# Critical Appraisal of the Study Using the CASP Checklist

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## 1 Validity of the Study

**Did the study address a clearly focused issue?**

Yes. The study aimed to determine whether **fosfomycin is noninferior to ceftriaxone or meropenem** for the treatment of bacteremic urinary tract infections (bUTIs) caused by multidrug-resistant (*MDR E. coli*).

**Was the assignment of patients to treatments randomized?**

Yes. The study was a **randomized clinical trial (RCT)** where patients were **randomly assigned (1:1)** to receive either **fosfomycin or a comparator (ceftriaxone or meropenem, depending on resistance profile).**

**Were all of the patients who entered the trial properly accounted for at its conclusion?**

Yes. A **CONSORT flowchart** was provided. A total of **161 patients were randomized**, but **143 patients** were included in the **modified intention-to-treat (MITT) analysis**, ensuring transparency in patient attrition.

**Were patients, health workers, and study personnel *blind* to treatment?**

No. The study was **open-label**, meaning investigators and patients were aware of the treatment allocation. However, **two investigators were blinded** for outcome assessment, reducing potential bias.

**Were the study groups similar at the start of the trial?**

Mostly yes. The **fosfomycin and comparator groups** had similar baseline characteristics. However, **recent invasive urinary procedures** were more frequent in the **fosfomycin group (17.1%)** than in the **comparator group (5.5%)**, which might have influenced the results.

**Aside from the experimental intervention, were the groups treated equally?**

Mostly yes. However, **switching to oral therapy** was handled differently between groups: the comparator group had a **wider range of options, including ertapenem**, which may have influenced the outcomes.

# 2 Study Results

**How large was the treatment effect?**

**Primary Outcome: Clinical and Microbiological Cure (CMC) 5-7 days after treatment completion**

- **Fosfomycin Group:** 68.6% (48/70)
- **Comparator Group:** 78.1% (57/73)
- **Risk difference:** -9.4% (1-sided 95% CI: -21.5% to X, $P = .10$) $\rightarrow$ **Did not meet noninferiority criteria**.

**How precise was the estimate of the treatment effect?**

The **confidence interval (CI) crossed the noninferiority margin (-7%)**, indicating that **fosfomycin did not demonstrate noninferiority**. The **P-value of 0.10** suggests a **trend but no statistical significance**.

**Were all clinically important outcomes considered?**

Yes. The study analyzed:

- **Adverse events (AEs):** More **discontinuations due to AEs** with **fosfomycin (8.5%) vs. comparators (0%)**.
- **Mortality: Similar in both groups** (fosfomycin: 3.2%, comparators: 2.8%).
- **Antibiotic resistance: Lower rectal acquisition** of ceftriaxone-resistant or carbapenem-resistant bacteria with **fosfomycin (0%) vs. comparators (23.5%)**.

# 3 Applicability

**Can the results be applied to the local population?**

Yes, with caution. The study was conducted in **22 Spanish hospitals**, making it applicable to **European hospital settings**, especially for treating **MDR *E. coli* infections**.

**Were all clinically important outcomes considered?**

Yes. The study assessed **efficacy, safety, and ecological impact**, providing a comprehensive evaluation of **fosfomycin's role in treating bUTIs**.

**Are the benefits worth the harms and costs?**

Unclear. Fosfomycin **failed to achieve noninferiority** and had **higher adverse event-related discontinuations**. However, it may still be an **alternative for selected patients**, particularly those **at risk of carbapenem-resistant bacterial colonization**.

## 3.1 Overall CASP Conclusion

- The study was **well-designed**, but **fosfomycin failed to demonstrate noninferiority**.
- **Strengths:** Randomized, multicenter, robust methodology, pragmatic design.
- **Limitations:** Open-label design, sample size smaller than planned, potential selection bias.
- **Clinical Implication:** Fosfomycin may still be **an option for specific patients**, but **comparators remain superior** based on this trial.