Critical Appraisal of the Study Using the CASP Checklist

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The manuscript provided is a **randomized clinical trial (RCT)**, so the **CASP checklist for RCTs** will be used to evaluate it. The CASP checklist for RCTs consists of 11 questions that help assess the validity, results, and relevance of the study.

These are the steps of the CASP checklist:

Did the study address a clearly focused research question?

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) Escherichia coli**. The research question is clearly stated in the **Objective** section.

Was the assignment of participants to interventions randomized?

Yes. The study was a **multicenter, randomized, pragmatic, open clinical trial**. Participants were randomly assigned (1:1) to receive either **fosfomycin** or a comparator (**ceftriaxone** or **meropenem**). Randomization was stratified for empirical therapy and ceftriaxone susceptibility.

Were all participants who entered the trial properly accounted for at its conclusion?

Partially. The study provides a detailed flow diagram (Figure) showing the recruitment, randomization, and follow-up of participants. Out of 161 randomized patients, 143 were included in the **modified intention-to-treat (MITT)** population. However, there were some exclusions due to adverse events, missed assessments, and withdrawals, which are explained in the text.

Were participants, staff, and study personnel blind to the intervention?

No. The study was **open-label**, meaning participants, staff, and study personnel were aware of the treatment assignments. This could introduce bias, particularly in subjective outcomes like clinical cure.

Were the groups similar at the start of the trial?

Yes. The baseline characteristics of the participants in the **fosfomycin** and **comparator** groups were similar, as shown in **Table 1**. There were no significant differences in age, sex, comorbidities, or severity of infection between the groups.

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

Yes. Both groups received similar supportive care, and the study protocol allowed for a switch to oral therapy after 4 days of intravenous treatment. The comparator group could switch to oral drugs or parenteral **ertapenem**, depending on susceptibility.

How large was the treatment effect?

The **primary outcome** was **clinical and microbiological cure (CMC)** at 5-7 days after treatment. In the MITT population, **68.6%** of patients in the fosfomycin group and **78.1%** in the comparator group achieved CMC. The **risk difference** was **-9.4 percentage points** (1-sided 95% CI, -21.5 to ∞), which did not meet the noninferiority margin of 7%. This suggests that fosfomycin was **not noninferior** to the comparators.

How precise was the estimate of the treatment effect?

The precision of the treatment effect is reflected in the **confidence intervals (CIs)**. The 1-sided 95% CI for the risk difference (-21.5 to ∞) indicates some uncertainty in the results. The study did not reach the planned sample size, which may have affected the precision of the estimates.

Were all important outcomes considered?

Yes. The study evaluated several important outcomes, including **clinical cure**, **microbiological cure**, **relapse**, **reinfection**, **adverse events**, and **60-day mortality**. Additionally, exploratory analyses were conducted on **rectal colonization** and **resistance acquisition**.

Are the benefits worth the harms and costs?

Unclear. While fosfomycin showed efficacy, it was associated with a higher rate of **adverse event-related discontinuations** (8.5% vs. 0% in the comparator group). The most common adverse event was **heart failure**, particularly in older patients with comorbidities. The study suggests that fosfomycin may still be considered for **selected patients**, but the safety concerns need to be weighed against the benefits.

Can the results be applied to the local population?

Yes, with caution. The study was conducted in **22 Spanish hospitals**, and the patient population included older adults with comorbidities, which is representative of many real-world settings. However, the higher rate of adverse events with fosfomycin, particularly in older patients, suggests that the results should be applied cautiously, especially in populations with similar risk factors.

Summary of CASP Assessment:

Strengths: The study addressed a clear research question, used a randomized design, and evaluated multiple important outcomes. The baseline characteristics of the groups were similar, and the study was conducted in a real-world setting.

Limitations: The study was **open-label**, which could introduce bias. The **sample size was not reached**, and the noninferiority margin was not met. The higher rate of adverse events with fosfomycin is a significant concern, particularly in older patients.

Conclusions: The study provides valuable insights into the use of **fosfomycin** for **MDR E. coli bUTIs**, but the results should be interpreted with caution due to the limitations. Fosfomycin may still be a viable option for **selected patients**, particularly those without pre-existing heart or kidney conditions. Further studies with larger sample sizes and blinded designs are needed to confirm these findings.