28th ECCMID,
21-24 April 2018, Madrid, Spain

SHORTENING THERAPY for BLOODSTREAM INFECTIONS

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Antimicrobial Stewardship – BASIC ACTIVITIES

RIGHT PROTOCOLS OF SURGICAL PROPHYLAXIS

SHARED INTRODUCTION MODALITIES OF NEW DRUGS

HIERACHICAL PATTERN OF PRESCRIPTIONS

RIGHT APPROACH TO COLONIZATION / CONTAMINATION

RIGHT SAMPLING FOR CULTURE

FEASIBLE DE-ESCALATION

SHORTENED DURATION OF ANTIBIOTIC THERAPY WHEN POSSIBLE

EARLY DISCHARGE

AVOIDANCE OF REDUNDANT PRESCRIPTIONS for NON BACTERIAL DISEASES

WHY HAVE PHYSICIANS ROUTINELY PRESCRIBED LONG TERM COURSES OF ANTIBIOTICS IN THE PAST?

lack of appreciation of the ecological damage of antibiotics on the intestinal microbiome

limited comparative effectiveness studies exploring optimal durations of therapies

prolonged durations of therapy often used by default in infectious diseases trials

limited understanding that antibiotic resistance was a public health threat

IN THE PAST ?!?!?!?

Are infection specialists recommending short antibiotic treatment durations? An ESCMID international cross-sectional survey *Macheda G et al, J Antimicrob Chemother 2018; 73: 1084–1090*

Infection specialists were invited to participate in an online cross-sectional survey between September and December 2016. The questionnaire included 15 clinical vignettes corresponding to common clinical cases with favorable outcomes; part A asked about the antibiotic treatment duration they usually advise to prescribers and part B asked about the shortest duration they were willing to recommend. A total of 866 participants were included, both clinical microbiologists and ID specialists, of whom 73% (624/854) acting as members of an antibiotic stewardship team, coming from 58 countries on all continents.

Meningococcal meningitis	Uncomplicated C-R S.aureus BSI	Uncomplicated CAP	acute exacerbation of a severe COPD	uncomplicated bacterial sinusitis
Uncomplicated pyelonephritis In an adult woman	Complicated pyelonephritis in an adult woman		acute cholangitis, treated by biliary drainage	
Uncomplicated C-R K. pneumoniae BSI	First episode of acute otitis media in a 2 years old kid		diffuse peritonitis with an early source control	
uncomplicated erysipelas	Escherichia coli vertebral osteomyelitis	staphylococcal PJI 1-stage exchange	diabetic foot infection, not eligible for surgery	

Are infection specialists recommending short antibiotic treatment durations? An ESCMID international cross-sectional survey *Macheda G et al, J Antimicrob Chemother 2018; 73: 1084–1090*

Prevalence of short durations of antibiotic therapy and shortened durations by country

	N	% advising short duration	% willing to shorten duration
Argentina	29	42.3	42.3
Austria	37	20.8	84.2
France	165	46.0	50.4
Germany	79	63.6	60.7
Greece	13	0	54.6
Ireland	16	0	46.7
Israel	26	17.4	38.1
Netherlands	13	38.5	33.2
Slovenia	39	12.5	51.9
South Africa	16	73.3	35.7
Spain	82	44.4	46.0
Sweden	22	10.0	33.3

Concerns of undertreating override concerns of overtreating

36% of participants (271/749) already advised short durations of antibiotic therapy (compared with the literature) to prescribers for more than half of the vignettes and 47% (312/662) were ready to shorten durations of treatment

Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis

Havey TC et al Critical Care 2011, 15:R267

Twenty-four eligible trials were identified, including one trial focusing exclusively on bacteremia, zero in catheter related bloodstream infection, three in intra-abdominal infection, six in pyelonephritis, thirteen in pneumonia and one in skin and soft tissue infection. Thirteen studies reported on 227 patients with bacteremia allocated to 'shorter' or 'longer' durations of treatment. Outcome data were available for 155 bacteremic patients

KEY MESSAGES

The optimal duration of treatment for bloodstream infections remains understudied.

Available data from bacteremic subgroups of prior randomized controlled trials suggest that shorter duration therapy (not more than 7 days) may be as effective as longer-duration therapy in achieving clinical cure, microbiologic cure, and survival among most patients with bloodstream infections.

A high rate of failure was seen among the small number of patients receiving short-duration treatment for *S. aureus* bacteremia, highlighting the potential importance of considering S. aureus bacteremia separately

How much is it correct to pool BSI data from multiple infectious sites and multiple etiologic agents into a single analysis ?

Duration of Antimicrobial Treatment for Bacteremia in Canadian Critically Ill Patients

Daneman N et al. Crit Care Med 2016; 44:256–264

Multicenter retrospective cohort study on 1202 patients who had BSI across 14 ICUs

Exclusion criteria:

- **only 1 BC pos for contamitants**
- **pts who normally need > 2 wk of therapy (IE, osteomyelitis, septic arthritis, unremoved prosthetic material, undrained abscess)**
- **No antimicrobial therapy**
- **Early death (within 10 days)**

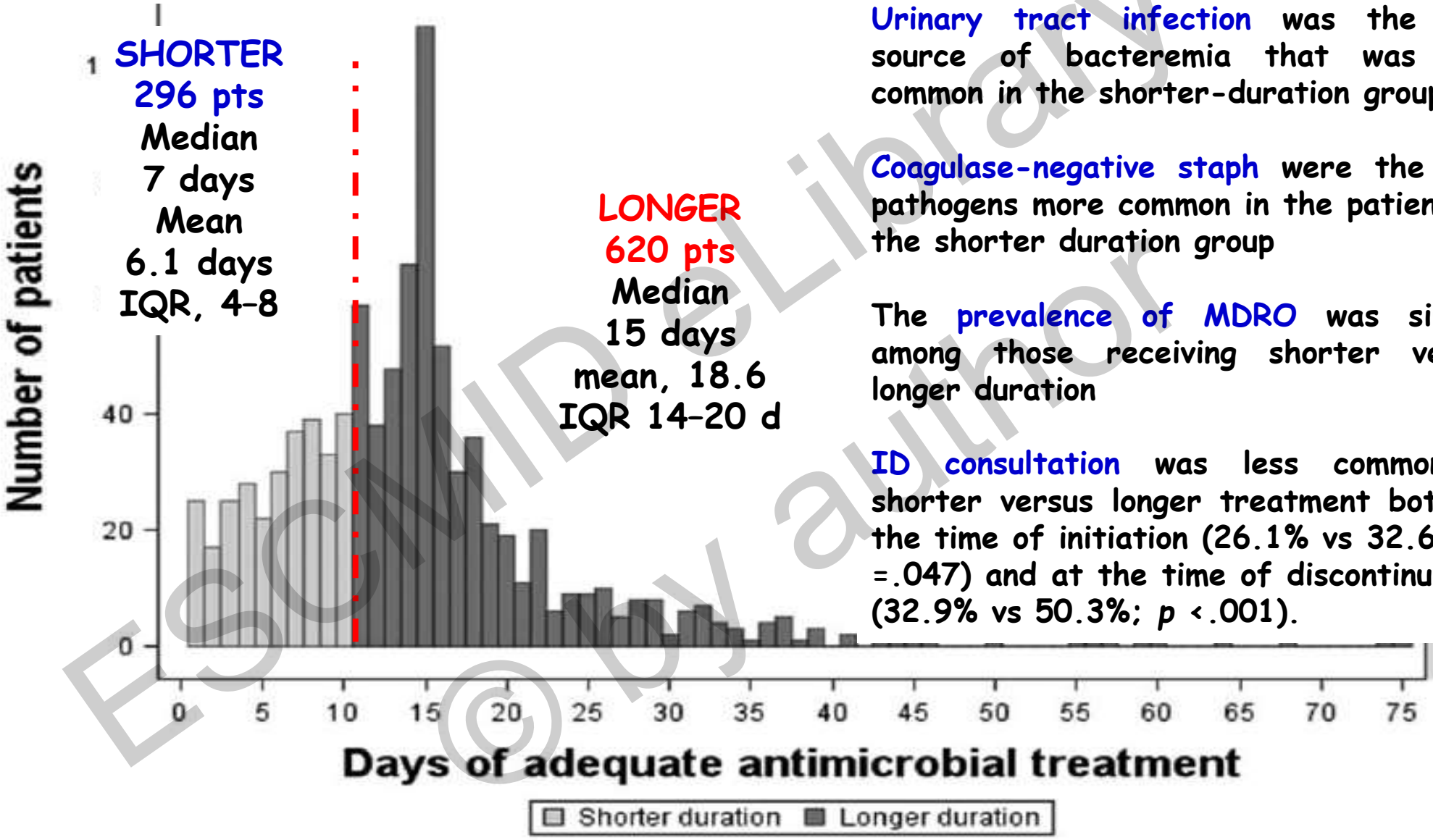
A total 916 ICU patients whose duration of antimicrobial treatment could be determined, with a median duration of treatment of 14 days, (9 to 17.5).

Antimicrobial treatment duration was dichotomized as shorter (≤ 10 d) and longer (> 10 d)

To account for selection bias propensity score matching was attempted , including the following variables :age, sex, APACHE score, comorbidities, community versus hospital versus ICU acquisition of infection, pathogen, and underlying syndrome.

Duration of Antimicrobial Treatment for Bacteremia in Canadian Critically Ill Patients

Daneman N et al. Crit Care Med 2016; 44:256-264



Urinary tract infection was the only source of bacteremia that was less common in the shorter-duration group

Coagulase-negative staph were the only pathogens more common in the patients in the shorter duration group

The **prevalence of MDRO** was similar among those receiving shorter versus longer duration

ID consultation was less common in shorter versus longer treatment both at the time of initiation (26.1% vs 32.6%; *p* =.047) and at the time of discontinuation (32.9% vs 50.3%; *p* <.001).

Duration of Antimicrobial Treatment for Bacteremia in Canadian Critically Ill Patients

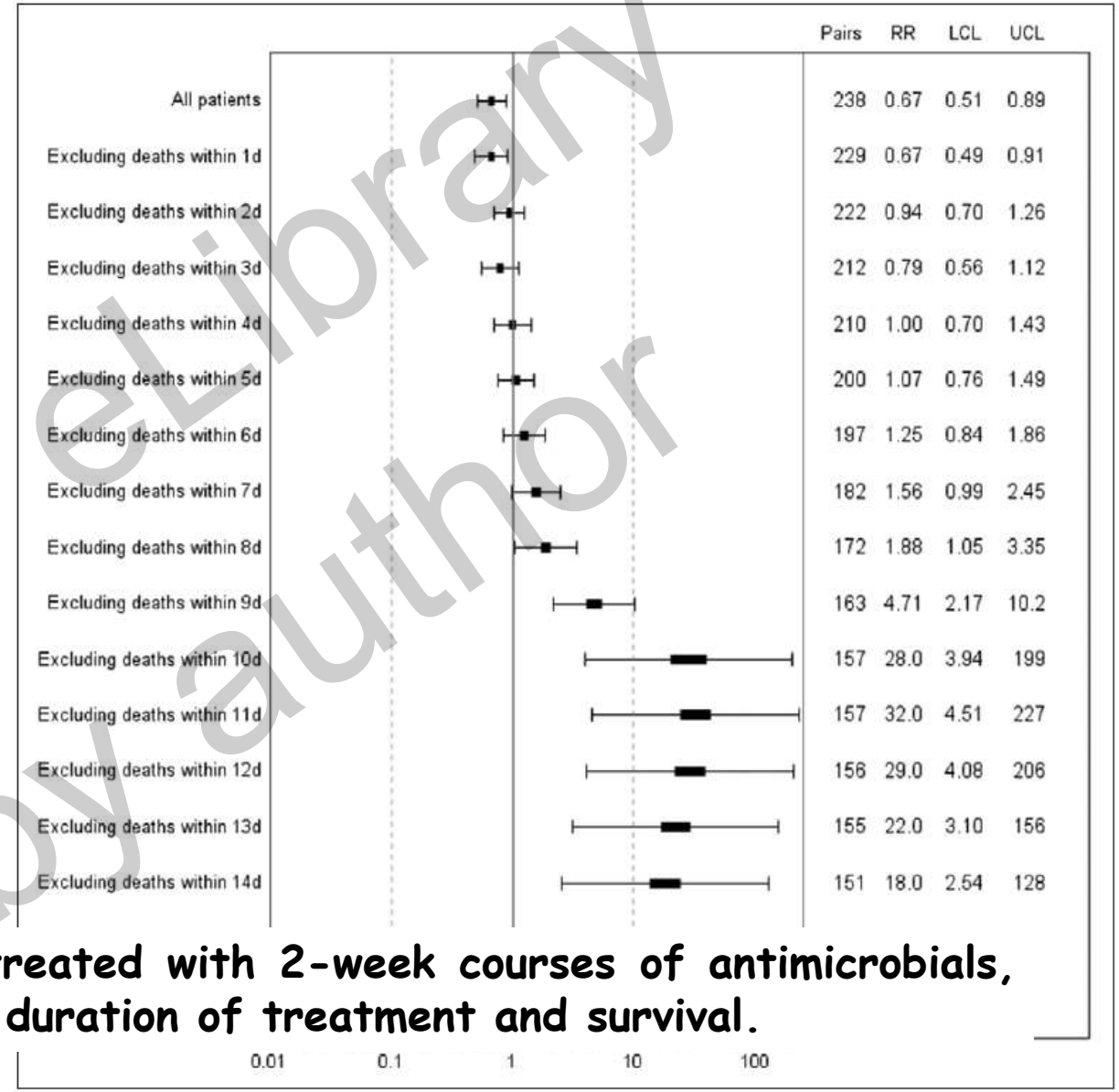
Daneman N et al. Crit Care Med 2016; 44:256-264

OUTCOME

Impact of excluding early deaths

Crude hospital survival was lower among patients who had shorter duration of treatment (66% vs 77% in the longer duration group; $p < 0.001$).
After propensity matching a decreased survival among patients who had a shorter duration of treatment remained but, when early death were succesively excluded, a progressive shift in the relative risk of survival toward favouring patients receiving shorter duration was observed.

The risk of relapse was similar in those receiving shorter versus longer duration treatment (6% vs 8%; $p = 0.29$).



Key message: most patients are treated with 2-week courses of antimicrobials, with no clear relationship between duration of treatment and survival.

Optimal duration of antimicrobial therapy for uncomplicated Gram-negative bloodstream infections.

Nelson AN et al, Infection 2017; 45:613-620

Retrospective cohort study aimed to examine effectiveness of short (7–10 days) and long (>10 days) courses of antimicrobial therapy for uncomplicated Gram-negative BSI. Treatment failure was defined as mortality or recurrent infection within 90 days of index BSI.
Uncomplicated Gram-negative BSI was defined as the absence of in-hospital mortality, prolonged hospitalization for >14 days, or deep-seated infections such as intra-abdominal or pelvic abscesses.
During the study period, 411 pts were enrolled, 117 and 294 patients receiving short and long courses of antimicrobial therapy for uncomplicated Gram-negative BSI, respectively.
Multivariate Cox proportional hazards regression with propensity score adjustment was used to examine risk of treatment failure in the two groups.

Overall,
the median age was 67
258 (63%) were women,
282 (69%) had a urinary source
271 (66%) had BSI due to *E. coli*

Microbiology

Bacteria	Duration of therapy	
	7–10 days ($n = 117$)	>10 days ($n = 294$)
Escherichia coli	79 (68)	192 (65)
Klebsiella species	15 (13)	46 (16)
Proteus mirabilis	8 (7)	17 (6)
Pseudomonas aeruginosa	6 (5)	12 (4)
Enterobacter species	3 (3)	9 (3)
Other	6 (5)	18 (6)

Optimal duration of antimicrobial therapy for uncomplicated Gram-negative bloodstream infections.

Nelson AN et al, Infection 2017; 45:613–620

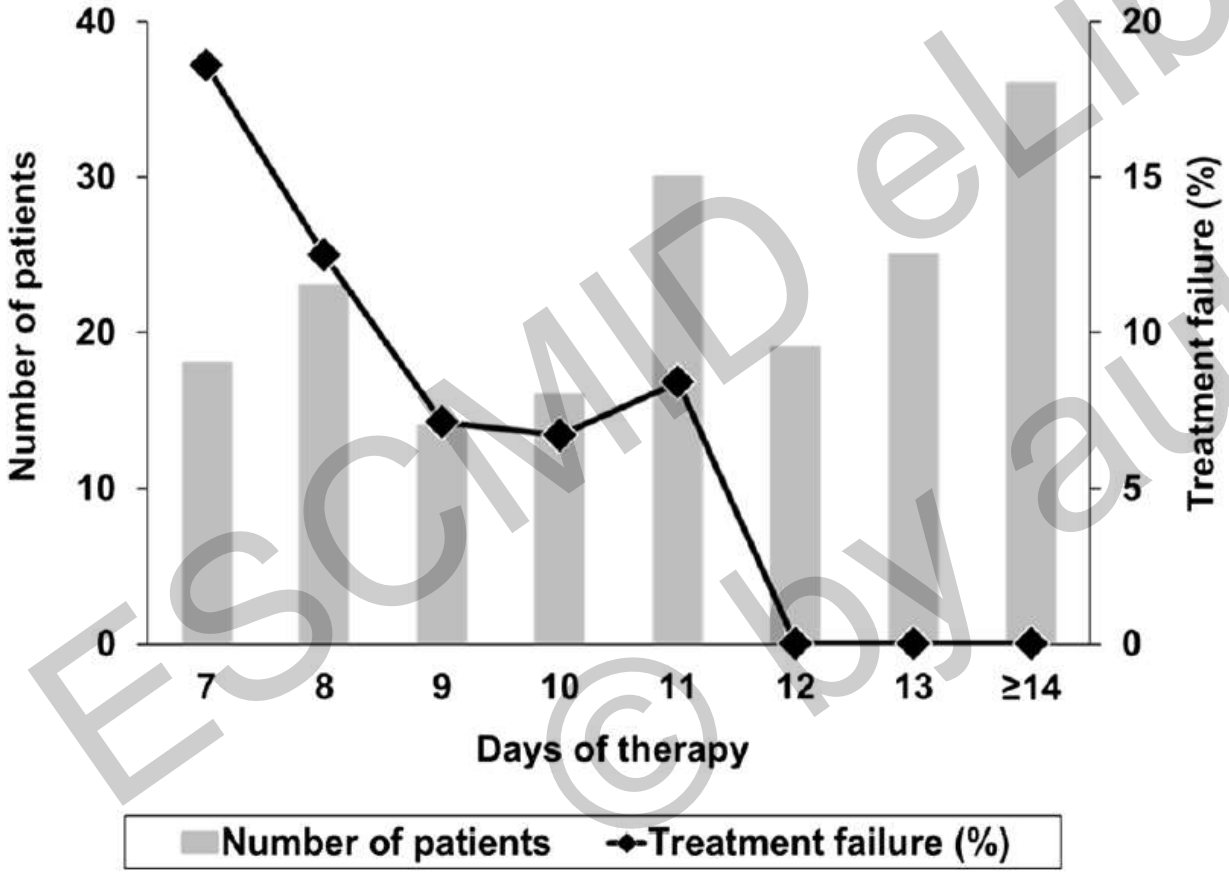
Patients in the short and long antimicrobial therapy groups were comparable in most baseline demographics and clinical characteristics. Baseline variables that were evaluated in propensity analysis included demographics, chronic comorbidities, site of infection acquisition, presence of indwelling central venous catheters or urologic disorders prior to BSI.
The median duration of adequate antimicrobial therapy was 8.5 and 13.3 days in the short and long treatment groups, respectively, including approximately 5 days of intravenous therapy in either group. Overall, within 90 days of BSI, 32 patients had treatment failures (11 deaths and 21 recurrences).

Risk factors for treatment failure in multivariate Cox model adjusting for the propensity to receive a short course of antimicrobial therapy

Variable	HR	(95% CI)	*p*-value
Liver cirrhosis	5.83	(1.89–15.02)	0.004
Immune compromised host	4.30	(1.57–10.80)	0.006
Central venous catheter	1.50	(0.52–3.93)	0.44
Definitive therapy with IV/high bioavailability oral agents	0.33	(0.14–0.73)	0.006
Total duration of adequate therapy			
>10 days	1	Referent	
7–10 days	2.60	(1.20–5.53)	0.02

Optimal duration of antimicrobial therapy for uncomplicated Gram-negative bloodstream infections. *Nelson AN et al, Infection 2017; 45:613-620*

Treatment failure rates by days of antimicrobial therapy in a subgroup of 181 patients who received intravenous or high bioavailability oral agents



KEY MESSAGE

More than 10 days of right treatment are needed in uncomplicated gram neg BSI

Treatment duration for Escherichia coli bloodstream infection and outcomes: retrospective single-centre study.

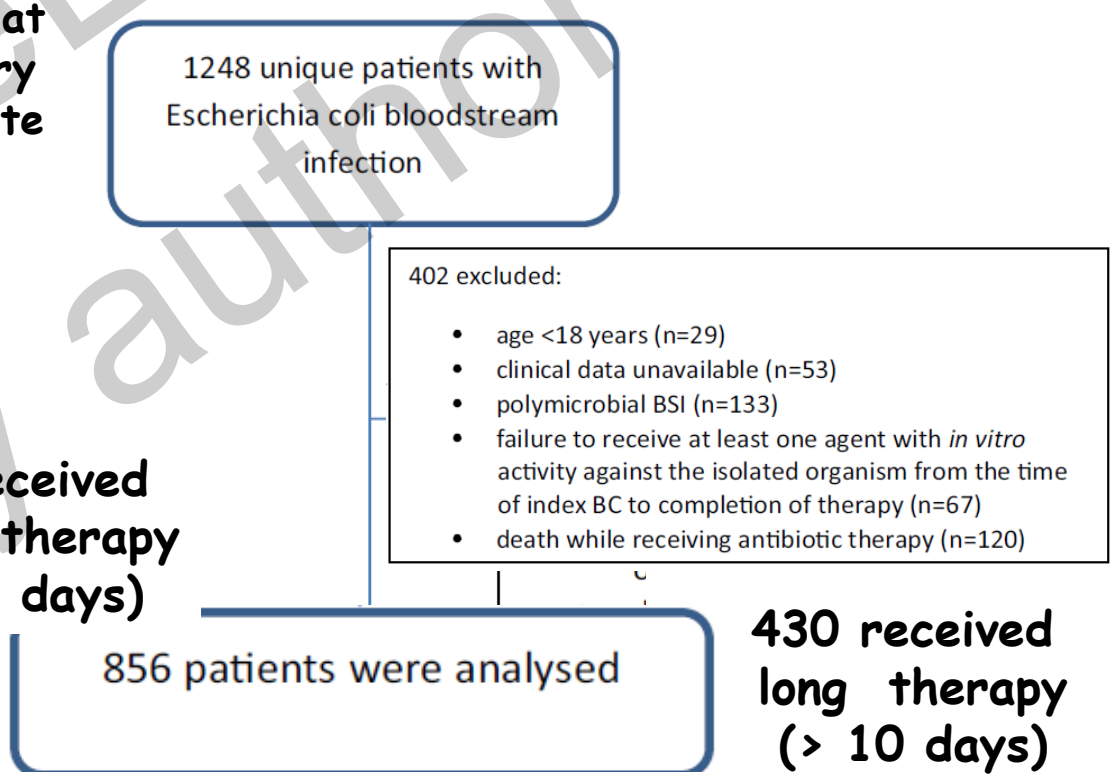
Giannella M et al, Clin Microbiol Infect. 2018 Jan 31

Retrospective study of patients diagnosed with E. coli BSI over a 4-year period, aimed to investigate the impact of treatment duration on mortality and on relapse. Exclusion criteria were age <18 years, clinical data not available, polymicrobial BSI, failure to receive in vitro active therapy, and death while receiving antibiotic therapy.

Propensity score of receiving a short course of therapy was calculated using a multivariate logistic regression model in which the outcome variable was short treatment duration (10 days). The following variables were introduced into the model: age, sex, chronic kidney disease, COPD,Charlson index, SOFA score at BSI onset, septic Shock at BSI onset, urinary and biliary tract as BSI sources, appropriate empiric therapy and source control.

Primary end point was all-cause mortality within 90 days after index BSI.

Secondary end point was relapse, defined as repeat isolation of E. coli from blood cultures within 90 days after index BSI, in patients with documented clinical cure and completion of therapy for the initial episode.



Treatment duration for Escherichia coli bloodstream infection and outcomes: retrospective single-centre study. *Giannella M et al, Clin Microbiol Infect. 2018 Jan 31*

All-cause mortality at day 90 occurred in 47 patients

Multivariate analysis of risk factors for all-cause mortality at day 90

	Unadjusted for the propensity score of receiving short therapy			Adjusted for the propensity score of receiving short therapy		
	aHR	95%CI	p	aHR	95%CI	p
Age	1.03	1.00-1.06	.02	1.04	1.01-1.07	.009
Chronic kidney disease	2.66	1.38-5.15	.004	1.38	0.39-4.81	.61
SOFA at BSI onset	1.19	1.07-1.34	.001	1.10	0.92-1.31	.27
LRT as BSI source	2.95	0.95-9.24	.06	3.69	1.09-12.4	.03
C-R BSI	5.62	1.74-18.2	.004	6.65	1.97-22.4	.002
HCA-BSI	2.72	1.13-6.54	.02	2.68	1.11-6.46	.03
H-BSI	2.64	1.13-6.13	.02	2.73	1.17-6.40	.02
Appropriate empiric tx	0.36	0.19-0.70	.002	0.16	0.04-0.69	.01
Short treatment duration	1.14	0.60-2.16	.69	1.15	0.69-1.15	.67

Treatment duration for Escherichia coli bloodstream infection and outcomes: retrospective single-centre study. *Giannella M et al, Clin Microbiol Infect. 2018 Jan 31*

Relapse occurred in 42 patients

Multivariate analysis of risk factors for relapse within 90 days

	aHR	95%CI	p	SHR*	95%CI	p
ESLD	2.59	1.23-5.46	.013	2.58	1.22-5.46	.02
Immunosuppression	4.51	2.40-8.48	<.001	4.67	2.46-8.87	<.001
ESBL producing strain	1.88	1.02-3.50	.04	1.74	0.87-3.48	.12
UTI as BSI source	0.54	0.27-1.08	.08	0.50	0.24-1.03	.06
Treatment > 10 days	0.74	0.40-1.38	.35	0.72	0.39-1.35	.31

SHR* was obtained using death as competing risk

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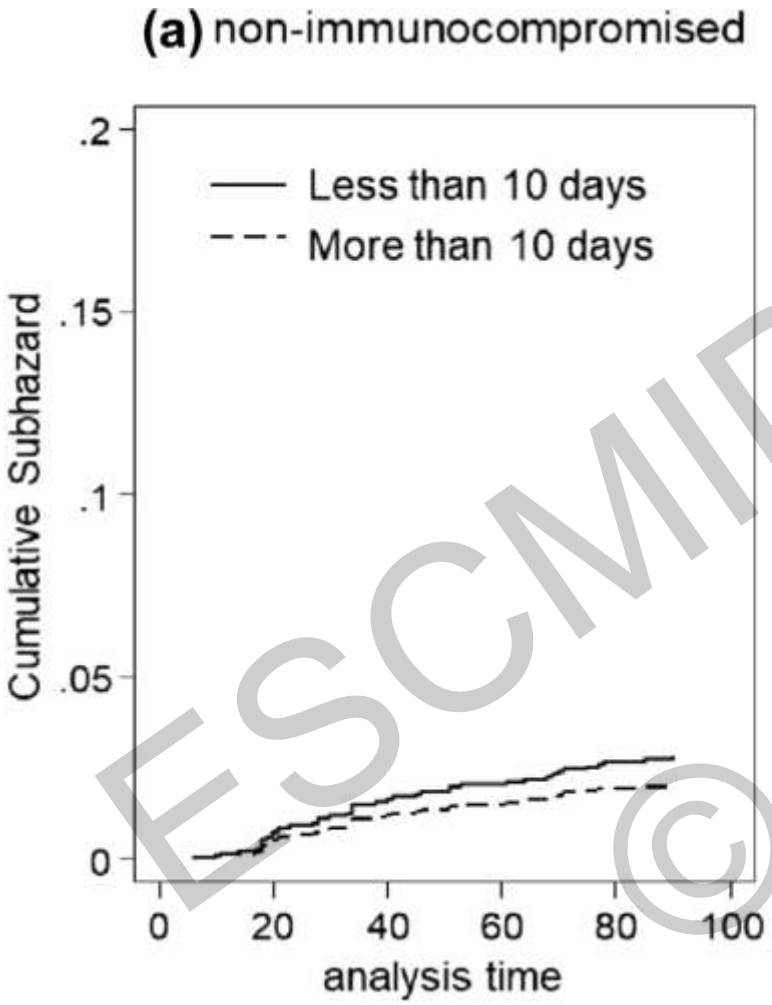
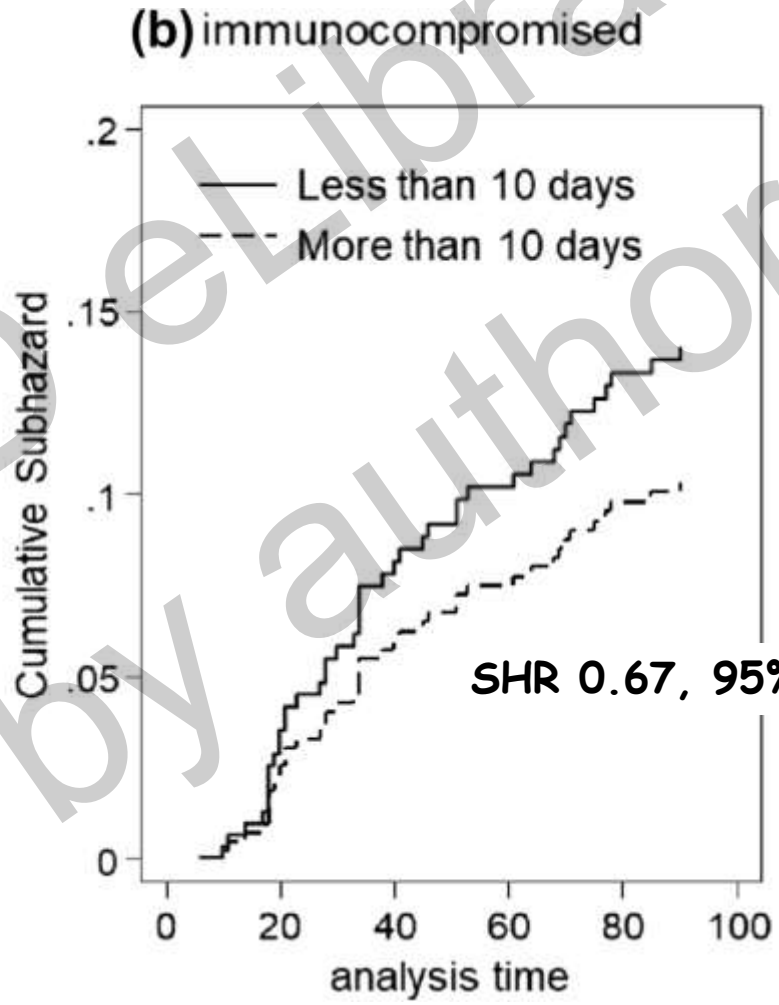
Competing risk subhazards for recurrent E. coli bloodstream infection





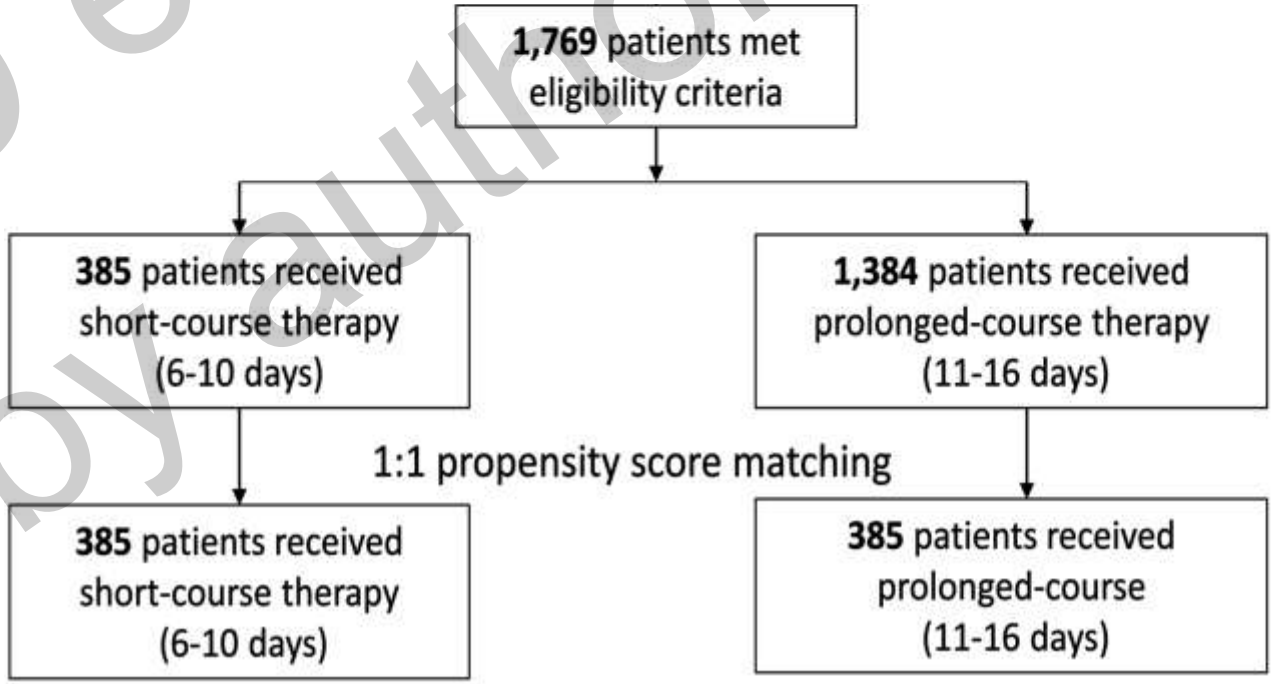
SHR 0.67, 95% CI 0.30-1.47, p 0.32

Comparing the Outcomes of Adults With Enterobacteriaceae Bacteremia Receiving Short-Course Versus Prolonged-Course Antibiotic Therapy in a Multicenter, Propensity Score-Matched Cohort. *Chotiprasitsakul D et al Clin Infect Dis 2018;66:172-177.*

A retrospective cohort study, conducted at 3 medical centers including patients with mono-microbial Enterobacteriaceae BSI treated with in vitro active therapy in the range of 6–16 days from 2008 to 2014. Propensity scores were calculated using a multivariable logistic regression model in which the dependent variable was a binary indicator of antibiotic duration. Covariates used in generating the propensity score included calendar year of BSI, age, comorbities, immunocompromising conditions, Pitt score, ICU stay on day 1 of bacteremia, source of bacteremia, and source control measures.

1:1 nearest neighbor propensity score matching without replacement was performed prior to regression analysis to estimate the risk of all cause mortality within 30 days comparing patients in the 2 treatment groups.

Secondary outcomes included recurrent BSI, *C. diff.* infections, and the emergence of MDR gram-neg bacteria, all within 30 days after the end of antibiotic therapy.



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Baseline characteristics of the two matched groups were well-balanced when evaluating standardized biases.

The median duration of therapy in the short-course group and prolonged-course groups was 8 days (IQR 7–9 days) and 15 days (IQR, 13–15 days), respectively.

The most common organisms identified were *Escherichia coli* (46.9%) followed by *Klebsiella* species (32.6%), and *Enterobacter* species (11.7%)

All patients were initiated on β-lactam therapy at the time blood cultures were obtained.

Approximately 30% of bloodstream infections occurred in ICU patients.

Less than 1% of patients had inadequate source control within 7 days, indicating that most patients had "uncomplicated" bacteremia.

Approximately 34% of included patients were immunocompromised (instead of for solid organ transplant or haematological condition)

After propensity score matching, there were 37 (9.6%) and 39 (10.1%) deaths within the 30-day follow-up period in the short course and prolonged-course groups, respectively

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Primary outcome - Thirty-Day All-Cause Mortality
Univariate and multivariate models

Variable	HR	P value	95% CI	aHR	95% CI	P value
Short-course therapy	1.12	.64	0.70-1.80	1	0.62-1.63	.97
Urinary source	0.36	.001	0.19-0.67	0.49	0.26-0.94	.03
Pneumonia	3.06	<.001	1.73-5.42	1.60	0.85-3.02	.15
Pitt score	1.31	<.001	1.21-1.42	1.29	1.17-1.43	<.001
ICU stay on day 1	2.38	<.001	1.21-1.42	0.99	0.56-1.76	.98
ESLD	3.58	<.001	2.05-6.06	4.12	2.30-7.39	<.001
Immunosuppression	1.03	.89	0.63-1.70	1.40	0.83-2.36	.21

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There were 5 (1.3%) and 9 (2.3%) episodes of recurrent bloodstream infections in the short- and prolonged-course treatment groups, respectively

CDI occurred in 7 (1.8%) and 6 (1.6%) patients within 30 days

There were 17 (4.4%) reports of incident MDRO in the short-course and 28 (7.3%) in the prolonged-course treatment groups

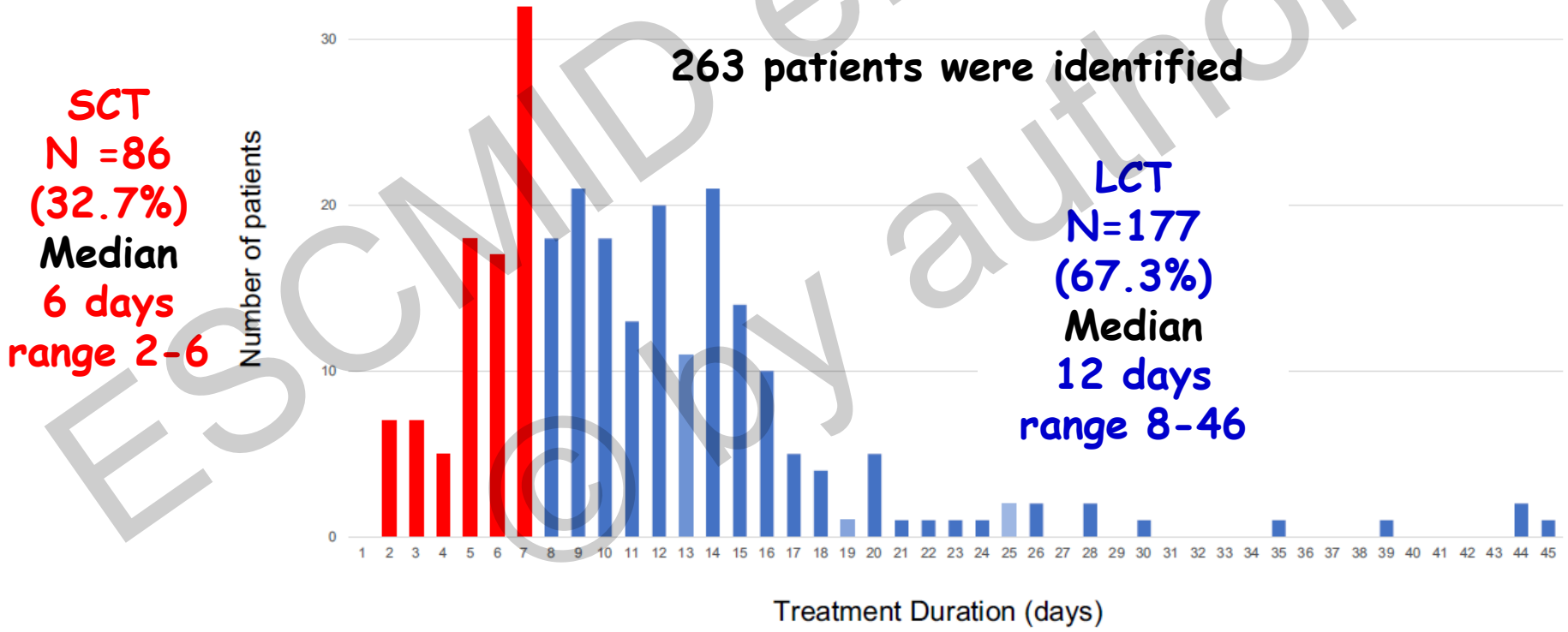
secondary outcomes

measure	Short	Prolonged	OR	95% CI
Recurrent BSI (%)	1.3%	2.3%	1.32	0.48-3.41
CDI (%)	1.81%	1.6%	1.16	0.39-3.51
Incident MDRO (%)	4.4%	7.3%	0.59	0.32-1.09

Shorter duration of antibiotic treatment for acute bacteraemic cholangitis with successful biliary drainage: a retrospective cohort study.

Doi A et al, Clin Microbiol Infect. 2018 Mar 7. [Epub ahead of print]

Retrospective cohort study of patients with acute bacteraemic cholangitis with successful biliary duct drainage at a single centre in Japan. Short-course antimicrobial therapy (7 days) and long-course therapy (8 days) were compared, with a primary outcome of 30-day mortality. A logistic regression models for mortality and a composite outcome, including mortality, recurrence, recrudescence, new bacteraemia, liver abscess or other complications related to cholangitis were constructed . A propensity score for short course with inverse probability weighting for both the primary outcome and the composite outcome was developed.



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Endoscopic retrograde cholangiopancreatography was performed in most patients (85/86 (98.8%) and 171/177 (96.6%) for SCT and LCT, respectively, p 0.43).

Co-morbidities in both groups were largely similar.

Medical treatments that might have affected the immune systems of the patients were similar between SCT and LCT, including use of glucocorticoids, other immunosuppressive agents and on-going chemotherapy.

The most common causative organisms found in blood cultures were Gram-negative bacteria (75/86 (87.2%) in SCT group and 157/177 (88.7%) in LCT group, p 0.88).

The median qSOFA scores for SCT and LCT were 0 (range 0-3) and 1 (range 0-3), respectively (p 0.02).

Shorter duration of antibiotic treatment for acute bacteraemic cholangitis with successful biliary drainage: a retrospective cohort study.

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Results of primary and secondary outcomes between short-course therapy and long-course therapy

	OUTCOME		UNIVARIATE ANALISYS		LOGISTIC REGRESSION	
	STC	LTC	OR	95%CI	OR	95%CI
Mortality	4.7%	5.7%	0.82	0.18-2.95	1.07	0.25-4.52
Recrudescence	3.9%	3.9%	0.99	0.26-3.87		
Recurrence	6.5%	7.9%	0.82	0.30-2.24		
New Bacteremia	5.6%	9.1%	0.61	0.20-1.83		
Composite Outcome	16.3%	15.3%	1.07	0.59-2.29	1.08	0.48-2.45

Variables used for logistic regression analysis: empirical antimicrobials covering the causative organisms, qSOFA score, time to drainage, polymicrobial infections, Gram-positive organisms identified

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Results of primary and secondary outcomes between short-course therapy and long-course therapy

	PROPENSITY SCORE ANALYSIS (IPW)				
OUTCOME MEASURES	STC	LTC	ATE	95%CI	P
Mortality	4.7%	5.7%	0.02	-0.05-0.08	0.65
Recrudescence	3.9%	3.9%	0.99	0.26-3.87	
Recurrence	6.5%	7.9%	0.82	0.30-2.24	
New Bacteremia	5.6%	9.1%	0.61	0.20-1.83	
Composite Outcome	16.3%	15.3%	1.07	0.59-2.29	0.95

Variables used for propensity score analysis were: detection of Gram-positive organisms, presence of polymicrobial infections, presence of infectious diseases consultation, empirical antimicrobials covering the causative organisms, qSOFA score, time to drainage, liver mass and white blood cell count

Seven versus 14 days of antibiotic treatment for critically ill patients with BSI: a pilot randomized clinical trial

Daneman N et al, Trials 2018; 19: 111

Open, pilot RCT across 11 Canadian intensive care units (ICUs).

Antibiotic selection, dosing and route were at the discretion of the treating team. Patients were randomized 1:1 to intervention arms consisting of two fixed durations of treatment – 7 versus 14 days.

Patients with severe immunosuppression, foci of infection with an established requirement for prolonged treatment, single cultures with potential contaminants, or cultures yielding Staphylococcus aureus or fungi were excluded.

The primary feasibility outcomes were recruitment rate and adherence to treatment duration protocol.

Secondary outcomes included 90-day, ICU and hospital mortality, relapse of bacteremia, lengths of stay, mechanical ventilation and vasopressor duration, antibiotic-free days, Clostridium difficile, antibiotic adverse events, and secondary infection with antimicrobial-resistant organisms.

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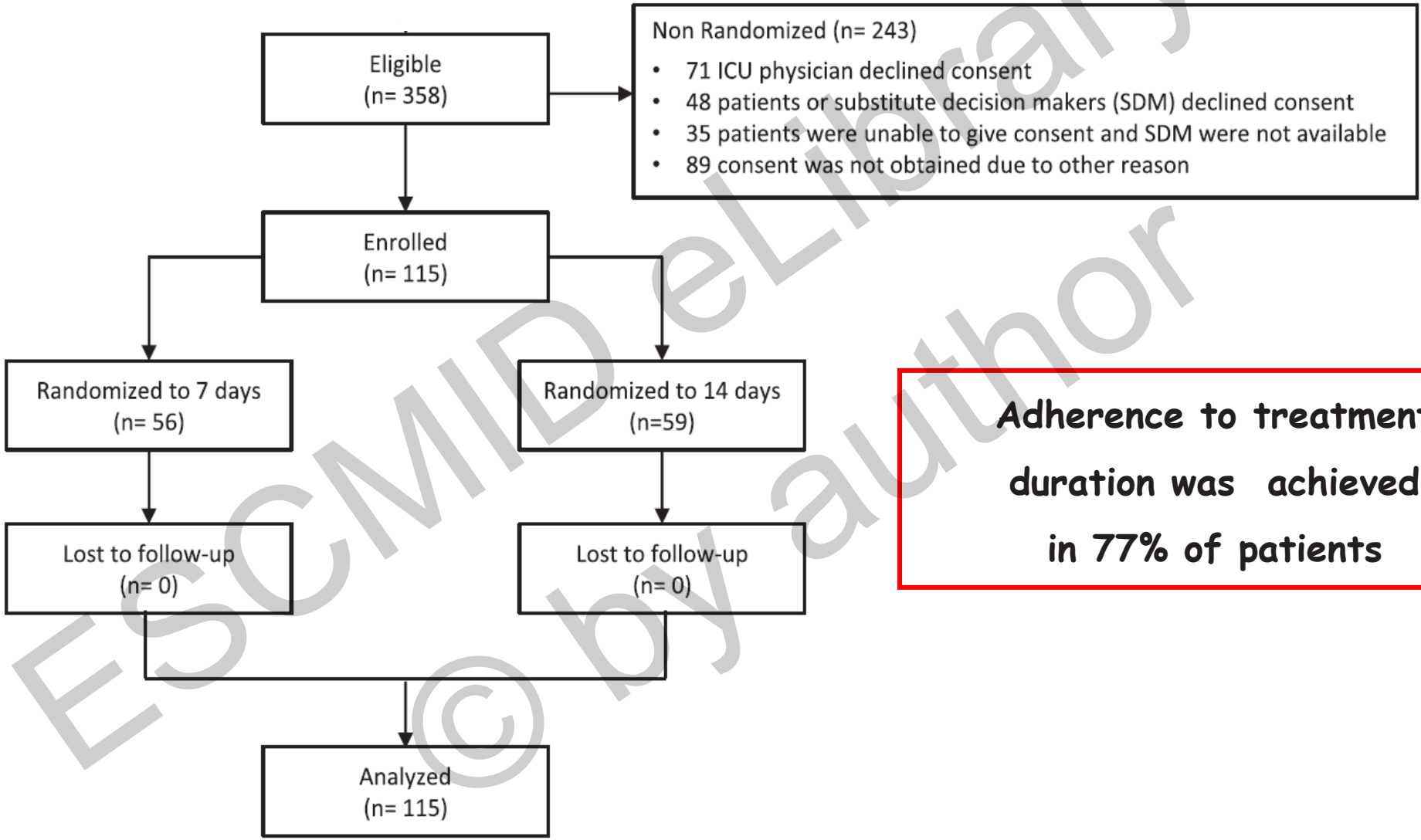

Adherence to treatment duration was achieved in 77% of patients

Seven versus 14 days of antibiotic treatment for critically ill patients with BSI: a pilot randomized clinical trial

Daneman N et al, Trials 2018; 19: 111

Acquisition of BSI	%
Community-acquired	60
Hospital extra ICU-acquired	17
Hospital ICU-acquired	24
Source of BSI	**%**
Lung	27
Intra-abdominal/hepato-biliary	25
Urinary tract	23
Indwelling vascular catheter	8
Skin Soft Tissue	3
Unknown	10

Etiological agents – top ten	%
Escherichia coli	22
Klebsiella spp.	14
Enterococcus spp.	13
Streptococcus pneumoniae	10
Coagulase-neg staphylococci	9
Enterobacter spp.	5
Pseudomonas spp.	3
Serratia spp.	3
Citrobacter spp.	2
Streptococcus anginosus group	2

28th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
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O1120 Seven versus 14 antibiotic days for the treatment of Gram-negative bacteraemia: non-inferiority randomized controlled trial

Dafna Yahav*[1], Adi Turjeman[2], Tanya Babitch[2], Fidi Koppel[3], Roni Bitterman[4], Ami Neuberger[4], Nesrin Ghanem-Zoubi[4], Erica Franceschini[5], Cristina Mussini[5], Antonella Santoro[5], Noa Eliakim - Raz[6], Barak Pertzov[6], Tali Steinmetz[6], Leonard Leibovici[6], Mical Paul[3]

Multicentre, investigator-initiated, open-label, non-inferiority randomized controlled trial comparing 7 (intervention) versus 14 (control) days of covering antibiotic therapy for GNB in hospitalized patients. Patients with ongoing sepsis or uncontrolled source of infection were excluded.

The primary outcome was a composite of all-cause mortality, clinical failure, re-admission or extended (>14 days) hospital stay, evaluated at 90 days.

A total of 604 patients (306 intervention, 298 control) were included. Source of infection was urinary in 68% (411/604); causative pathogens were Enterobacteriaceae in 90% (543/604).

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O1120 **Seven versus 14 antibiotic days for the treatment of Gram-negative bacteraemia: non-inferiority randomized controlled trial**

Dafna Yahav*[1], Adi Turjeman[2], Tanya Babitch[2], Fidi Koppel[3], Roni Bitterman[4], Ami Neuberger[4], Nesrin Ghanem-Zoubi[4], Erica Franceschini[5], Cristina Mussini[5], Antonella Santoro[5], Noa Eliakim - Raz[6], Barak Pertzov[6], Tali Steinmetz[6], Leonard Leibovici[6], Mical Paul[3]

At 90 days, the composite primary outcome of mortality, failure or re-admission/extended hospitalization occurred in 141 of 306 patients in the 7 days group (46.1%) versus 149 of 298 patients (50.0%) in the 14 days group (absolute risk difference -3.9%, 95% CI -11.9 % to 4.0%).
No significant differences in fatality rate at 90 days (7 days: 36 (11.8%), 14 days: 32 (10.7%), ARD 1.0, 95% CI -4.0 to 6.1) or other secondary outcomes were demonstrated between study arms.

<u>Conclusions</u>: In patients hospitalized with GNB and sepsis resolution before day 7, a course of 7 covering antibiotic days was non-inferior to 14 days, reduced 1551 antibiotic days and resulted in a more rapid return to baseline activity

Antibiotic Treatment Duration (7 vs 14 Days) Comparison in Blood Stream Infection Causes by Enterobacteriaceae (SHORTEN)

ClinicalTrials.gov Identifier: NCT02400268

To prove that 7-days course of antibiotic therapy is more efficient than 14-days course when treating Enterobacteriaceae bacteremia, in terms of number of days at the end of follow up.

Country : Spain

SHORTENING THERAPY for BLOODSTREAM INFECTIONS SEEMS A FEASIBLE GOAL …

BUT

Is shortening treatment duration of therapy our definitive aim or could we consider it the first step toward a personalized time of treatment ?