

The Addition of Intravenous Metronidazole to Oral Vancomycin Improves Mortality in Critically Ill Patients with *Clostridium difficile* Infection (CDI)

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Background

- Minimal data exist for the preferred regimen in patients presenting with severe and/or complicated CDI requiring admission to an ICU
- SHEA/IDSA clinical practice guidelines recommend¹
 - Oral vancomycin ± IV metronidazole for patients with severe, complicated CDI
- It is unclear whether the addition of IV metronidazole provides any benefit

Objective

- To evaluate the difference in mortality among critically ill patients with CDI who received oral vancomycin (**monotherapy**) versus oral vancomycin with IV metronidazole (**combination therapy**)

Methods

Study Design

- Single-center, retrospective, observational, comparative study
- Approved by WFBMC Institutional Review Board
- Patients from June 2007 to September 2012 who had a positive *C. difficile* PCR or toxin assay were identified from a data repository
- Patients were matched based on APACHE II scores

Inclusion Criteria

- Bedded or transferred to an ICU within 48 hours of positive assay
- Received oral vancomycin
- To be included in combination therapy, IV metronidazole was administered within 48 hours of vancomycin

Exclusion Criteria

- <18 years old
- Co-existing gastrointestinal disease
 - Crohn's disease
 - Ulcerative colitis
 - Irritable bowel syndrome

Methods Continued

To ensure severity of illness, patients met ≥3 of 7 criteria within 24 hours of treatment initiation

Albumin <2.5 g/dL
Heart Rate (HR) >90 beats per minute
White Blood Cell (WBC) count ≥15,000/mm ³
Mean Arterial Pressure (MAP) <60 mmHg
Temperature (Temp) ≥100.4°F
Age >60 years
Serum Creatinine (SCr) ≥1.5 x baseline (BL)

Primary Outcome Measure

- In-hospital mortality

Secondary Outcome Measures

- Clinical success at day 6 defined as:
 - Improvement of diarrhea (↓ in the number of stools and/or volume)
 - Absence of fever
 - WBC count <15,000 cells/mm³
 - Normalization of tachycardia
 - MAP >60 mmHg without the use of vasopressors
- ICU length of stay (LOS) after CDI diagnosis
- Overall LOS

Statistical Analysis

- Descriptive statistics
- Comparisons between groups were analyzed using Chi-Squared or Fisher's Exact tests for categorical data, Mann-Whitney U-test for ordinal data, and Student's t-test for continuous data

Results

Patient Characteristics

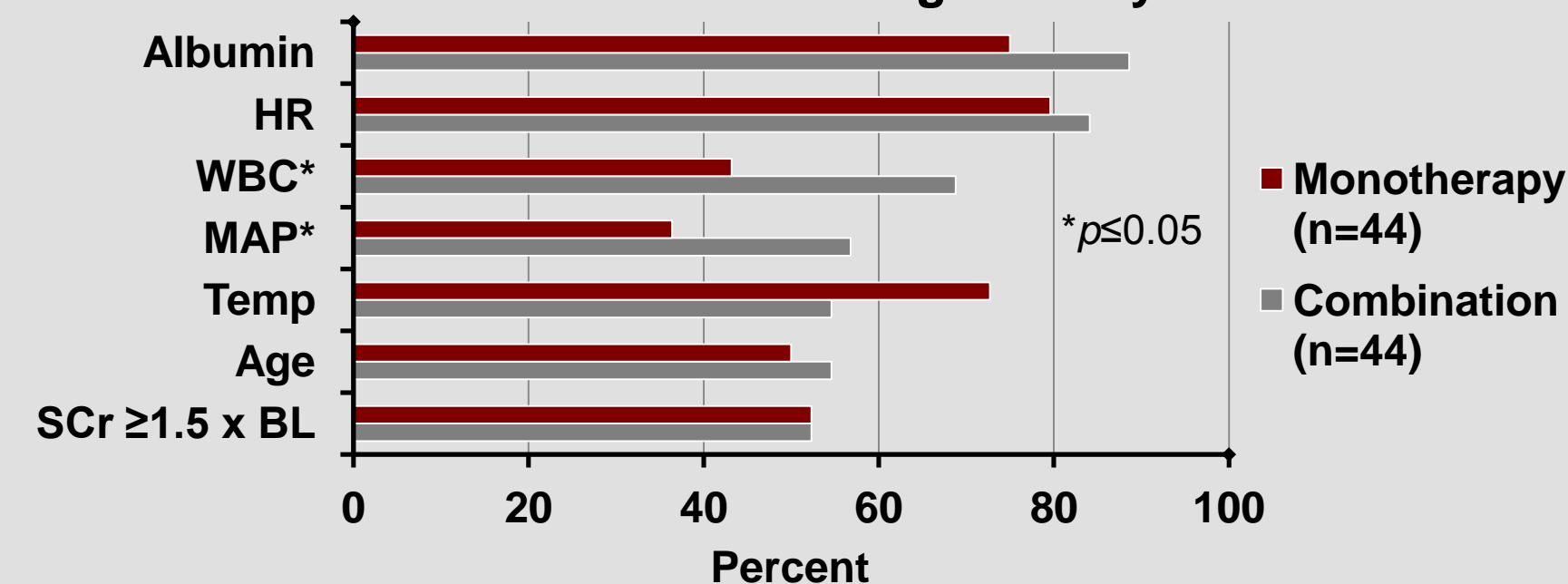
Characteristic	Monotherapy (n=44)	Combination (n=44)	p
Female gender, n (%)	24 (54.5)	28 (63.6)	0.39
Age, mean ± SD	60.5 ± 15.3	60.9 ± 14.8	0.90
APACHE II, mean ± SD	26.4 ± 6.9	26.8 ± 6.9	0.80
CCI, mean ± SD	5.2 ± 2.7	5.9 ± 2.4	0.22
HO-HCFA, n (%)	38 (86.4)	30 (68.2)	0.04

APACHE II= Acute Physiology and Chronic Health Evaluation II; CCI=Charlson Comorbidity Index; HO-HCFA CDI=Healthcare facility-onset, healthcare facility associated CDI

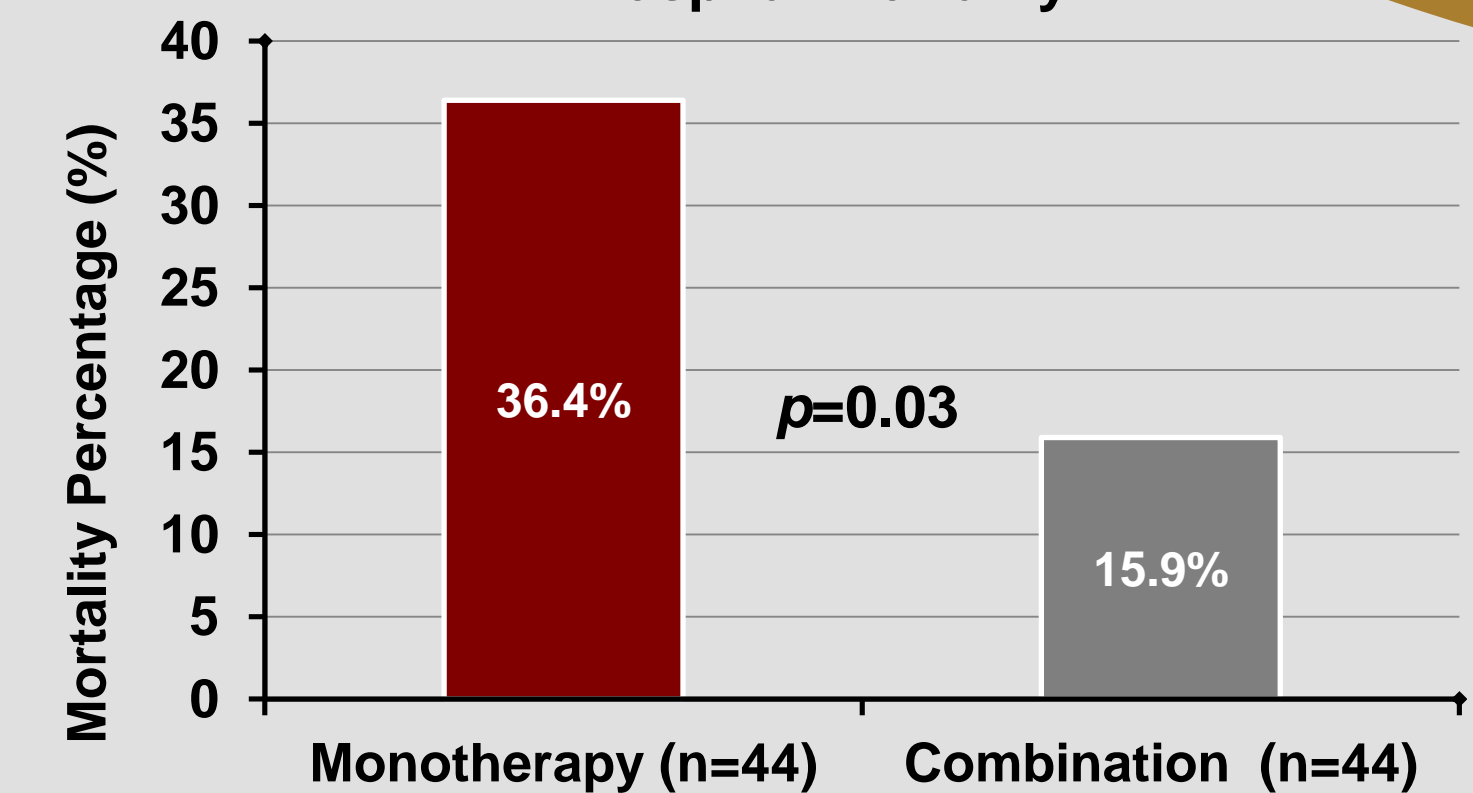
Immune Status Indicators

Characteristic	Monotherapy (n=44)	Combination (n=44)	p
ANC<1,000/mm ³ , n(%)	8 (18.2)	3 (6.8)	0.11
Solid organ transplant, n (%)	2 (4.5)	1 (2.3)	0.56
AIDS, n (%)	2 (4.5)	1 (2.3)	0.56
Chronic immunosuppressive medications, n (%)	3 (6.8)	6 (13.6)	0.48
Total # of immunosuppressed patients, n (%)	13 (29.5)	10 (22.7)	0.47

Percent of Patients Meeting Severity Criteria



In-Hospital Mortality



Secondary Outcomes

Outcome	Monotherapy (n=44)	Combination (n=44)	p
Clinical success, n (%)	8 (18.2)	5 (11.4)	0.37
LOS ¹ , median (range)	32 (6-170)	27 (7-223)	0.80
ICU LOS after CDI ¹ , median (range)	9 (4-60)	11 (3-68)	0.93

¹Monotherapy n=28 and Combination n=37

Conclusions

- Critically ill patients with CDI should receive combination therapy with oral vancomycin and IV metronidazole
- Further studies defining optimal treatment regimens in critically ill patients with CDI are warranted

References

1. Cohen SH, Gerding DN, Johnson S, et al. *Infect Control Hosp Epidemiol.* 2010;31(5):431-55.