Time to Change the Complicated Urinary Tract Infection Primary Endpoint? The problem and a potential solution

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Background

- Clinicians use the clinical response to determine treatment success in cUTI.
  - Patients and clinicians are most interested in the resolution of symptoms.
  - Treatment of asymptomatic bacteriuria (clinical success and microbiologic persistence) is not recommended by guidelines.
- Registration clinical studies use a composite responder endpoint (clinical success and microbiologic eradication) as the basis for regulatory approval.
- The objective of this analysis was to evaluate the cUTI composite response and test characteristics of using asymptomatic bacteriuria to predict late clinical failure.

Methods

- The calculations and data used to assess the test characteristics of asymptomatic bacteriuria in cUTI were provided by the FDA at an uUTI workshop on 03 June 2022.
- 13 Phase 3 cUTI studies conducted from 2011 to 2019 with a total of 4842 patients.
- Patients in the microITT population had a qualifying urinary pathogen at ≥ 10^5 CFU/mL.
- 3425 (70.7%) patients with clinical cure and microbiologic eradication (<10^3 CFU/mL) and 871 (18.0%) patients with asymptomatic bacteriuria (clinical cure and microbiologic persistence) at the test-of-cure (TOC) visit approximately 7-10 days following the end of therapy were used to evaluate test characteristics of using microbiological persistence at TOC to predict clinical failure at LFU for those patients who are a clinical success at TOC (Table 1).
- Two definitions of clinical failure at the late follow-up (LFU) visit were used: (1) any clinical failure; (2) symptom worsening and/or new symptom development.
- The sensitivity / specificity / positive predictive value (PPV) / negative predictive value (NPV) of asymptomatic bacteriuria at TOC relative to clinical failure at LFU in the subgroup of patients who were a clinical success at TOC using definition 1 and 2 were calculated.
  - PPV: % of micro failures at TOC who are also clinical failures at LFU
  - NPV: % of micro successes at TOC who are also clinical successes at LFU
  - Sensitivity: % of clinical failures at LFU who are also micro failures at TOC
  - Specificity: % of clinical successes at LFU who are also micro successes at TOC

Results / Discussion

1. The Microbiologic Response component is being used a biomarker.
- Complicated Urinary Tract Infections: FDA Guidance for Industry, June 2018
  - "**Continued bacteriuria at greater than 10^4 CFU/mL in patients recently completing treatment for cUTI represents a known risk for enhanced rate of relapse of cUTIs."**
- FDA Biomarker Website : **"A biomarker is not an assessment of how an individual feels, functions, or survives."**
- Bacteriuria has not been qualified as a biomarker by the FDA and EMA.
- The sensitivity / specificity / PPV / NPV of asymptomatic bacteriuria at TOC relative to clinical failure at LFU in the subgroup of patients who were a clinical success at TOC using definition 1 and 2 are shown in Table 2.
- Microbiological failure at TOC poorly predicted those patients who were clinical failures at LFU, whether this is measured by way of the PPV (only 26.8% of all micro failures are clinical failures at LFU) or sensitivity (only 52.4% of patients who were clinical failures at LFU were also micro failures at TOC).

2. The cUTI Composite Endpoint is not optimally constructed.
- The components in a good composite endpoint should be relevant to patients, occur at similar frequency, and have similar effect sizes. The Composite Response for cUTI is evaluated in Table 5.
- cUTI trial Composite Response (clinical plus microbiologic) was largely driven by the microbiologic outcomes. Figure 1 shows the Composite Response, Microbiologic Response, and Clinical Response for recent cUTI registrational trials.

cUTI Design Proposal

- Move to a Clinical Response primary endpoint (i.e., patient centered outcome)
  - Use structured questionnaire or patient reported outcome (future work)
  - Statistics including NI margin will have to be determined (future work)
- Move Microbiologic Response / resistance to a secondary endpoint.
  - Is the <10^3 CFU/mL truly the most relevant threshold? (future work)
- Lengthen the time between TOC and LFU (to ~ 4 weeks from EOT) to evaluate for clinical relapse (i.e., another patient centered outcome).

Table 1: Outcomes at TOC for 4842 patients in the microITT population

	Microbiologic Eradication at TOC	Microbiologic Persistence at TOC
Clinical Cure at TOC	3425 (70.7 %)	871 (18.0 %)*
Clinical Failure at TOC	222 (4.6 %)	324 (6.7 %)

*asymptomatic bacteriuria

Table 2: Test Characteristics of Asymptomatic Bacteriuria at TOC in Predicting Clinical Failure at LFU

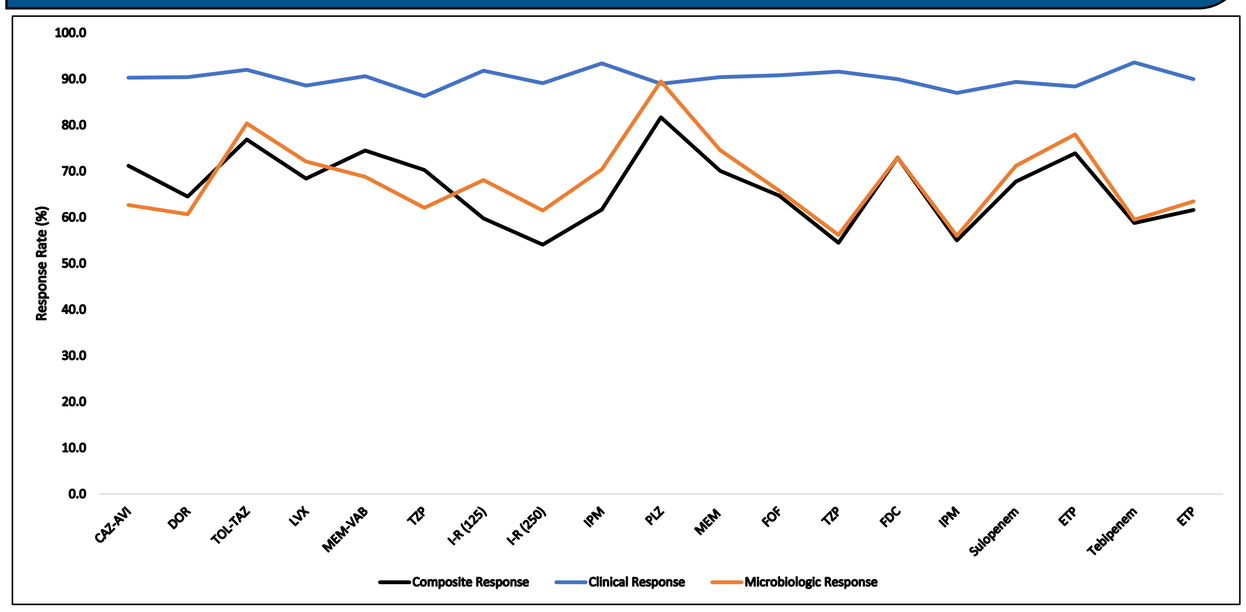
Test Characteristic	Definition 1 Any Clinical Failure	Definition 2 Symptomatic Clinical Failure
Sensitivity	52.4 %	46.5 %
Specificity	83.4 %	81.9 %
PPV	26.8 %	17.5 %
NPV	93.8%	94.9 %

Table 3: Outcomes at TOC for 4842 patients in the microITT population

Criterion	Microbiologic Response	Clinical Response
Relevant to Patients?[1]	No	Yes
Similar Frequency?	Dominates Composite Response	-
Similar Effect Size?	Moderate and Variable Microbiologic Success	Consistently High Clinical Success[2]

[1]Reflects how a patient feels, functions, and survives; [2]for effective antibiotics (i.e., clinical response has sufficient sensitivity to detect an ineffective antibiotic
Palileo-Villaneuva et al J Clin Epidemiol 2020; McCoy et al West J Emerg Med 2018

Figure 1 Composite, Clinical, and Microbiologic Responses for recent cUTI Registrational Trials



Conclusions

- The Composite Response in cUTI fails to meet the criteria for an adequately constructed Composite Endpoint and may lead to erroneous conclusions on efficacy due to the prevalence of asymptomatic bacteriuria, particularly when microbiological responses / outcomes are assessed using the stringent <10^3 CFU/mL threshold.
- Persistent bacteriuria, which is used as a biomarker at TOC, poorly predicted clinical failure at LFU.
- A clinical response-only primary endpoint with key secondary microbiologic and longer-term clinical endpoints should be considered in future registration cUTI studies.

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