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DIAGNOSTIC TESTING AMONG PATIENTS WITH SUSPECTED RECURRENT *CLOSTRIDIOIDES DIFFICILE* INFECTION (rCDI) IN ECOSPOR-III A PHASE 3 CLINICAL TRIAL: IMPLICATIONS FOR CLINICAL PRACTICE VS CLINICAL TRIALS

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Background

- *Clostridioides difficile* infection (CDI) is a two-hit process characterized by disruption of the microbiome and exposure to *C. difficile* spores. The leading risk factor for CDI is exposure to antibiotics, which cause collateral damage to beneficial microbes in the GI microbiome.[1]
- The most common symptom of CDI is diarrhea, often in isolation without any other pathognomonic sign or symptom.
- Toxin production is key to CDI pathogenesis and is the hallmark of disease[2]
- Accurate diagnosis is challenging due to:
  - Limitations in diagnostic test performance (e.g., sensitivity, specificity, predictive value)
  - Alternative causes of diarrhea following CDI

CDI is a clinical diagnosis and may be difficult to differentiate from other causes of diarrhea

Limitations of diagnostic testing

- Stool enzyme immunoassay toxin testing (EIA-TOX) is the best predictor of active disease[4] but may miss cases of CDI when toxins are below the limit of detection.[5,6]
- Cytotoxicity neutralization assay (CCNA) is considered the "gold standard", due to performance sensitivity but is only available from reference laboratories and is time and labor intensive.
- In contrast, glutamate dehydrogenase (GDH) has high sensitivity but cannot differentiate colonization from infection, leading to possible overdiagnosis.[6,7,8]
- *"Testing for* recurrent *CDI should ideally include toxin testing"* – IDSA 2018 guidelines[5]

Alternative causes of diarrhea following treatment of CDI

- Diarrhea after CDI treatment with negative *C. difficile* toxin testing is consistent with post-infection irritable bowel syndrome (IBS), reported in up to 25% of CDI patients[9].
- Studies of fecal transplant for recurrent CDI have also shown that transient diarrhea is one of the most common adverse events observed after dosing[10,11].
  - 60% of patients (n=609) reported diarrhea symptoms during short term follow up to FMT[10]

Phase 3 double-blind, placebo-controlled ECOSPOR III trial of investigational microbiome therapeutic SER-109

281 adult subjects ≥18 years screened

182 toxin+ adult subjects with symptom resolution on antibiotics enrolled

10 oz magnesium citrate administered prior to randomization to minimize residual antibiotic

Subjects stratified by age and antibiotic received

→ 4 Capsules once daily for 3 Days

	Primary endpoint: Recurrence at 8 weeks	Safety: through 24 weeks
SER-109		
Placebo		

Recurrences evaluated through 24 weeks

Toxin testing required at study entry and at suspected recurrence to ensure enrollment of patients with active disease and accurate assessment of endpoint

- All subjects had acute infection
- No chronic suppressive antibiotics allowed

ClinicalTrials.gov Identifier: NCT03183128

Study definitions and diagnostic algorithm

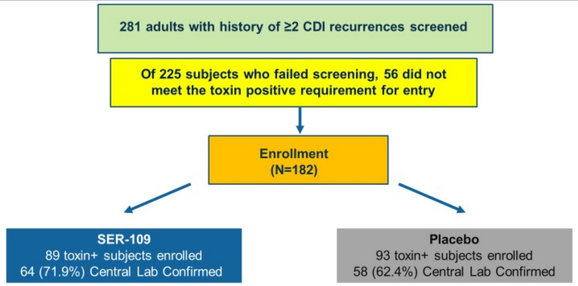
Table A

Study entry:

CDI was defined as ≥3 unformed stools/day for ≥48 hours with a positive *C. difficile* toxin assay

- Patients were diagnosed either by a local certified lab (EIA toxin with or without GDH testing) or at the central lab (EIA toxin with routine GDH testing) (Eurofins; Framingham, MA).
- Subjects with a GDH+/toxin- tests at the central lab had reflex confirmatory testing with a cell cytotoxicity neutralization assay (CCNA), considered the "gold standard" for toxin testing.

Overview of diagnostic testing at study entry



Diagnostic testing for CDI recurrence in ITT population: *Patients who qualified at study entry*

Test for qualifying episode	SER-109 N=89 n (%)	Placebo N=93 n (%)
LOCAL LAB	24 (26.9)	35 (37.6) *
TOX+ alone	14 (15.7)	19 (20.4)
TOX+ GDH+	10 (11.2)	15 (16.1)
CENTRAL LAB	64 (71.9)	58 (62.4)
GDH+ TOX+	44 (49.4)	43 (46.2)
GDH+ TOX- CCNA+	20 (22.5)	15 (16.1)
GDH+ TOX- CCNA-	0	0
GDH- TOX+ CCNA-	0	0
GDH- TOX+ CCNA+	0	0
MISSING	1 (1.1)	0

Percentages are based on the number of subjects in the ITT Population in each treatment group. One subject in the Placebo arm had negative central lab results and positive local lab results on the same day. The positive local lab results were used for the qualifying episode. *Includes 1 patient enrolled with PCR+ test.

Most subjects (81.9%) were tested for GDH and toxin production (EIA TOX and CCNA), consistent with a 2-step diagnostic algorithm.

Study limitations

At study entry:

- Local lab results for subjects who did not qualify for the study are not available.
- This data set is not a random sample. Patients who were selected to participate may have been tested for CDI by treating physician with tests of their preference
- Some patients who were GDH+, TOX- and CCNA+ may have initiated CDI antibiotics before testing, limiting conclusions about EIA TOX sensitivity.

Diagnostic testing data have implications for clinical practice and design of clinical trials

The Art of Clinical Medicine

- CDI is a clinical diagnosis verified by testing.
- Clinicians may select a particular CDI assay based on clinical assessment and assumptions about prior probability of disease.
- EIA toxin testing has a high predictive value for true disease but may miss cases of CDI due to lower sensitivity than CCNA, which is only available from reference labs
- Tests that don't use toxin testing (such as GDH or PCR) alone may lead to overdiagnosis and inappropriate treatment.

Diagnostic testing data have implications for clinical practice and design of clinical trials

The Rigor of Clinical trials

- Conclusions about the safety and efficacy of any investigational agent requires certainty that the study population has the disease in question.
- Although the requirement for toxin testing may prolong enrollment times due to lower rates of recruitment of patients with toxin-proven disease, it assures physicians and patients of accurate estimates of efficacy and safety of the therapeutic intervention.
- In ECOSPOR III, most subjects had GDH and toxin testing, consistent with 2-step testing algorithms.

Conclusions

- In ECOSPOR III, the diagnostic algorithm used to qualify patients for study eligibility may serve as a model for future CDI therapeutic trials.

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