Interpreting randomized controlled trials

Mical Paul
Leonard Leibovici
Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults

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
Internal validity

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

656 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

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

1055 Were assigned to receive beta-lactam–macrolide
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

739 Were included in study
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

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

1277 Were assigned to receive fluoroquinolone
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

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

<table>
<thead>
<tr>
<th>Pneumonia Classification</th>
<th>RCT</th>
<th>Observational</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
</tr>
<tr>
<td>CAP all trials</td>
<td>54.0 ± 9.6 (23)</td>
<td>66.2 ± 8.1 (113)</td>
</tr>
<tr>
<td>CAP—ambulatory</td>
<td>45 ± 4.2 (2)</td>
<td>58.2 ± 17.5 (1)</td>
</tr>
<tr>
<td>CAP—ambulatory/hospitalized</td>
<td>45.6 ± 1.6 (3)</td>
<td>63.7 ± 7.04 (11)</td>
</tr>
<tr>
<td>CAP—hospitalized</td>
<td>55.0 ± 9.1 (16)</td>
<td>65.3 ± 8.2 (81)</td>
</tr>
</tbody>
</table>
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.
Paul M et al.

*Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by meticillin 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 meticillin 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.
Is the question of interest to my patients?

- Patients
- Intervention
- Comparison
- Outcome
Internal validity

- Randomization
- Allocation concealment
- Blinding
- Intention to treat analysis
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).
Paul M et al.

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

*BMJ Open* 2015; 5:e008838
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?