

Interpreting randomized controlled trials

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Postma DF et al.

Antibiotic Treatment Strategies for
Community-Acquired Pneumonia in Adults

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METHODS

In a **cluster-randomized, crossover trial** with strategies rotated in 4-month periods, we tested the noninferiority of the **beta-lactam** strategy to the **beta-lactam–macrolide** and **fluoroquinolone** strategies with respect to **90-day mortality**, in an intention-to-treat analysis, using a noninferiority margin of 3 percentage points and a two-sided 90% confidence interval.

Is the question of interest to my patients?

- Patients
- Intervention
- Comparison
- Outcome

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Internal validity

- Randomization
- Allocation concealment
- Blinding
- Intention to treat analysis

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Inclusion and exclusion criteria

- Inclusion:
 - Patients 18 years of age or older with clinically suspected CAP who required antibiotic treatment and hospitalization in a non-ICU ward.
- Exclusion:
 - cystic fibrosis

3325 Patients were eligible

993 Were assigned to receive beta-lactam

1055 Were assigned to receive beta-lactam-macrolide

1277 Were assigned to receive fluoroquinolone

337 (34.0%) Were excluded
134 (13.5%) Declined to participate
96 (9.7%) Were discharged before consent was given
88 (8.9%) Were unable to give consent
19 (1.9%) Had unknown reason

316 (30.0%) Were excluded
78 (7.4%) Declined to participate
123 (11.7%) Were discharged before consent was given
80 (7.6%) Were unable to give consent
35 (3.3%) Had unknown reason

389 (30.5%) Were excluded
133 (10.4%) Declined to participate
98 (7.7%) Were discharged before consent was given
130 (10.2%) Were unable to give consent
28 (2.2%) Had unknown reason

656 Were included in study

739 Were included in study

888 Were included in study

610 (93.0%) Were in the strategy-adherent population
468 (71.3%) Were in the antibiotic-adherent population
142 (21.6%) Had motivated deviation
46 (7.0%) Were nonadherent

650 (88.0%) Were in the strategy-adherent population
538 (72.8%) Were in the antibiotic-adherent population
112 (15.2%) Had motivated deviation
89 (12.0%) Were nonadherent

823 (92.7%) Were in the strategy-adherent population
712 (80.2%) Were in the antibiotic-adherent population
111 (12.5%) Had motivated deviation
65 (7.3%) Were nonadherent

90-Day mortality
2 (0.3%) Had missing data
59 (9.0%) Were in the intention-to-treat population
52 (8.5%) Were in the strategy-adherent population
42 (9.0%) Were in the antibiotic-adherent population

90-Day mortality
1 (0.1%) Had missing data
82 (11.1%) Were in the intention-to-treat population
68 (10.5%) Were in the strategy-adherent population
55 (10.2%) Were in the antibiotic-adherent population

90-Day mortality
1 (0.1%) Had missing data
78 (8.8%) Were in the intention-to-treat population
70 (8.5%) Were in the strategy-adherent population
53 (7.4%) Were in the antibiotic-adherent population

Table 2. Baseline Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Antibiotic Treatment Strategy		
	Beta-Lactam (N = 656)	Beta-Lactam–Macrolide (N = 739)	Fluoroquinolone (N = 888)
Median age (interquartile range) — yr	70 (60–79)	70 (59–80)	71 (59–79)
Male sex — no. (%)	381 (58.1)	431 (58.3)	505 (56.9)
Median duration of symptoms (interquartile range) — days	3 (1–7)	3 (1–7)	3 (1–7)
Received antibiotics before admission — no./total no. (%)	219/637 (34.4)	227/721 (31.5)	303/873 (34.7)
Current smoker — no./total no. (%)	109/627 (17.4)	154/723 (21.3)	196/872 (22.5)
Past smoker — no./total no. (%)	379/627 (60.4)	398/723 (55.0)	490/872 (56.2)
Received influenza vaccination — no./total no. (%)	453/624 (72.6)	466/700 (66.6)	572/847 (67.5)
Received pneumococcal vaccination — no./total no. (%)			
PPSV23	16/594 (2.7)	18/671 (2.7)	13/822 (1.6)
PCV13	19/656 (2.9)	7/739 (0.9)	10/888 (1.1)
Dependency in ADL — no./total no. (%)†	199/637 (31.2)	200/714 (28.0)	257/870 (29.5)
Had one or more hospital stays in the previous year — no./total no. (%)	271/653 (41.5)	298/722 (41.3)	351/881 (39.8)
Had coexisting condition — no. (%)			
Cardiovascular disease	153 (23.3)	154 (20.8)	172 (19.4)
COPD or asthma	260 (39.6)	281 (38.0)	377 (42.5)
Other chronic pulmonary disease	64 (9.8)	97 (13.1)	61 (6.9)
Diabetes mellitus	118 (18.0)	101 (13.7)	161 (18.1)
Cancer‡	106 (16.2)	124 (16.8)	151 (17.0)
HIV/AIDS — no. (%)	3 (0.5)	6 (0.8)	6 (0.7)
Chronic renal failure or nephrotic syndrome	10 (1.5)	14 (1.9)	7 (0.8)
Receiving immunosuppressive therapy — no. (%)	59 (9.0)	57 (7.7)	93 (10.5)

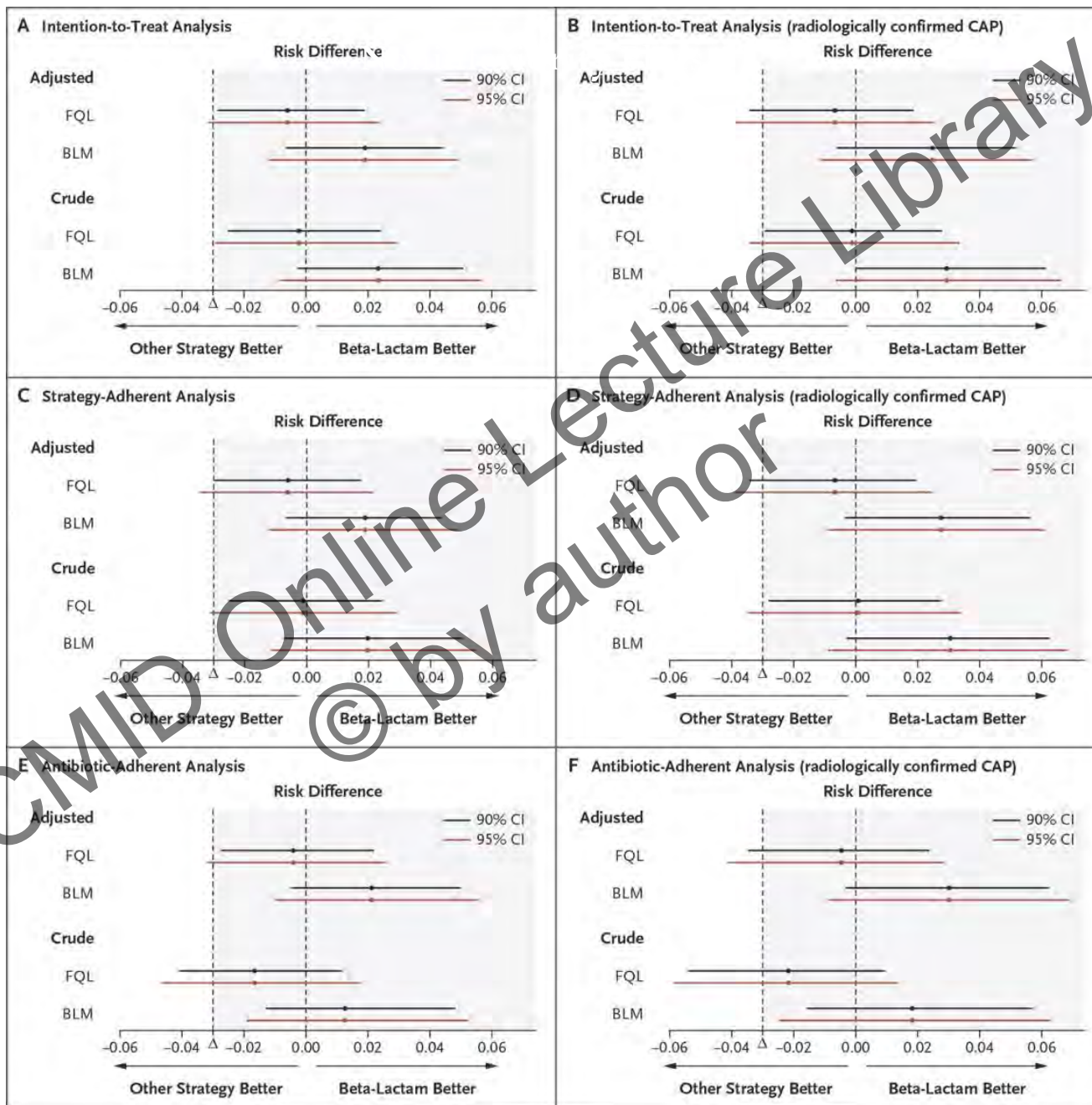
Avni T et al. Journal of the American Geriatric Society
63:233–243, 2015

Table 3. Mean Participant Age in Randomized Controlled Trials (RCTs) and Observational

Pneumonia Classification	RCT	Observational
	Mean \pm SD (n)	
CAP all trials ^a	54.0 \pm 9.6 (23)	66.2 \pm 8.1 (113)
CAP—ambulatory	45 \pm 4.2 (2)	58.2 \pm 17.5 (1)
CAP—ambulatory/hospitalized	45.6 \pm 1.6 (3)	63.7 \pm 7.04 (11)
CAP—hospitalized	55.0 \pm 9.1 (16)	65.3 \pm 8.2 (81)

Crude 90 day mortality rates:

- Beta-lactam : 9.0%
- Beta-lactam—macrolide: 11.1%
- Fluoroquinolone: 8.8%



Secondary outcomes

- The median length of hospital stay was 6 days for all strategies, but the upper quartile was higher during the beta-lactam–macrolide strategy periods
- The median duration of intravenous treatment was 3 days during the fluoroquinolone strategy periods and 4 days during the other strategy periods
- The proportions of patients whose treatment started with oral antibiotics were 27% during the fluoroquinolone strategy periods, as compared with 13% and 10% during the beta-lactam and beta-lactam–macrolide strategy periods, respectively.

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Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by methicillin resistant Staphylococcus aureus: randomised controlled trial.

BMJ 2015;350:h2219

Objective To show non-inferiority of trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of severe infections due to methicillin resistant *Staphylococcus aureus* (MRSA).

Design Parallel, open label, randomised controlled trial.

Setting Four acute care hospitals in Israel.

Participants Adults with severe infections caused by MRSA susceptible to trimethoprim-sulfamethoxazole and vancomycin. Patients with left sided endocarditis, meningitis, chronic haemodialysis, and prolonged neutropenia were excluded.

Primary outcome:

Treatment failure at seven days: a composite of:

- Death
- Persistence of fever or hypotension
- Non-improving Sequential Organ Failure Assessment (SOFA) score
- Persistent bacteraemia on day 7.

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Assessed for eligibility (n=782)

Excluded (n=530):

Did not meet inclusion criteria (n=286):

Treatment with study drugs >48 h (n=164)

Allergy (n=19)

Chronic haemodialysis (n=49)

MRSA resistant to trimethoprim-sulfamethoxazole (n=15)

Left sided endocarditis, meningitis, or leukaemia/BMT (n=28)

Participating in another trial (n=10)

Polymicrobial infection excluded (n=1)

Inability to provide informed consent/no legal guardian (n=165)

Declined to participate (n=79)

Randomised (n=252)

Allocated to trimethoprim-sulfamethoxazole (n=135)

Received allocated intervention (n=135)

Analysed by intention to treat (n=135):

Analysed per protocol (n=110)

Excluded (n=25):

Received <7 days' treatment (n=24)

Post-randomisation exclusion criteria (n=1)

Allocated to vancomycin (n=117)

Received allocated intervention (n=117)

Analysed by intention to treat (n=117):

Analysed per protocol (n=96)

Excluded (n=21):

Received <7 days' treatment (n=16)

Post-randomisation exclusion criteria (n=5)

Results

- The failure rate with trimethoprim-sulfamethoxazole was 51/135 (38%) compared with 32/117 (27%) with vancomycin, and the 95% confidence interval for the difference fell outside the lower limit of the 15% predefined for non-inferiority (-1.2% to 21.5%).
- Restricting the analysis to patients in the vancomycin group whose isolates' minimum inhibitory concentrations were below 2 µg/mL resulted in a larger risk ratio in favour of vancomycin (1.64, 0.99 to 2.68).
- All cause 30 day mortality did not differ significantly between groups.
- Among patients with bacteraemia, mortality was nearly twice as high with trimethoprim-sulfamethoxazole—14/41 (34%) versus 9/50 (18%) with vancomycin (risk ratio 1.90, 0.92 to 3.93).

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**External validity of a randomised
controlled trial on the treatment of severe
infections caused by MRSA**

BMJ Open 2015;5:e008838

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Design

- **Objectives** To assess the external validity of a pragmatic, investigator-initiated RCT on treatment of severe infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), we compared patient characteristics and treatment effect estimates for **patients included in the RCT versus those excluded**.
- **Participants and outcomes** The RCT included hospitalised patients with documented or highly-probable invasive MRSA infections who were randomised to vancomycin versus trimethoprim-sulfamethoxazole (TMP-SMX) treatment, between 2007 and 2014. **A concomitant observational study prospectively included all consecutive patients, between 2008 and 2011, who were excluded from the RCT due to no consent, meningitis, left-sided endocarditis, severe neutropaenia, chronic renal dialysis or treatment with study medications for longer than 48 h.**

Results

- Excluded patients' functional and cognitive performance was significantly poorer than that of included patients.
- Sepsis was more severe among excluded patients.
- Clinical failure occurred in 83/252 (32.9%) versus 175/220 (79.5%) and deaths in 32 (12.7%) versus 64 (29.1%) for included versus excluded patients, $p < 0.001$ for both comparisons.
- Comparing vancomycin to TMP-SMX, in the RCT mortality, was non-significantly lower with vancomycin (OR 0.76, 95% CIs 0.36 to 1.62), while in the observational analysis of excluded patients, mortality was significantly higher with vancomycin (OR 2.63, 1.04 to 6.65), $p = 0.04$ for the difference.

Can I learn from this RCT?

- Is the question important to my patients?
 - Similar conditions/diseases?
 - Intervention of interest?
 - Control of interest?
 - The right outcome?
- Are my patients similar to the ones included in the study?
- Solid internal validity?
- Magnitude of results expressed as absolute measures?