local guidelines would recommend
  - Adjust for weight and clearance as you would normally do
  - Recommended doses in protocol, including adjustment for renal function provided

Recommended antibiotic dose and frequency

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The doses specified are recommended minimum doses. These should be modified in accordance with local guidelines and/or practice.

Normal Renal Function:

	Amoxicillin-clavulanate (Augmentin)	Ceftaroline	Ceftriaxone	Levofloxacin	Moxifloxacin	Piperacillin-tazobactam (Tazocin)
Minimum dose	1.2 g	600 mg	1 g	750 mg	400 mg	4.5 g
Route of administration	Intravenous	Intravenous	Intravenous	Intravenous	Intravenous	Intravenous
Frequency	8 hourly	12 hourly	24 hourly	24 hourly	24 hourly	8 hourly
Plus Macrolide (refer to Section 3)	YES	YES	YES	NO	NO	YES

Abnormal Renal Function:

Agent	eGFR >50 ml/min	eGFR10-50 ml/min	eGFR <10	Continuous Veno-Venous Hemofiltration (CVVHF)
Amoxicillin-clavulanate	1.2g IV q8h	1.2g IV q8h	1.2g IV q12h	1.2g IV q8h
Ceftaroline	600mg IV q12h	400mg IV q12h	200mg IV q12h	400mg IV q12h
Ceftriaxone	1g-2g IV daily	1g-2g IV daily	1g IV daily	1g IV daily
Levofloxacin	750mg IV q24h	(eGFR 20-50) 750mg IV load, 750mg IV q48h	(eGFR<20) 750mg IV load, 500mg IV q48hr	750mg IV load, 500mg IV q48hr
Moxifloxacin	400mg IV q24h	400mg IV q24h	400mg IV q24h	400mg IV q24h
Piperacillin-tazobactam	4.5g IV q6h – q8h	(eGFR 20-40) 4.5g IV q8h	(eGFR<20) 4.5g IV q12h	4.5g IV q8h

Interventions

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Macrolide Administration

- If allocated to any of beta-lactam arms **must** also **receive a macrolide**
- Site's preferred macrolide
- IV (at least initially) preferred over enteral
- Azithromycin preferred over others. Erythromycin is permitted but excludes from macrolide domain

Interventions

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Macrolide preference:

1. IV azithromycin
2. IV clarithromycin
3. Enteral azithromycin
4. Enteral azithromycin or roxithromycin
5. IV or enteral erythromycin

Interventions

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Duration of therapy

- As determined by treating clinician
- Change to any antibiotic if microbiological diagnosis made
- Switch from IV to enteral / oral when clinically appropriate
- Cease antibiotics if alternative diagnosis made
- Cease antibiotics when sufficient clinical response has occurred

Interventions

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Changes to empiric antibiotic therapy:

Treating clinicians need to document (in the patient's medical record) the reason for **ANY** change to antibiotic therapy while the patient was in the ICU.

Concomitant Care

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Permitted additional antibiotics:

- If suspected MRSA, add vancomycin, linezolid or other antibacterial active against MRSA (but not ceftaroline)
- Other beta-lactams, carbapenems, monobactams or quinolones not permitted (unless based on results of microbiological tests)
- If allocated to moxifloxacin or levofloxacin, addition of macrolide, beta-lactam, carbapenem, or monobactam not permitted
- Additional aminoglycoside, clindamycin, cotrimoxazole all permitted
- If immune-suppressed should have been excluded from domain
- If site has resistance pattern for CAP organisms that is not appropriate for at least two antibiotic interventions, site should not participate in the domain

End-point

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Primary endpoint

- All-cause mortality at day 90

Questions?

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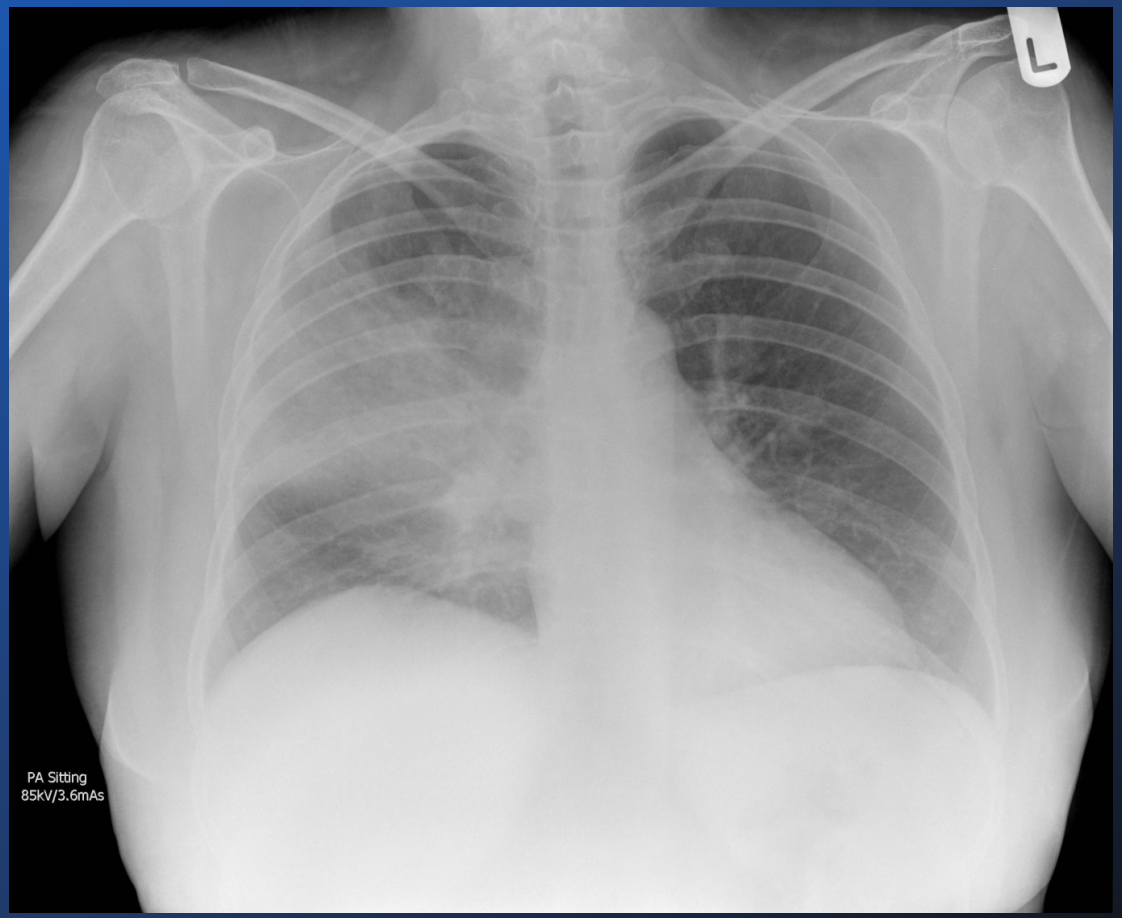

Randomized, **E**mbedded, **M**ultifactorial, **A**daptive **P**latform
For **C**ommunity-**A**cquired **P**neumonia