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MAJOR ARTICLE

What Is the Role for Metronidazole in the Treatment of *Clostridium difficile* Infection? Results From a National Cohort Study of Veterans With Initial Mild Disease

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Background

- C. difficile Infektion häufigste nosokomiale Infektion in den USA
- Vor 2018, Metronidazol Therapie der 1.Wahl für milde bis moderate C. difficile Infektion (CDI)
- 2018 Update der IDSA Guidelines Metronidazol nicht mehr empfohlen
  - Neue Definition; Differenzierung zwischen nicht-schwerer und schwere CDI
  - Update der Therapieempfehlung basierte auf Studien welche ein besserer Outcome in Bezug auf die Mortalität für Vancomycin aufzeigten
  - Andere Studien/beziehungsweise Subgruppenanalysen ergaben allerdings keinen Unterschied zwischen Metronidazol und Vancomycin bei milder CDI, insbesondere in Bezug auf Rezidive
  - Einige Experten empfehlen weiterhin Metronidazol als 1. Wahl bei Patienten mit milder CDI und ohne erhöhtes Risiko für Komplikationen

- Johnson S, et al, Polymer Alternative for CDI Treatment, PACT Investigators, CID 2014
- Steven VW, et al, Comparative Effectiveness of Vancomycinan vs Metronidazol for the Prevention of recurrence and death in Pat. with CDI, JAMA 2017

Ziel der Studie

1. Identifizierung unabhängiger Faktoren für eine erfolgreiche Therapie mit Metronidazol p.os

1. Wirksamkeit zwischen Metronidazol und Vancomycin zu vergleichen

Methodik

- Studiendesign
  - Retrospektive Studie
  - Daten zwischen Mai 2010 und Dezember 2014
  - 2-Stage Analyse
- Studienpopulation
  - Veteranenkohorte aus 125 verschiedenen nationalen in-/outpatient Veteranenzentren
- Einschlusskriterien
    - erstmalige Episode einer CDI
      - Def: positive Stuhlprobe für C. diff. Toxin und ≥ 2 Tage Therapie
    - milde Fälle von CDI
      - Def: Leukozyten ≤ $15x10^3$ Zellen/µl, Kreatintin ≤ 1.5 mg/dl
    - Therapie gemäss Guidelines von 2010
      - 10-14 Tage Monotherapie mit Metronidazol oder Vancomycin po
- Ausgeschlossen wurden Patienten mit fehlenden Laborwerten

1. Stage Analyse

- Prädiktive Analyse
  - 45 potentielle Prädiktoren a priori selektioniert
- Patienten mit erfolgreichem und erfolglosem Outcome verglichen am Tag 30 nach Therapie mit Metronidazol p.os
- Erfolg definiert:
  - Kein Tod (jeglicher Ursache) innert 30 Tage nach Therapieende
  - Kein Rezidiv innert 30 Tagen nach Therapieende
- Misserfolg:
  - Tod (jeglicher Ursache) innert 30 Tagen nach Therapieende
  - Rezidiv innert 30 Tagen nach Therapieende

Table 1. Baseline Characteristics Among a National Cohort of Veterans With an Initial Episode of Mild *Clostridium difficile* Infection Treated With Metronidazole With and Without Successful Outcomes

Characteristic	Patients With Success (n = 3282)		Patients Without Success (Failure) (n = 374)		*P* Value
Demographics					
Age ≤ 65 y	1985	(60.5)	148	(39.6)	<.001
Male sex	2982	(90.9)	357	(95.5)	.003
White race	2494	(76.0)	281	(75.1)	.714
Hispanic ethnicity	148	(4.5)	16	(4.3)	.838
Married	1459	(44.5)	159	(42.5)	.474
Treatment setting					
Acute care	401	(12.2)	109	(29.1)	<.001
Long-term care	84	(2.6)	21	(5.6)	…
Outpatient	2797	(85.2)	244	(65.2)	…
Principal diagnosis of CDI on hospital admission[a]	92	(2.8)	31	(8.3)	<.001
BMI ≥ 30 kg/m^2	1995	(60.8)	278	(74.3)	<.001
Albumin <1.5 mg/dL	1292	(39.4)	244	(65.2)	<.001
Hypervirulent CDI strain	190	(5.8)	22	(5.9)	.942
Charlson comorbidity score at or above the median	2281	(69.5)	310	(82.9)	<.001
Elixhauser score at or above the median	2055	(62.6)	289	(77.3)	<.001
Comorbidities					
Cardiopulmonary disease	1871	(57.0)	261	(69.8)	<.001
Chronic renal disease	362	(11.0)	75	(20.1)	<.001
Dementia	127	(3.9)	22	(5.9)	.062
Diabetes	1108	(33.8)	130	(34.8)	.699
Gastrointestinal/nutritional disorder	1412	(43.0)	175	(46.8)	.164
Liver disease	344	(10.5)	56	(15.0)	.008
Malignancy	620	(18.9)	133	(35.6)	<.001
Paralysis	137	(4.2)	26	(7.0)	.014
Rheumatic disease	1263	(38.5)	167	(44.7)	.021

Characteristic	Patients With Success (n = 3282)		Patients Without Success (Failure) (n = 374)		*P* Value
Current acute event or infection					
Meningitis	<5	…	<5	…	.277
Gram negative	136	(4.1)	27	(7.2)	.006
Intestinal infection	769	(23.4)	148	(39.6)	<.001
Acute bronchitis	12	(0.4)	<5	…	.625
Pneumonia	121	(3.7)	35	(9.4)	<.001
Septicemia	100	(3.0)	27	(7.2)	<.001
Bacteremia	46	(1.4)	10	(2.7)	.058
Shock	13	(0.4)	7	(1.9)	.003
Skin and soft tissue	198	(6.0)	45	(12.0)	.001
MRSA	18	(0.5)	8	(2.1)	.003
Pseudomonas	20	(0.6)	6	(1.6)	.043
Urinary tract infection	167	(5.1)	42	(11.2)	<.001
Respiratory failure	64	(2.0)	36	(9.6)	<.001
Acute renal failure	171	(5.2)	50	(13.4)	<.001
Fever of unknown origin	76	(2.3)	6	(1.6)	.379
Previous acute event or infection					
Meningitis	11	(0.3)	<5	…	1.00
Gram negative	155	(4.7)	26	(7.0)	.060
Influenza	24	(0.7)	<5	…	.752
Intestinal infection	883	(26.9)	173	(46.3)	<.001
Acute bronchitis	177	(5.4)	12	(3.2)	.071
Pneumonia	382	(11.6)	87	(23.3)	<.001
Septicemia	246	(7.5)	62	(16.6)	<.001
Bacteremia	118	(3.6)	22	(5.9)	.029
Shock	40	(1.2)	16	(4.3)	<.001
Skin and soft tissue	692	(21.1)	106	(28.3)	<.001
MRSA	78	(2.4)	16	(4.3)	.028
Pseudomonas	51	(1.6)	9	(2.4)	.219

Characteristic	Patients With Success (n = 3282)		Patients Without Success (Failure) (n = 374)		*P* Value
Urinary tract infection	515	(15.7)	93	(24.9)	<.001
Respiratory failure	164	(5.0)	56	(15.0)	<.001
Healthcare exposures					
Surgery, during CDI treatment	133	(4.1)	23	(6.1)	.057
VA hospitalization or long-term care, prior 90 d	1152	(35.1)	241	(64.4)	<.001
Medication exposures					
Non-CDI antibiotic use, 30 d before or during CDI treatment	2082	(63.4)	277	(74.1)	<.001
Gastric acid suppressant use, 7 d before or during CDI treatment	1123	(34.2)	189	(50.5)	<.001
Immunosuppressant use, 7 d before or during CDI treatment	192	(5.9)	61	(16.3)	<.001
Probiotic use, 7 d before or during CDI treatment	110	(3.4)	43	(11.5)	<.001

Multivariablen Analyse

Table 2. Independent Predictors of Success and Failure at 30 Days After *Clostridium difficile* Infection Treatment With Metronidazole Monotherapy

Predictor	Adjusted OR (95% CI)	
Predictors of success—absence of mortality or CDI recurrence at day 30 posttreatment (OR > 1)		
Age ≤ 65 y	1.63	(1.29–2.06)
Predictors of failure—mortality or CDI recurrence within 30 d posttreatment (OR > 1)		
Probiotic exposure, 7 d prior or during CDI treatment	0.33	(.22–.49)
Current respiratory failure	0.34	(.22–.54)
VA hospital or long-term care exposure, 90 d prior	0.52	(.41–.67)
Hypoalbuminemia[a]	0.53	(.42–.68)
Principal diagnosis of CDI on hospital admission	0.54	(.34–.85)
Malignancy	0.60	(.47–.77)
BMI ≥ 30 kg/m^2	0.74	(.57–.96)
Current intestinal infection	0.74	(.58–.95)

2. Stage Analyse

- Effekt von Metronidazol vs. Vancomycin auf Therapieversagen
  - 30-Tag Mortalität (jeglicher Ursache)
  - CDI Rezidiv innerhalb 30 Tagen
- Subgruppenanalyse mit Patienten welche Charakteristika aufweisten die mit erfolgreicher Metronidazoltherapie assoziert war
  - Patienten ≤ 65J
- Propensity Score-matched Cox proportional Hazard models

Table 3. Patient Characteristics of Patients Aged ≤65 Years With Mild Disease Treated With Metronidazole or Vancomycin: Unmatched and Matched Cohorts

Characteristic	Unmatched Cohort						Matched Cohort					
	Metronidazole (n = 2133)		Vancomycin (n = 118)		*P* Value	SB	Metronidazole (n = 115)		Vancomycin (n = 115)		*P* Value	SB
Demographics												
Age, y, median (IQR)	57	(47–62)	59	(51–64)	.003	0.23	58	(52–63)	59	(51–64)	.436	0.04
Male sex	1853	(86.9)	105	(89.0)	.507	0.06	101	(87.8)	103	(89.6)	.677	0.05
White race	1576	(73.9)	82	(69.5)	.291	0.10	77	(67)	81	(70.4)	.570	0.08
Hispanic ethnicity	114	(5.3)	7	(5.9)	.783	0.03	7	(6.1)	7	(6.1)	1.000	0.00

Table 3. Patient Characteristics of Patients Aged ≤65 Years With Mild Disease Treated With Metronidazole or Vancomycin: Unmatched and Matched Cohorts

Characteristic	Unmatched Cohort						Matched Cohort					
	Metronidazole (n = 2133)		Vancomycin (n = 118)		*P* Value	SB	Metronidazole (n = 115)		Vancomycin (n = 115)		*P* Value	SB
2013	439	(20.6)	30	(25.4)	…	0.12	28	(24.3)	28	(24.3)	…	0.00
2014	522	(24.5)	30	(25.4)	<.028	0.02	31	(27.0)	30	(26.1)	.492	0.00
Principal diagnosis of CDI	46	(2.2)	7	(5.9)	.019	0.19	7	(6.1)	6	(5.2)	.775	0.04
BMI ≥ 30 kg/m^2	1190	(55.8)	85	(72.0)	<.001	0.34	78	(67.8)	82	(71.3)	.5667	0.08
Albumin <1.5 mg/dL	754	(35.3)	70	(59.3)	<.001	0.49	57	(49.6)	67	(58.3)	.186	0.18
Hypervirulent strain CDI	111	(5.2)	11	(9.3)	.054	0.16	14	(12.2)	11	(9.6)	.525	0.08
Treatment duration, d, median (IQR)	11	(11–11)	11	(11–12)	<.001	0.31	11	(11–12)	11	(11–12)	.792	0.03
Charlson comorbidity score at or above the median	1298	(60.9)	92	(78.0)	<.001	0.38	84	(73)	89	(77.4)	.445	0.10
Elixhauser score at or above the median	1215	(57.0)	90	(76.3)	<.001	0.42	89	(77.4)	87	(75.7)	.756	0.04
Comorbidities												
Cardiopulmonary disease	983	(46.1)	73	(61.9)	<.001	0.32	69	(60)	72	(62.6)	.685	0.05
Chronic renal disease	173	(8.1)	14	(11.9)	.150	0.13	9	(7.8)	13	(11.3)	.370	0.12
Dementia	14	(0.7)	<5	…	.203	0.10	<5	…	<5	…	1.00	0.06
Diabetes	625	(29.3)	34	(28.8)	.910	0.01	33	(28.7)	34	(29.6)	.885	0.02
Gastrointestinal/nutritional disorder	918	(43.0)	51	(43.2)	.969	0.00	56	(48.7)	51	(44.3)	.509	0.09
Liver disease	299	(14.0)	23	(19.5)	.088	0.15	18	(15.7)	22	(19.1)	.487	0.09
Malignancy	290	(13.6)	23	(19.5)	.072	0.16	17	(14.8)	23	(20)	.297	0.14
Paralysis	82	(3.8)	9	(7.6)	.052	0.16	7	(6.1)	9	(7.8)	.604	0.07
Rheumatic disease	745	(34.9)	54	(45.8)	.017	0.22	49	(42.6)	52	(45.2)	.690	0.05
Acute events or infections												
Current acute renal failure	83	(3.9)	9	(7.6)	.055	0.16	6	(5.2)	9	(7.8)	.423	0.11
Current fever of unknown origin	52	(2.4)	<5	…	1.0	0.05	<5	…	<5	…	1.00	0.06
Current infection	651	(30.5)	62	(52.5)	<.001	0.46	64	(55.7)	60	(52.2)	.597	0.07
Current septicemia/bacteremia/shock	58	(2.7)	12	(10.2)	<.001	0.31	7	(6.1)	11	(9.6)	.326	0.13
Previous infection	1085	(50.9)	91	(77.1)	<.001	0.57	90	(78.3)	88	(76.5)	.753	0.04
Previous septicemia/bacteremia/shock	152	(7.1)	21	(17.8)	<.001	0.33	18	(15.7)	20	(17.4)	.723	0.05
Healthcare exposures												
Surgery, 30 d before or during CDI treatment	79	(3.7)	10	(8.5)	.024	0.20	10	(8.7)	9	(7.8)	.811	0.03
VA hospitalization or long-term care, prior 90 d	680	(31.9)	74	(62.7)	<.001	0.65	72	(62.6)	72	(62.6)	1.00	0.00
Medication exposures												
Non-CDI antibiotic use, 30 d before or during CDI treatment	1320	(61.9)	77	(65.3)	.463	0.07	65	(56.5)	75	(65.2)	.177	0.18
Gastric acid suppressant use, 7 d before or during CDI treatment	704	(33.0)	59	(50.0)	<.001	0.35	57	(49.6)	58	(50.4)	.895	0.02
Immunosuppressant use, 7 d before or during CDI treatment	103	(4.8)	16	(13.6)	<.001	0.31	17	(14.8)	15	(13)	.703	0.05
Probiotic use, 7 d before or during CDI treatment	83	(3.9)	8	(6.8)	.142	0.13	6	(5.2)	8	(7)	.581	0.07

Table 4. Unadjusted and Propensity Score–Matched Hazard Ratios for the Effect of Metronidazole Versus Vancomycin on Outcomes Among Patients Aged ≤65 Years With an Initial Episode of Mild *Clostridium difficile* Infection

Clinical Outcome	No. of Events/ No. of Metronidazole-Treated Patients	No. of Events/ No. of Vancomycin-Treated Patients	Unadjusted HR (95% CI)	No. of Events/ No. of Metronidazole-Treated Patients	No. of Events/ No. of Vancomycin-Treated Patients	Matched HR (95% CI)
All-cause mortality	33/2133	8/118	0.22 (.10–.48)	2/115	8/115	0.29 (.06–1.38)
Recurrence	116/2133	15/118	0.42 (.24–.72)	8/115	14/115	0.62 (.26–1.49)
Failure (mortality or recurrence)	148/2133	23/118	0.33 (.21–.51)	10/115	22/115	0.50 (.23–1.07)

Propensity score matched within 0.01 caliper. The propensity was derived from an unconditional logistic regression model controlling for age, region, Charlson comorbidity index, Elixhauser score, body mass index, race, ethnicity, marital status, principal diagnosis of *Clostridium difficile* infection (CDI), albumin, CDI treatment duration, sex, gastric acid suppressant use, antibiotic use, probiotic use, immunosuppressant use, Veterans Affairs long-term care or hospital exposure prior 90 days, cardiopulmonary disease, gastrointestinal/nutritional disorder, liver disease, diabetes, rheumatic disease, chronic renal disease, dementia, current acute renal failure, human immunodeficiency virus, current fever, surgery, current sepsis/shock/bacteremia, history of sepsis/shock/bacteremia, history of infection, current infection, treatment setting, and virulent strain.

Abbreviations: CI, confidence interval; HR, hazard ratio.

Zusammenfassung/Diskussion

- Alter (≤ 65) einziger Prädiktor für Erfolg bei der Therapie mit Metronidazol
  - Ältere Patienten (Immuninkompetent, reduzierter funktioneller Status, mehr Komorbiditäten)
- Mehrere Prädiktoren für Therapieversagen wo Patienten wahrscheinlich nicht von Metronidazol profitieren
  - Probiotika, Resp.Versagen, Vorausgehende Hospitalisation, Hypalbuminämie, CDI Hauptdiagnose und stat. Aufnahme, Malignom, Adipositas, Abdmominale Infektion
- Bei Patienten jünger als 65J ergab sich gemäss Autoren kein Unterschied im Outcome in Bezug auf die Therapie mit Metronidazol versus Vancomycin bei einer milden CDI

Limitationen

- Population von Veteranen (v.a. ältere weisse Männer)
- Mögliche Missklassifikation von Rezidiven
  - Zeitpunkt des Assessement am Tag 30
  - Rezidive nach 30 Tagen nicht berücksichtigt
- Outcome für Erfolg oder Misserfolg sind composite Outcomes (Mortaliät und Rezidiv)
- Kein Assessment bezüglich Resolution der Symptome
- Retrospektive Analyse und keine Randomisierung in der Vergleichsanalyse
- Während der Studienperiode war die empfohlene Erstlinientherapie für eine milde bis moderate CDI Metronidazol, Vancomycin empfohlen für eine schwere CDI
  - Kränkere Patienten mit Vancomycin behandelt
  - Trotz Matching mögliche Confounding bias durch unbekannte Faktoren
  - Studiendefinition für nicht schwere Infektion einzig laborchemisch und nicht klinisch
  - Patienten wahrscheinlich aufgrund der Klinik mit Metronidazol oder Vancomycin behandelt

Danke für die Aufmerksamkeit!