CAP-START: Beta-lactam vs. beta-lactam plus macrolide or fluoroquinolone in Adults with Community-Acquired Pneumonia [1,2]

Community-Acquired Pneumonia – Study on the initial Treatment with Antibiotics of lower Respiratory Tract infections

BOTTOM LINE

- In **CAP-START**, patients from the Netherlands with community-acquired pneumonia (CAP) (median CURB-65 score of 1 [IQR 1-2], mean Pneumonia Severity Index (PSI) ~ 85 [SD ~28]) who were admitted to non-ICU hospital ward:
  - 90-day **mortality**: beta-lactam monotherapy was **non-inferior** to the combination of beta-lactam + macrolide
  - Median **length of hospital stay**, and major & minor **complications** were **similar** between three treatment strategies (beta-lactam, beta-lactam + macrolide, fluoroquinolone)
- The need for atypical coverage (e.g. with a macrolide) in CAP has been questioned, particularly for outpatients. **CAP-START** was a hospital-based study, but the CURB-65 & PSI scores would not have resulted in a hospital admission in Canada (i.e. admit to hospital if CURB-65 ≥2 or PSI ≥91).[3,4] As such, we have reviewed the study from the context of an outpatient setting.
- Current Canadian CAP guidelines/references recommend *S.pneumoniae* & atypical coverage for outpatients with comorbid factors or for hospitalized CAP.[3,5] Recommendations for atypical coverage vary for outpatient CAP with no comorbid factors see below.[3,5]
- For outpatients, if beta-lactam monotherapy is started empirically, consider adding a macrolide for atypical coverage if the patient worsens after 2-3 days. See RxFiles Community-Acquired Pneumonia for additional information.

BACKGROUND

- *Streptococcus pneumoniae* is the most common pathogen to cause CAP, even in patients with comorbidities.
- Atypical pathogens (i.e. *Mycoplasma pneumoniae*, *Chlamydophilia pneumoniae*, *Legionella*) can also cause CAP, and the prevalence of atypical organisms in Canada is estimated to be 9-33%.[3,4,6,7] Estimates vary widely, & may depend on demographics.
- **Current Canadian guidelines/references recommend the following for the treatment of CAP:**
  - **-Outpatient CAP with no comorbid factors**:
    - 2013 Anti-infective Guidelines for Community-acquired Infections:[5] beta-lactam (i.e. amoxicillin) **or** an antibiotic with atypical coverage (i.e. macrolide [e.g. azithromycin or clarithromycin] or doxycycline)
    - Bugs & Drugs app accessed Dec 2016:[3] doxycycline ± amoxicillin, **or** beta-lactam (i.e. amoxicillin) + macrolide (i.e. azithromycin or clarithromycin)
  - **-Outpatient CAP with comorbid factors, or Hospitalized CAP:**[3,5]
    - beta-lactam (e.g. amoxicillin or amoxicillin/clavulanate) plus an antibiotic with atypical coverage (i.e. macrolide or doxycycline), or
    - Moxifloxacin or levofloxacin monotherapy, **which should not be first line**.
      Reserve these agents for suspected Gram- negative organisms or when there are contraindications to the other options. Concerns with ↑ resistance rates & harms, including recent black box warnings, have made FQs less favourable.[8]
  - In **Saskatchewan**, doxycycline has good activity against both *S. pneumoniae* & atypical pathogens, and therefore is a reasonable first choice as monotherapy for adult outpatients with or without comorbidities.
  - Macrolide monotherapy is no longer recommended because of decreased susceptibility of *S. pneumoniae.*
- The evidence to support atypical coverage is limited, & prior to **CAP-START**, was based on observational studies.
- A narrower spectrum strategy, such as beta-lactam monotherapy, would reduce adverse events, antimicrobial resistance & cost.[9]
- **CAP-START** was designed to test the non-inferiority of beta-lactam monotherapy to current empiric therapy for 90-day mortality.

TRIAL BACKGROUND [1, 10]

DESIGN: Cluster-randomized, crossover, non-inferiority, multi-centre in the Netherlands (n=7 hospitals), pragmatic trial, February 2011 - August 2013, intention-to-treat (ITT) analysis, non-inferiority margin of 3% and two-sided 90% confidence interval.
Funding: Netherlands Organization for Health and Research Development (this group is the responsibility of the Dutch Ministry).

INTERVENTION: beta-lactam vs. beta-lactam + macrolide or FQ

- each strategy was used for 4 months, and implemented twice over the study period (unless there was a medical reason not to, such as adverse effects, or antibiotic step-down)
- the strategy order was randomized for each hospital, and used consecutively, without washout periods
- **Beta-lactam**: amoxicillin, amoxicillin-clavulanate, or a 3rd generation cephalosporin. Penicillin was not allowed as empirical tx.
- **Beta-lactam + macrolide**: beta-lactam (including penicillin) + azithromycin, erythromycin or clarithromycin.
- **FQ**: moxifloxacin or levofloxacin.

INCLUSION: ≥18 years old with clinically suspected CAP requiring antibiotic treatment & hospitalization on a non-ICU ward. Clinically suspected CAP met ≥2 criteria: cough, purulent sputum or change in character; >38°C or <36.1°C; ausculatory findings consistent with pneumonia, ± evidence of pulmonary consolidation; leukocytosis; C-reactive protein >3x upper limit of normal; dyspnea, tachypnea, or hypoxemia; new or increased infiltrate on CXR or CT.

EXCLUSION: Cystic fibrosis, obvious non-respiratory source of infxn, recent hospitalization for >48hr in the last 2wks, LTC residents

POPULATION at baseline: n=2283, ~58% ♂. Baseline characteristics were fairly similar between treatment strategies.

TABLE 1: Baseline characteristics continued on next page

	BETA-LACTAM n=656	BETA-LACTAM + MACROLIDE n=739	FLUOROQUINOLONE n=888
Age (median, IQR)	70 yrs (60-79)	70 yrs (59-80)	71 yrs (59-79)
Pneumonia severity index score (mean±SD)	84.6 ± 29	84.8 ± 27.8	85.4 ± 28.5
CURB-65 (median) (IQR)	1 (1-2)	1 (1-2)	1 (1-2)
Current smoker	17.4% (109/627)	21.3% (154/723)	22.5% (196/872)
Past smoker	60.4% (379/627)	55% (398/723)	56.2% (490/872)

TABLE 1: Baseline characteristics continued from previous page	BETA-LACTAM n=656	BETA-LACTAM + MACROLIDE n=739	FLUOROQUINOLONE n=888
Cardiovascular disease	23.3% (n=153)	20.8% (n=154)	19.4% (n=172)
COPD or asthma	36.9% (n=260)	38% (n=281)	42.5% (n=377)
Diabetes	18% (n=118)	13.7% (n=101)	18.1% (n=161)
Cancer	16.2% (n=106)	16.8% (n=124)	17% (n=151)
HIV/AIDS	0.5% (n=3)	0.8% (n=6)	0.7% (n=6)
Receiving immunosuppressive therapy	9% (n=59)	7.7% (n=57)	10.5% (n=93)
Received influenza vaccination	72.6% (453/624)	66.6% (466/700)	67.5% (572/847)
Received pneumococcal polysaccharide vaccine (23-valent)	7.7% (16/594)	2.7% (18/671)	1.6% (13/822)
Received pneumococcal conjugate vaccine (13-valent)	2.9% (19/656)	0.9% (7/739)	1.1% (10/888)
Received antibiotics before admission	34.4% (219/637)	31.5% (227/721)	34.7% (303/873)
Blood culture obtained	77.4% (n=506)	75.6% (559)	75.5% (670)
Sputum culture obtained	46.6% (n=306)	47% (n=347)	43.9% (n=390)
Pneumococcal urinary antigen test performed	76.8% (n=504)	78.8% (n=582)	80.1% (n=711)
Legionella urinary antigen test performed	75% (n=492)	77.7% (n=547)	75.2% (n=668)
Radiologically confirmed CAP	77.1% (n=506)	76.6% (n=566)	74.9% (n=665)

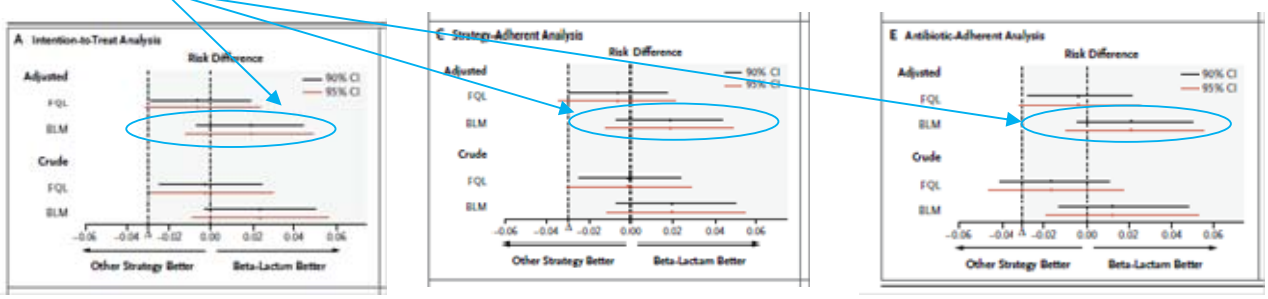
RESULTS

follow-up: 90-days

TABLE 2: EFFICACY/SAFETY BETA-LACTAM NONINFERIOR, 90% CONFIDENCE INTERVAL	BETA-LACTAM n=656	BETA-LACTAM + MACROLIDE n=739	FLUOROQUINOLONE n=888	COMMENTS
PRIMARY ENDPOINT				
Crude 90-day mortality (ITT)	9% (59/656)	11.1% (82/739)	8.8% (78/888)	In x-ray confirmed CAP: Microbiological causes were fairly similar among tx groups: - *S. pneumoniae* 15.9% - *H. influenzae* 6.8% - atypicals 2.1% - no pathogen detected in 63.5% (1103/1737) - of the ones tested, resistance for *S. pneumoniae* : beta-lactam (1.1%), 2nd/3rd gen. cephalosporin (0%) macrolide (4.8%) FQ (0%)
Crude 90-day mortality (strategy adherent)	8.5% (52/610)	10.5% (68/650)	8.5% (70/823)	
Crude 90-day mortality (antibiotic adherent)	9% (42/468)	10.2% (55/538)	7.4% (53/712)	
Missing data	0.3% (2/656)	0.1% (1/739)	0.1% (1/888)	
SECONDARY ENDPOINTS				
Median length of hospital stay (IQR)	6 (4-8) days	6 (4-10) days	6 (4-8) days	
Median time receiving IV antibiotics (IQR)	4 (3-5) days	4 (3-5) days	3 (0-4) days	
Major or minor complications (ITT, strategy adherent, antibiotic adherent)	reference	NS vs beta-lactam	NS vs beta-lactam	
OTHER				
Atypical coverage (initial)	26.8% (176/656)	81.3% (601/739)	86.7% (770/888)	
Atypical coverage (during hospitalization)	38.7% (254/656)	83.6% (618/739)	89.6% (796/888)	
Strategy adherent	93% (610/656)	88% (650/739)	92.7% (823/888)	
Antibiotic adherent	71.3% (468/656)	72.8% (538/739)	80.2% (712/888)	
Motivated deviation	21.6% (142/656)	15.2% (112/739)	12.5% (111/888)	
Non-adherent	7% (46/656)	12% (89/739)	7.3% (65/888)	

Strategy adherent: treatment in accordance with the assigned strategy or had deviation from the strategy for medical reasons (i.e., motivated deviation), irrespective of subsequent switches of antibiotic treatment to a non-assigned antibiotic.
Antibiotic adherent: initial treatment with the assigned antibiotic, irrespective of subsequent switches of antibiotic treatment to a non-assigned antibiotic.

- **PRIMARY ENDPOINT** (90-day mortality):
  - The authors concluded that beta-lactam monotherapy was non-inferior to beta-lactam + macrolide or FQ. This was based on an adjusted ITT analysis with a 90% CI.
  - However, using the adjusted analyses with 95% CI, in the ITT and per-protocol analyses, beta-lactam was only non-inferior to beta-lactam + macrolide (and not FQ). 95% CI were presented visually, and not reported numerically.

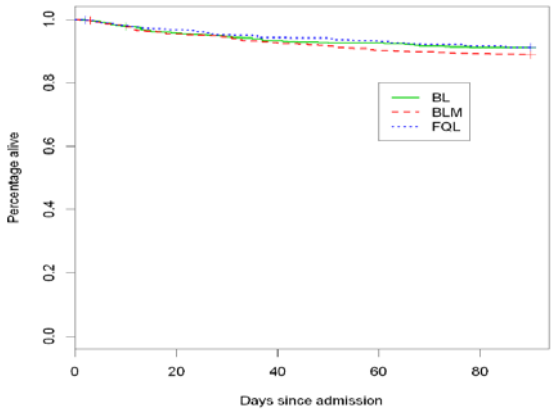


  - Similar analyses were also conducted in those with radiologically confirmed CAP, with results only demonstrating noninferiority of beta-lactam to beta-lactam + macrolide.
  - Non-inferiority of beta-lactams to beta-lactam + macrolide was consistent demonstrated in all analyses.

RESULTS continued

- Top 3 therapies used in hospital within each strategy:
  - **beta-lactam:** amoxicillin/clavulanate (50%), amoxicillin (34.9%), ciprofloxacin (19.6%)
  - **beta-lactam + macrolide:** amoxicillin/clavulanate (47.9%), erythromycin (35.6%), amoxicillin (29.9%)
  - **FQ:** moxifloxacin (60.9%), levofloxacin (23.2%), amoxicillin/clavulanate (14.3%)

Figure S4: Survival curve



Kaplan-Meier curve for the primary endpoint (90-day mortality).
BL=beta-lactam, BLM=beta-lactam + macrolide, FQL=fluoroquinolone

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Cross-over design minimized confounding factors with each hospital implementing all three treatment strategies at least once.
- 90-day mortality, the primary endpoint, was not subject to observation bias.
- Baseline population characteristics were fairly similar between treatment groups.
- Sample size of at least n=650 in each arm was achieved.
- Results were adjusted for patient characteristics and clustering.
- Only 4 patients were lost to follow-up for mortality.
- Processes were implemented to ensure standard case definitions were used, eligible patients were screened, awareness of current strategy, and appropriate follow up.

LIMITATIONS:

- Patients were mostly elderly (median age~70 years old)
- The beta-lactam monotherapy arm had up to 38.7% who also received atypical coverage.
- The beta-lactam + macrolide or the FQ strategy had at least 10.4% who did not receive atypical coverage (had 81.3%-89.6% atypical coverage).
- Doses and duration of antibiotics were not provided.
- Although there was no significant difference between major or minor complications, the study was not powered to show a difference.
- Hospital vs community settings: criteria for CAP hospital admission vary geographically, despite using the same severity of illness scores.

UNCERTAINITIES:

- The authors concluded that the beta-lactam strategy was non-inferior to the other two treatment strategies; however this should be interpreted with caution. Non-inferiority trials results should be interpreted using both ITT and per protocol analyses.[11] The data show that only beta-lactams are non-inferior to beta-lactams + macrolide; it cannot be concluded that beta-lactams are non-inferior to FQ.
- The hospitalized patients, standard of care, and pathogens in the Netherlands may not be generalizable to Canada:
  - The patients in this study may not be as sick as the ones admitted to hospital in Canada. Dutch CAP guidelines thresholds for admission to hospital are lower: outpatient (CURB-65 0-1 or PSI <70).[12] In Canada, recommendation are to admit to hospital if CURB-65 $\geq$2 or PSI $\geq$91, which is higher than the baseline characteristics of this study.[3,4]
  - The median length of stay was 6 days, however the CURB-65 and PSI score would not have triggered hospital admission in Canada. It is unknown what effect hospitalization had on patient outcome.
  - In this study, atypical pathogens were found in 2.1% of patients, whereas in Canada they may account for almost 9-33% of pathogens in CAP.[3,4,6,7]

RxFILES RELATED LINKS

- RxFiles Community-Acquired Pneumonia: http://www.rxfiles.ca/rxfiles/uploads/documents/members/ABX-CAP.pdf
- RxFiles Community-Acquired Pneumonia Empiric Antibiotic Selections (Adult): http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-CAP.pdf
- RxFiles Community-Acquired Pneumonia Severity Assessment Tools: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-CAP-PSI%20only.pdf

♂=male **AIDS**=acquired immunodeficiency syndrome **CAP**=community-acquired pneumonia **CI**=confidence interval **COPD**=chronic obstructive pulmonary disease **CT**=computerized tomography **CURB-65**= confusion, urea, respiratory rate, blood pressure, 65 years old **CXR**=chest x-ray **FQ**=fluoroquinolone **HIV**=human immunodeficiency virus **ICU**=intensive care unit **infxn**=infection **IQR**=interquartile range **ITT**= intention to treat **IV**=intravenous **LTC**=long-term care **NS**=non-statistically significant **PSI**=Pneumonia Severity Index **SD**=standard deviation **tx**=treatment

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