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

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**Background**

- Clostridiodes difficile infection (CDI) is a serious process characterized by the recurrence of symptoms weeks, months, or even years after a patient has completed therapy for their initial CDI.
- The most common symptom of CDI is diarrhea, often in isolation without any other signs of infection.
- Colonization with clindamycin-resistant or vancomycin-resistant strains is likely.
- Infections are often associated with nosocomial settings such as hospitals and nursing homes.
- The diagnosis is often challenging due to the nonspecific nature of symptoms and tests, leading to frequent misdiagnosis.

**Limitations of the diagnostic testing**

- There are many tests available, but no single test is perfect to diagnose CDI accurately.
- Limitations: sensitivity and specificity, false-negative and false-positive results, and overuse.

**Goals of the diagnostic testing**

- To diagnose CDI accurately and effectively to prevent further complications and ensure appropriate treatment.
- To reduce the risk of misdiagnosis and unnecessary treatment.

**Study definitions and diagnostic algorithm**

| Test for CDI Recurrence in ITT Population: Patients who qualified at study entry |
|--------------------------------------|------------------|------------------|------------------|
| **Test for qualifying episode**      | **ITT eligibility** |
| Sigmoid and rectal swab and/or stool samples positive for C. difficile toxins A and B by an FDA-approved test. | CDI was defined as 1 or more stool samples positive for C. difficile toxins A and B by an FDA-approved test. | CDI was defined as 1 or more stool samples positive for C. difficile toxins A and B by an FDA-approved test. |
| **Study entry**                      |                  |
| Local laboratory stool cultures positive for C. difficile toxins A and B by an FDA-approved test. | CDI was defined as 1 or more stool samples positive for C. difficile toxins A and B by an FDA-approved test. | CDI was defined as 1 or more stool samples positive for C. difficile toxins A and B by an FDA-approved test. |
| **ITT population**                   |                  |
| Local laboratory stool cultures positive for C. difficile toxins A and B by an FDA-approved test. | CDI was defined as 1 or more stool samples positive for C. difficile toxins A and B by an FDA-approved test. | CDI was defined as 1 or more stool samples positive for C. difficile toxins A and B by an FDA-approved test. |
| **ITT analysis population**          |                  |
| Local laboratory stool cultures positive for C. difficile toxins A and B by an FDA-approved test. | CDI was defined as 1 or more stool samples positive for C. difficile toxins A and B by an FDA-approved test. | CDI was defined as 1 or more stool samples positive for C. difficile toxins A and B by an FDA-approved test. |

**Study limitations**

- 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/or CNMA+ may have had CDI antibiotics before testing, leading to inconclusive results about CDI 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.
  - Toxigenic or toxigenic positive value for true disease but may miss some cases of CDI due to lower sensitivity than CNMA, which is only available from reference labs.
  - Tests that don’t use toxin testing (such as GDH or PCR) alone may lead to overdagnosis 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 investigational agents require 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 enrollment for patients with toxin-positive disease, it assures physicians and patients of accurate estimates of efficacy and safety of the therapeutic intervention.
  - In ECOSPOR II, most subjects had GDH and toxin testing, consistent with 2-step testing algorithms.

**Conclusions**

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

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**References**