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Effect of C-Reactive Protein–Guided Antibiotic Treatment Duration, 7-Day Treatment, or 14-Day Treatment on 30-Day Clinical Failure Rate in Patients With Uncomplicated Gram-Negative Bacteremia

A Randomized Clinical Trial

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Einleitung

- Verlängerte Antibiotika-Gabe fördert Auftreten von
  - Resistenzen, NW (*C. difficile* Infektion), längere Hospitalisation (mehr Kosten)
- Meist 10-14 Tage Antibiotika
- Fixe Antibiotika-Therapiedauer vs. Patientencharakteristika und Ansprechen auf Therapie

Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial

Dafna Yahav,[1,2] Erica Franceschini,[3] Fidi Koppel,[4] Adi Turjeman,[2,5] Tanya Babich,[2,5] Roni Bitterman,[4] Ami Neuberger,[4,6] Nesrin Ghanem-Zoubi,[4] Antonella Santoro,[3] Noa Eliakim-Raz,[1,2] Barak Pertzov,[5] Tali Steinmetz,[5] Anat Stern,[4] Yaakov Dickstein,[4] Elias Maroun,[4] Hiba Zayyad,[4] Jihad Bishara,[1,2] Danny Alon,[7] Yonatan Edel,[2,8] Elad Goldberg,[9] Claudia Venturelli,[3] Cristina Mussini,[3] Leonard Leibovici,[2,5] Mical Paul[4,6]; for the Bacteremia Duration Study Group[a]

Variable	Short-duration Arm (7 d) (n = 306)	Long-duration Arm (14 d) (n = 298)
Bacteria type[c]		
Escherichia coli	186 (60.8)	194 (65.1)
Klebsiella spp	47 (15.3)	33 (11.1)
Other Enterobacteriaceae	40 (13.1)	43 (14.4)
Acinetobacter spp	2 (0.7)	4 (1.3)
Pseudomonas spp	28 (9.2)	20 (6.7)
Other	3 (1)	4 (1.3)
MDR gram-negative bacteremia[d]	58 (18.9)	51 (17.1)
Source of bacteremia		
Urinary tract	212 (69.3)	199 (66.8)
Primary bacteremia	23 (7.5)	28 (9.4)
Abdominal	37 (12.1)	34 (11.4)
Respiratory	14 (4.6)	10 (3.4)
Central venous catheter	15 (4.9)	23 (7.7)
Skin and soft tissue	5 (1.6)	4 (1.3)

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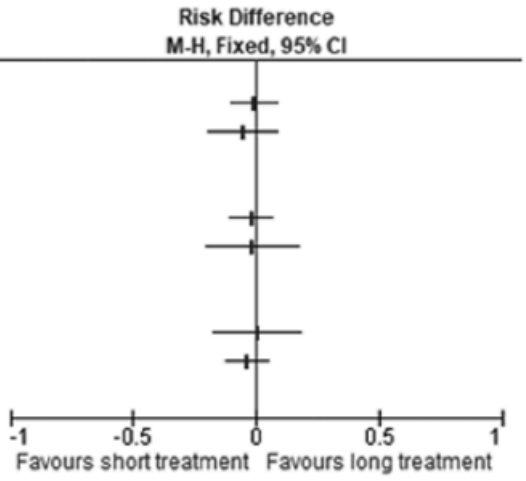
Outcome

Outcome	Short Arm (7 d) (n = 306)	Long Arm (14 d) (n = 298)	Risk Difference (95% CI)	*P* Value
Primary outcome	140 (45.8)	144 (48.3)	–2.6 (–10.5 to 5.3)	.527
90-d all-cause mortality	36 (11.8)	32 (10.7)	1.0 (–4.0 to 6.1)	.702
Readmissions	119 (38.9)	127 (42.6)	–3.7 (–11.5 to 4.1)	.363
Extended hospitalization beyond 14 d	15 (4.9)	19 (6.4)	–1.5 (–5.1 to 2.2)	.483
Distant complications	2 (0.7)	1 (0.3)	…	1.0
Relapse of bacteremia	8 (2.6)	8 (2.7)	–0.07 (–2.6 to 2.5)	.957
Suppurative complications	16 (5.2)	10 (3.4)	1.8 (–1.4 to 5.1)	.257
14-d mortality	7 (2.3)	4 (1.3)	0.95 (–1.42 to 3.44)	.288
28-d mortality	15 (4.9)	13 (4.4)	0.54 (–2.98 to 4.06)	.753
New clinically or microbiologically documented infection	70 (22.9)	68 (22.8)	0.06 (–6.6 to 6.8)	.987
Functional capacity: needs assistance/dependent in ADL or bedridden at 30 d	150 (51.4) (n = 292)	163 (57.2) (n = 285)	–5.8 (–13.9 to 2.3)	.031
Resistance development				
Time to return to baseline activity, wk (90 d)				
Total hospital days (90 d from randomization)—su				
Total hospital days (90 d from randomization)—all				
Duration of appropriate antibiotic therapy for bact				
Total antibiotic days from culture collection to day postrandomization				
Adverse events				
Acute kidney injury				
Liver function abnormalities				
Diarrhea during hospital stay				
Diarrhea until day 90[a]				
Rash				
Clostridium difficile infection				

Subgroup	Short Events	Short Total	Long Events	Long Total	Risk Difference M-H, Fixed, 95% CI
.1 Bacteremia source					
UTI	92	212	88	199	-0.01 [-0.10, 0.09]
non-UTI	48	94	56	99	-0.06 [-0.20, 0.09]
.2 Empirical antibiotic treatment					
Covering empirical	112	260	109	242	-0.02 [-0.11, 0.07]
Non-covering empirical	28	46	35	56	-0.02 [-0.21, 0.17]
.3 Multi-drug resistance					
MDR	39	58	34	51	0.01 [-0.17, 0.18]
Non-MDR	101	248	110	247	-0.04 [-0.13, 0.05]



Ein- / Ausschlusskriterien

Einschluss:

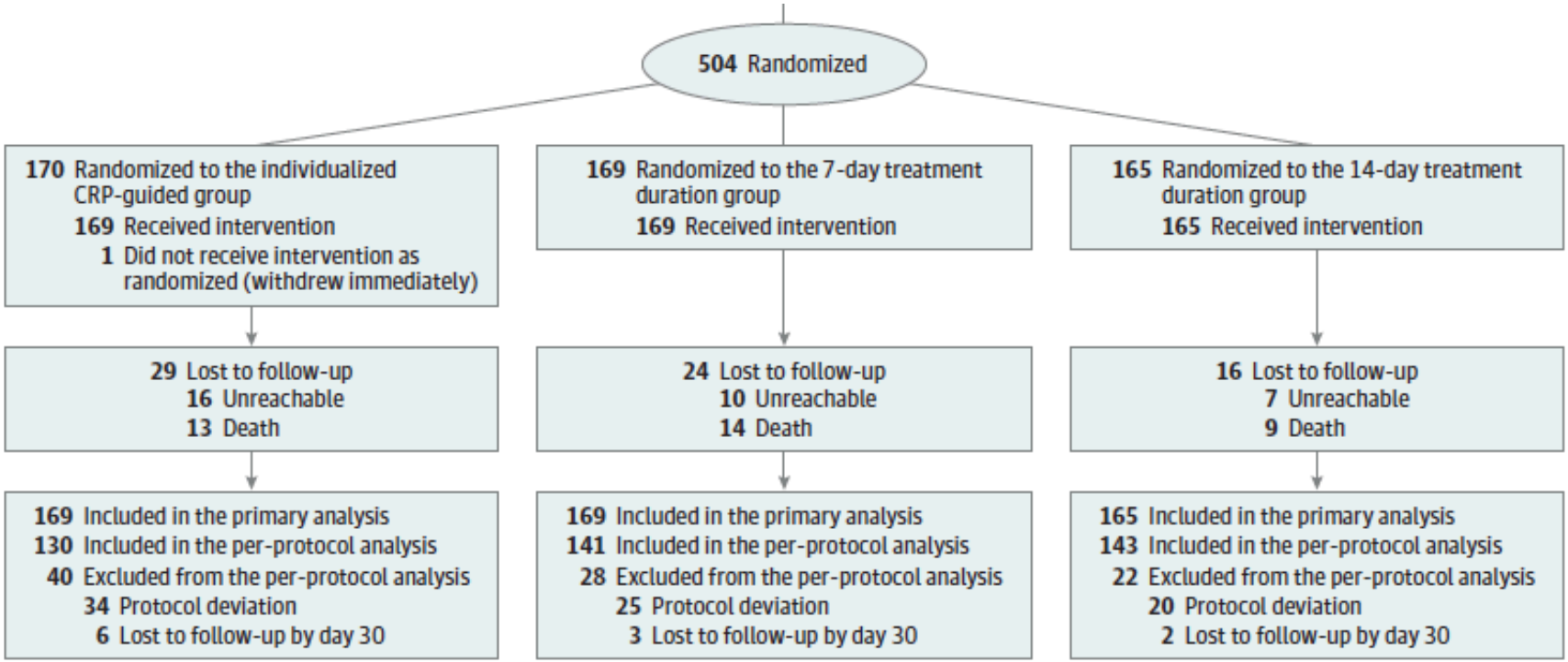
- Gramnegative Bakterien in mind. 1 Blutkultur
- Therapie mit mikrobiologisch effektiver Therapie

Ausschluss:

- Fieber oder hämodynamische Instabilität (in letzten 24h)
- schwere Immunsuppression
- Bakteriämie mit Non-Fermenter, polymikrobiell, grampositive Bakterien oder Rezidiv-Bakteriämie (in den letzten 60 Tagen)
- Komplizierte Infektion (Abszess, Endokarditis)

Flow der Studienteilnehmer

- Multicenter, April 2017 - Mai 2019
- Randomisierung an Tag 5 (+/- 1d) der Therapie



CRP-gesteuerte Gruppe

- Antibiotika-Stopp
  - wenn CRP um >75% gesunken (vom Maximum)
  - afebril >48h

- Follow-up telephonisch an Tag 30 (+/- 7d), Tag 60 (+/- 14d) und an Tag 90 (+/- 21d)

Baseline-Charakteristika der Patienten

Characteristic	Antibiotic therapy duration group, No. (%)		
	CRP-guided (n = 169)[a]	7 d (n = 169)	14 d (n = 165)
Sex			
Women	105 (62)	107 (63)	94 (57)
Men	64 (38)	62 (37)	71 (43)
Age, median (IQR), y	78 (69-86)	78 (69-86)	80 (67-85)
Race/ethnicity			
White	163 (96)	160 (95)	155 (94)
Asian	3 (2)	3 (2)	2 (1)
Hispanic	1 (1)	2 (1)	4 (2)
Black	1 (1)	2 (1)	2 (1)
BMI, median (IQR)	26 (23-30)	26 (23-30)	26 (23-29)
eGFR at inclusion, median (IQR), mL/min/1.73 m^2	51 (37-72)	51 (32-73)	55 (38-74)
Charlson Comorbidity Index score, median (IQR)[b]	1 (0-2)	1 (0-2)	1 (0-2)
Diabetes mellitus	38 (22)	33 (20)	36 (22)
Presence of removable urethral catheter	17 (10)	7 (4)	24 (14)
Presence of implanted material	41 (24)	36 (21)	31 (19)
Artificial joint	4 (2)	5 (3)	10 (6)
Implanted urinary tract device[c]	6 (4)	3 (2)	5 (3)
Endovascular device	6 (4)	2 (1)	1 (1)
Artificial valve	4 (2)	2 (1)	0 (0)
Other[d]	22 (13)	25 (15)	16 (10)

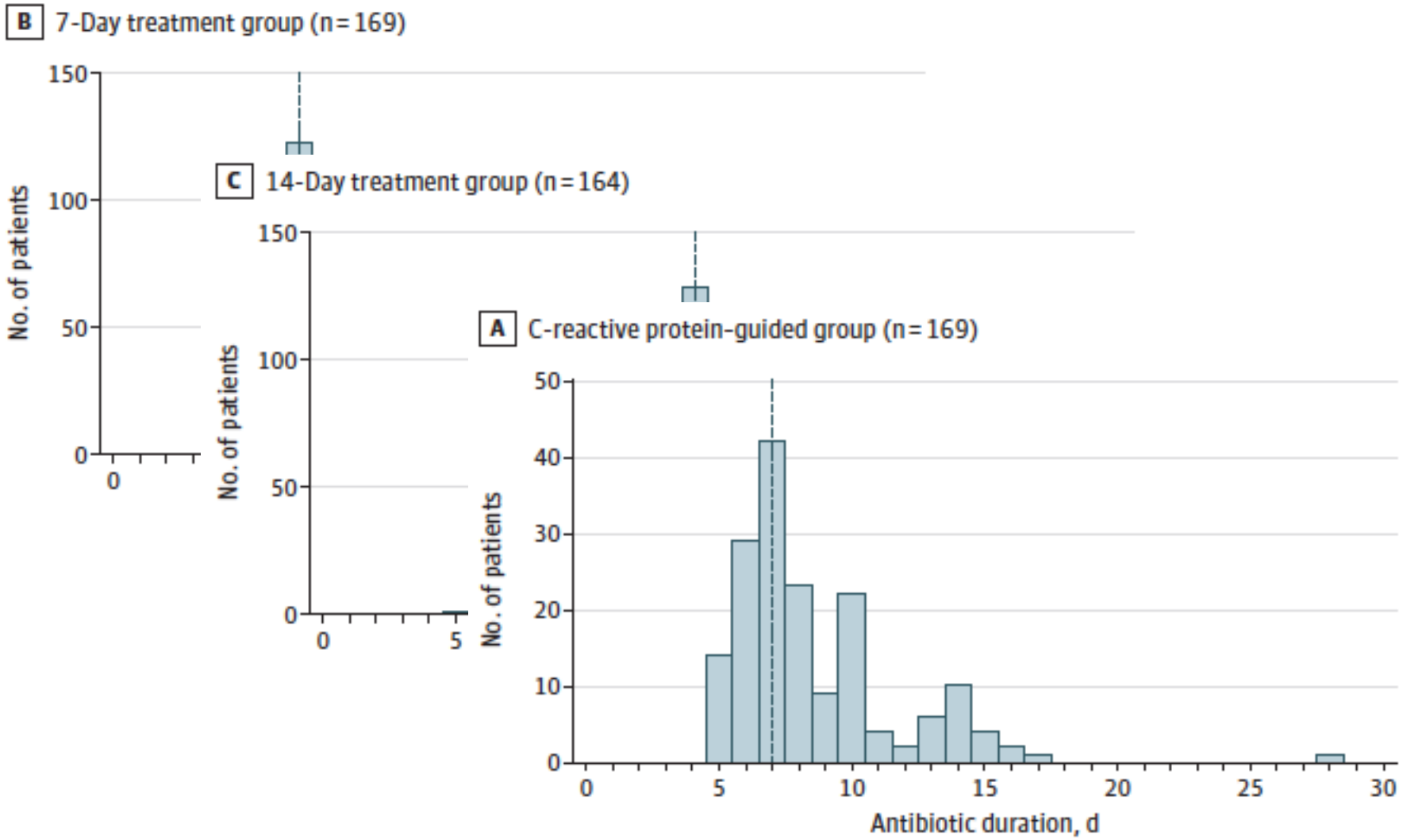
Baseline-Charakteristika der Patienten

Characteristic	Antibiotic therapy duration group, No. (%)		
	CRP-guided (n = 169)[a]	7 d (n = 169)	14 d (n = 165)
Source of bacteremia			
Urinary	124 (73)	107 (63)	117 (71)
Abdominal	30 (18)	37 (22)	20 (12)
Pulmonary	6 (4)	14 (8)	16 (10)
Endovascular device	1 (1)	5 (3)	5 (3)
Wound	0	2 (1)	2 (1)
Unknown	8 (5)	4 (2)	5 (3)
Bacteremia acquisition[e]			
Community-acquired	108 (64)	108 (64)	99 (60)
Nosocomial	45 (27)	45 (27)	45 (27)
Health care-associated	16 (9)	16 (9	21 (13)
qSOFA score, median (IQR)[f]	1 (0-2)	1 (0-2)	1 (0-1)

Baseline Blutkultur-Isolate

Blood culture isolate	Antibiotic therapy duration group, No. (%)		
	CRP-guided (n = 169)	7 d (n = 169)	14 d (n = 165)
Escherichia coli	126 (75)	123 (73)	124 (75)
Extended-spectrum β-lactamase	14 (8)	9 (5)	12 (7)
Klebsiella spp	27 (16)	35 (21)	26 (16)
Klebsiella pneumoniae	25 (15)	23 (14)	21 (13)
Extended-spectrum β-lactamase	1 (1)	2 (1)	1 (1)
Klebsiella oxytoca	1 (1)	11 (7)	1 (1)
Extended-spectrum β-lactamase	0	0	0
Klebsiella aerogenes	1 (1)	1 (1)	4 (2)
Extended-spectrum β-lactamase	1 (1)	0	0
Proteus spp	7 (4)	7 (4)	6 (4)
Proteus mirabilis	5 (3)	4 (2)	6 (4)
Extended-spectrum β-lactamase	0	0 (0)	0
Proteus vulgaris	2 (1)	3 (2)	0
Extended-spectrum β-lactamase	0	0	0
Enterobacter cloacae	6 (4)	3 (2)	1 (1)
Extended-spectrum β-lactamase	0	0	0
Other (%)[a]	9 (5)	10 (6)	12 (7)

Dauer der Antibiotika-Therapie



Outcome

Outcome	Antibiotic therapy duration group, No. (%)			CRP-guided vs 14 d		7 d vs 14 d	
	CRP-guided (n = 169)	7 d (n = 169)	14 d (n = 165)	Difference, % (1-sided 97.5% CI)	*P* value[a]	Difference, % (1-sided 97.5% CI)	*P* value[a]
Primary outcome							
Clinical response through day 30				−3.1 (−∞ to 1.1)	<.001	1.1 (−∞ to 6.3)	<.001
Clinical success	160 (97.6)	155 (93.4)	154 (94.5)				
Clinical failure	4 (2.4)	11 (6.6)	9 (5.5)				
Recurrent bacteremia	0	1 (9)[a]	2 (22)				
Suppurative local complication	0	2 (18)[b]	1 (11)				
Distal complication	0	0	0				
Targeted therapy restart	2 (50)	3 (27)	2 (22)				
30-d all-cause mortality[c]	2 (50)	6 (55)	4 (44)				
Missing[d]	5 (2.9)	3 (1.8)	2 (1.2)				

Outcome

Outcome	Antibiotic therapy duration group, No. (%)			CRP-guided vs 14 d		7 d vs 14 d	
	CRP-guided (n = 169)	7 d (n = 169)	14 d (n = 165)	Difference, % (1-sided 97.5% CI)	*P* value[a]	Difference, % (1-sided 97.5% CI)	*P* value[a]
Secondary outcomes							
Clinical response through day 60				−1.8 (−∞ to 3.7)	<.001	2.6 (−∞ to 8.9)	.010
Clinical success	146 (94.2)	141 (89.8)	146 (92.4)				
Clinical failure	9 (5.8)	16 (10.2)	12 (7.6)				
Recurrent bacteremia	0	1 (6)[b]	2 (17)				
Suppurative local complication	0	1 (6)[b]	1 (8)				
Distal complication	0	0	0				
Targeted therapy restart	7 (78)	9 (56)	5 (42)				
30-d all-cause mortality[c]	2 (22)	6 (38)	4 (33)				
Missing[d]	9 (5.3)	7 (4.1)	3 (1.8)				
Death after day 30	5 (3.0)	5 (3.0)	4 (2.4)				

Outcome

Outcome	Antibiotic therapy duration group, No. (%)			CRP-guided vs 14 d		7 d vs 14 d	
	CRP-guided (n = 169)	7 d (n = 169)	14 d (n = 165)	Difference, % (1-sided 97.5% CI)	*P* value[a]	Difference, % (1-sided 97.5% CI)	*P* value[a]
Clinical response through day 90				−3.5 (−∞ to 2.9)	<.001	0.1 (−∞ to 7.0)	.002
Clinical success	133 (93.0)	135 (89.4)	137 (89.5)				
Clinical failure	10 (7.0)	16 (10.6)	16 (10.5)				
Recurrent bacteremia	0	1 (6)[b]	2 (13)				
Suppurative local complication	0	1 (6)[b]	1 (6)				
Distal complication	0	0	0				
Targeted therapy restart	8 (80)	9 (56)	9 (56)				
30-d all-cause mortality[c]	2 (20)	6 (38)	4 (25)				
Missing[d]	15 (8.9)	10 (5.9)	7 (4.2)				
Death after day 30	11 (6.5)	8 (4.7)	5 (3.0)				

Kinetik vom CRP

	CRP-guided N=169	**7 days** N=169	**14 days** N=165
Median peak CRP concentration, mg/l (IQR)	171 (112-251)	164 (104-246)	154 (104-250)
Peak CRP, median study day* (IQR)	1 (0-2)	1 (0-2)	1 (0-2)
75% reduction from peak within 3 days (%)	36 (21)	38 (23)	54 (32)
50% reduction from peak within 3 days (%)	91 (53)	94 (56)	94 (57)

*Day 1 was the day that microbiologically efficacious antibiotic therapy was begun, thus day 0 was the day before.

Nebenwirkungen

- Relativ wenig, in allen Behandlungsgruppen ähnlich.
- Am häufigsten war *C. difficile* Infektion (13 von 493 Patienten, 3%), sonstige Diarrhoe (5 von 493, 1%)
- 6 schwere NW: Hospitalisationen (3 *C. difficile*, 1 Abdominal-Sz, 1 Kopf-Sz), 1 unerwarteter Todesfall

- *C. difficile* Infektion: anhand Antibiotika-Dauer
  - <7 Tage: 0 von 49 Patienten
  - 7-10 Tage: 5 von 245 Patienten (1%)
  - >10 Tage: 8 von 201 Patienten (4%)

Konklusion

- CRP-gestützte Antibiotika-Therapie ist non-inferior bei gramnegativen unkomplizierten Bakteriämien
- Unterstützen frühere Resultate, dass 7 Tage Antibiotika non-inferior ist zu 14 Tage bei gramnegativen Bakteriämien
- Am wenigsten Versagen zu jedem Zeitpunkt
- Median 7 Tage Antibiotika
- CRP-Erhöhung nicht spezifisch für Infektionen

Limitationen

- Verblindung nur zwischen Randomisierung und Antibiotika-Stopp
- Tägliche CRP-Kontrollen nicht durchgeführt, Routine-Kontrollen
- Interpretation der Resultate bei tiefer Event-Rate
- Tiefere Adhärenz zu zugewiesener Antibiotika-Dauer in der CRP-Gruppe, grosse Unterschiede in der Dauer
- Hohe Non-inferior Grenze (10%)