Ferrara, 20 giugno 2019

Shock settico e sepsi: diagnosi precoce e gestione terapeutica

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Il mantra della terapia antibiotica nel paziente critico

TANTO e SUBITO

TANTO …

TANTO ANTIBIOTICO? ⇐

TANTI ANTIBIOTICI?

Early recognition and adequate source control is the cornerstone of septic shock therapy. The hemodynamic alterations in sepsis (high CO/vasodilation/capillary leak) have antibiotic drug dosing implications.

Optimal dosing of antibiotics in septic shock is often not achieved with current recommended doses.

The challenge is in preventing underdosing while avoiding adverse effects associated with overdosing

Cecconi M et al, Lancet 2018; 392: 75–87

1

Loading Dose

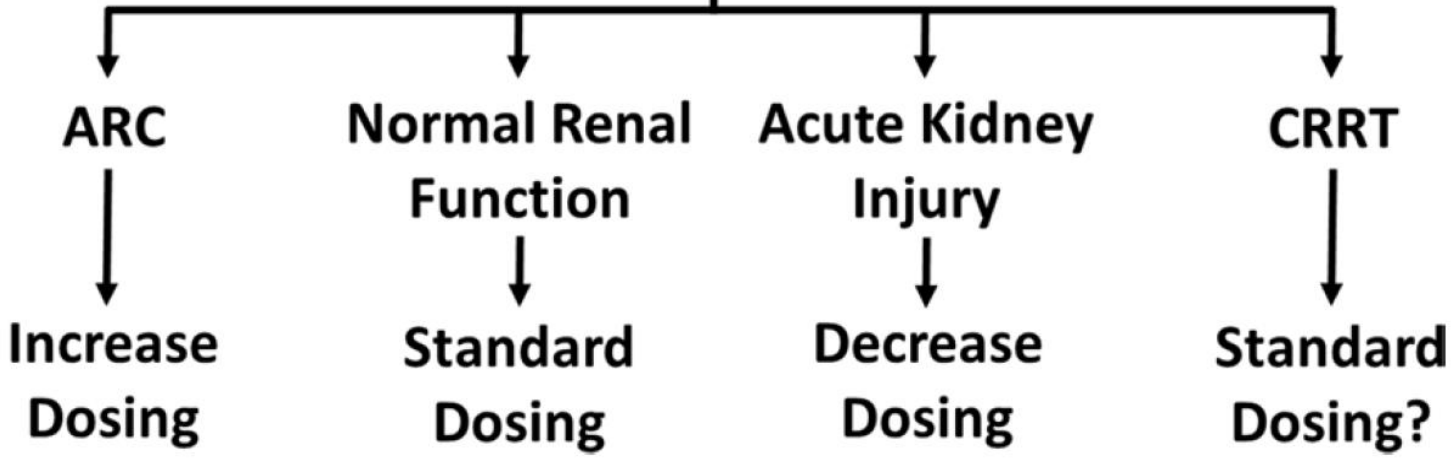
Beta-lactams, aminoglycosides, glycopeptides, colistin

~1.5 X standard dose

Loading doses for hydrophilic antibiotics should be given independently of subsequent dosing, which needs to be adjusted according to altered clearance

2

Maintenance Dose



Renal Dosing of Antibiotics: Are We Jumping the Gun?

Crass RL et al, Clin Infect Dis 2019;68:1596-602

Acute Kidney Injury on Admission in Patients With Common Infections

AKI Categories	All Patients (N = 18650)	Pneumonia (n = 2130)	Complicated Intraabdominal Infection (n = 2965)	Complicated Urinary Tract Infection (n = 7650)	Acute Bacterial Skin and Skin Structure Infection (n = 5905)
Any AKI[a]	3256 (17.5%)	578 (27.1%)	577 (19.5%)	1531 (20.0%)	570 (9.7%)
KDIGO stage[a]					
0	15394 (82.5%)	1552 (72.9%)	2388 (80.5%)	6119 (80.0%)	5335 (90.3%)
1	1697 (9.1%)	276 (13.0%)	279 (9.4%)	806 (10.5%)	336 (5.7%)
2	971 (5.2%)	188 (8.8%)	180 (6.1%)	445 (5.8%)	158 (2.7%)
3	588 (3.2%)	114 (5.4%)	118 (4.0%)	280 (3.7%)	76 (1.3%)
Transient AKI[b]	1862/3256 (57.2%)	267/578 (46.2%)	308/577 (53.4%)	923/1531 (60.3%)	364/570 (63.9%)

For antibiotics with wide safety margins, dose adjustment could be deferred until 48 hours after initiation of therapy when the trajectory of patient renal function is better characterized. The potential for toxicity is low but non-zero; therefore, the risk-to-benefit ratio is minimized by standard dosing in the first 48 hours with subsequent dose reduction if renal impairment persists

Rationalizing antimicrobial therapy in the ICU: a narrative review

Timsit JF et al, Intensive Care Med 2019; 45:172–189

	Step 1	Step 2	Step 3		
	PD index of choice	First dose	Daily dose (ARC – normal kidney function)	Daily dose (AKI)	Daily dose (CRRT)
Beta-lactams	T > MIC	Increased (up to double dose)	Continuous infusion	Reduced dose (except first 24h)	Unadjusted dose
Aminoglycosides	C_{max} / MIC	Doubled	Once daily (with TDM)	According to TDM	According to TDM
Glycopeptides	AUC / MIC	Weight-based (up to double dose)	Continuous infusion	According to TDM	According to TDM
Fluoroquinolones	AUC / MIC	Unchanged	q8h	According to residual CrCL	According to residual CrCL
Linezolid	AUC / MIC	Unchanged to increased	Unchanged	Unchanged	Increased dose – consider TDM
Colistin	AUC / MIC	Increased (up to 9 MIU)	Unchanged	According to residual CrCL	May need higher dose (up to 15 MUI)

Sequential optimization of antimicrobial pharmacokinetics in critically ill patients

PK/PD target attainment analyses to determine optimal dosing of ceftazidime-avibactam for the treatment of acute pulmonary exacerbations in patients with cystic fibrosis

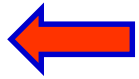
Bensman TJ et al. *Antimicrob Agent Chemother* 2017 Oct; 61

CUMULATIVE RESPONSE PROBABILITY OF CEFTAZIDIME AVIBACTAM 2.5 G Q8H vs. P. aeruginosa CF ISOLATES

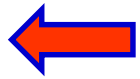
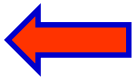
	CRP			
Infusion time (h)	Stasis ($fT_{>MIC}$, 40%)	1- to 2-log drop ($fT_{>MIC}$, 50%)	Nearly maximal response ($fT_{>MIC}$, 65%)	Maximal response ($fT_{>MIC}$, 100%)
0.5	0.824	0.805	0.76	0.449
2	0.836	0.815	0.788	0.554
5	0.844	0.829	0.814	0.757
8	0.825	0.825	0.825	0.825

… TANTO

TANTO ANTIBIOTICO?

TANTI ANTIBIOTICI? 

Ten commandments of antibiotic therapy

1. Communication and education
2. Updating local epidemiological data stratifying them for specific settings
3. Start always using a severity driven approach
4. Drafting local algorithms /bundles
5. Not being impulsive in starting antimicrobial therapy
6. Being parsimonious with combination regimens 
7. Strict collaboration with Microbiology lab in daily life
8. Being aware about PK/PD issues
9. Shortening therapy 
10. Creating multidisciplinary team/s for specific setting, syndromes etc

Severe Community Acquired Infections

Etiologies and resistance pattern HIGHY PREDICTABILE

Low need for empiric broad spectrum treatment

Severe Hospital Acquired Infections

Etiologies and Resistance patterns HIGHY UNPREDICTABLE

High need for empiric broad spectrum treatment

A Comparison of the Mortality Risk Associated With Ventilator-Acquired Bacterial Pneumonia and Non ventilator ICU-Acquired Bacterial Pneumonia

Ibn Saied W et al Crit Care Med 2018 Nov 7

Observational study using a multicenter longitudinal database fuelled from 1997 by 23 ICUs contributing to the OUTCOMEREA network

	VAP	ICU HAP
"microbiological" adequacy of initial treatment	69%	73%
30-day mortality	28.4%	23.9%
Median time of occurrence	6 days	2 days

An international multicenter retrospective study of *Pseudomonas aeruginosa* nosocomial pneumonia: impact of multidrug resistance. *Micek ST et al, Crit Care. 2015;19:219.*

A retrospective cohort study of adult patients with Pa-NP; 12 hospitals in 5 countries

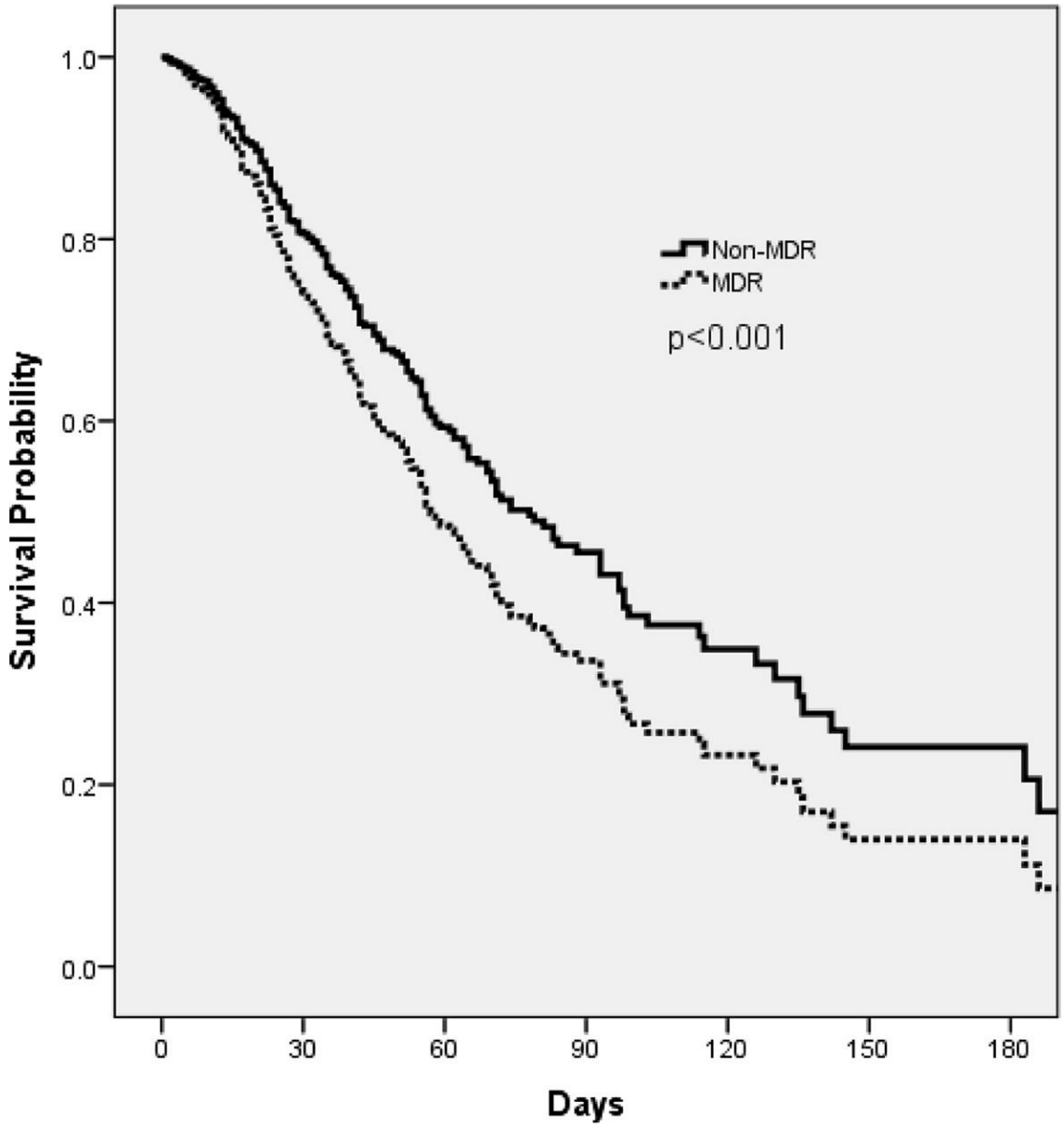
Of 740 patients with Pa-NP, 226 patients (30.5%) were infected with MDR strains

Antibiotic susceptibility

Antibiotic class	MDR (n = 226)	Non-MDR (n = 514)	P-value
Aminoglycosides	29.2%	91.1%	<0.001
Carbapenems	15.0%	84.6%	<0.001
Cephalosporins	26.5%	93.7%	<0.001
Fluoroquinolones	21.5%	88.4%	<0.001
Piperacillin/Tzb+	22.2%	89.0%	<0.001
Monobactams	13.9%	81.2%	<0.001
Fosfomycin	40.7%	81.0%	<0.001
Polymyxins	97.5%	92.1%	0.025

An international multicenter retrospective study of *Pseudomonas aeruginosa* nosocomial pneumonia: impact of multidrug resistance.

Micek ST et al, Crit Care. 2015;19:219.



MORTALITY

Cox proportional hazards model curve

Overall hospital mortality

35.7%

MDR **44.7%**

non MDR **31.7 %**

Clinical Infectious Diseases

IDSA GUIDELINE

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

Andre C. Kalil,[1,a] Mark L. Metersky,[2,a] Michael Klompas,[3,4] John Muscedere,[5] Daniel A. Sweeney,[6] Lucy B. Palmer,[7] Lena M. Napolitano,[8] Naomi P. O'Grady,[9] John G. Bartlett,[10] Jordi Carratalà,[11] Ali A. El Solh,[12] Santiago Ewig,[13] Paul D. Fey,[14] Thomas M. File Jr,[15] Marcos I. Restrepo,[16] Jason A. Roberts,[17,18] Grant W. Waterer,[19] Peggy Cruse,[20] Shandra L. Knight,[20] and Jan L. Brozek[21]

Clinical Infectious Diseases® 2016;63(5):575–82

Suggested Empiric Treatment Options

A. Gram-Positive Antibiotics With MRSA Activity	B. Gram-Negative Antibiotics With Antipseudomonal Activity: β-Lactam–Based Agents	C. Gram-Negative Antibiotics With Antipseudomonal Activity: Non-β-Lactam–Based Agents
Glycopeptides[a] Vancomycin 15 mg/kg IV q8–12h (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Antipseudomonal penicillins[b] Piperacillin-tazobactam 4.5 g IV q6h[b]	Fluoroquinolones Ciprofloxacin 400 mg IV q8h Levofloxacin 750 mg IV q24h
OR	OR	OR
Oxazolidinones Linezolid 600 mg IV q12h	Cephalosporins[b] Cefepime 2 g IV q8h Ceftazidime 2 g IV q8h	Aminoglycosides[a,c] Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h
	OR	OR
	Carbapenems[b] Imipenem 500 mg IV q6h[d] Meropenem 1 g IV q8h	Polymyxins[a,e] Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose) [135] Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses
	OR	
	Monobactams[f] Aztreonam 2 g IV q8h	

VENTILATOR ASSOCIATED PNEUMONIA

TOOLS FOR A TREATMENT DECISION-MAKING PROCESS

- COMORBIDITIES
- CPIS SCORE
- TIME FROM INTUBATION
- TIME FORM HOSPITALIZATION
- BAL SURVEILLANCE CULTURES
- LOCAL EPIDEMIOLOGY KNOWLEDGE
- ANTIBIOTIC EXPOSURE HISTORY

- COLONIZATION STATUS

Relationship between digestive tract colonization and subsequent VAP related to ESBL-producing *Enterobacteriaceae*.

Houard M et al, PLoS One. 2018;13:e0201688.

Single mixed intensive care unit, retrospective study during a 4-year period including all patients with confirmed VAP were included. Among the 410 patients, 43 (10.5%) had ESBLE VAP, 76 (19%) patients had polymicrobial VAP and 189 (46%) had VAP related to multidrug resistant bacteria.

Risk factor for VAP related to ESBLE by multivariate analysis

Female gender	**0.80**	**0.90 [0.39–2.07]**
Medical admission	0.33	0.61 [0.23–1.66]
Acute exacerbation of COPD	0.06	0.13 [0.02–1.12]
Acute respiratory distress syndrome	0.31	1.76 [0.59–5.29]
Shock	0.40	1.43 [0.62–3.33]
Infection at admission	0.15	2.81 [0.70–11.32]
Prior antibiotic exposure	0.84	1.10 [0.44–2.71]
Broad-spectrum antibiotics exposure	0.93	1.05 [0.35–3.13]
Prior digestive colonization	< 0.001	23.32 [9.89–54.97]

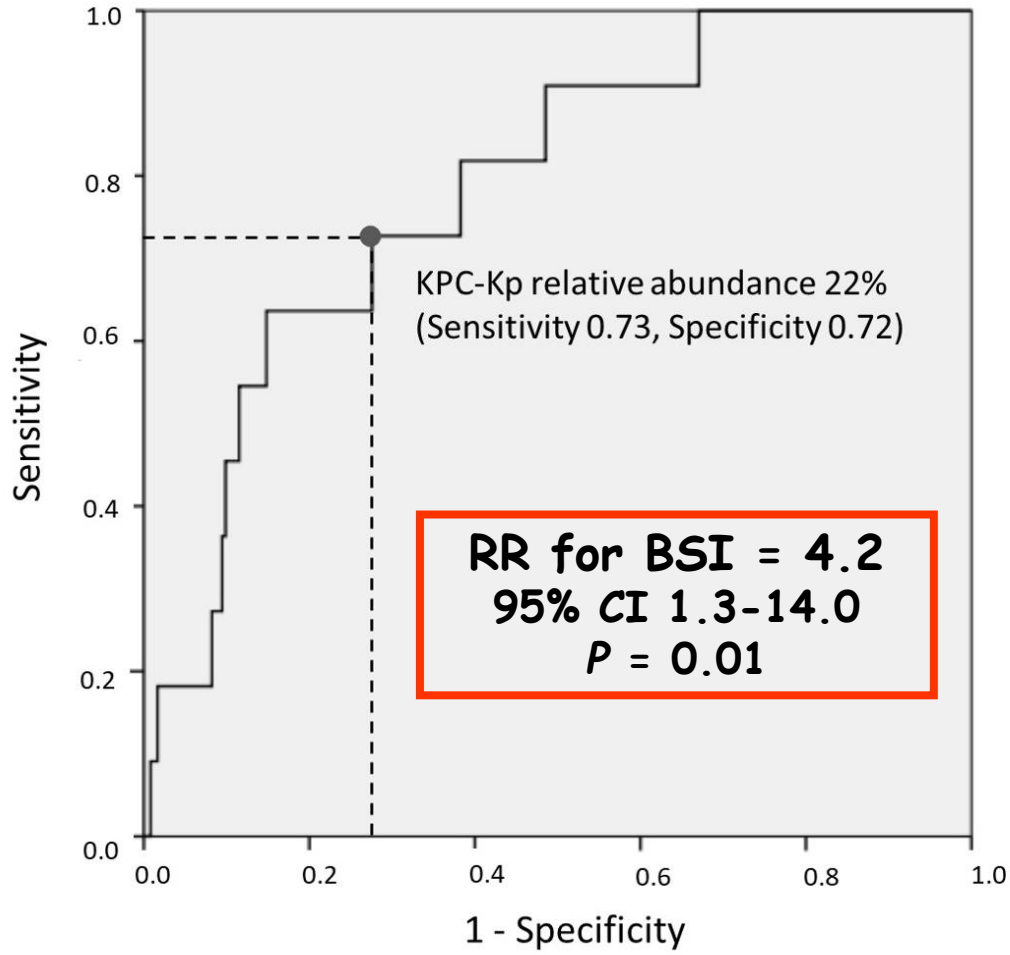
Risk factors for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection among rectal carriers: a prospective observational multicentre study *Giannella M. et al. Clin Microbiol Infect. 2014 Jul 1*

- Matched case-control study
- 1, 813 CR-KP rectal carriers hospitalized at 5 tertiary teaching hospitals in Italy over 2 years
- **143 developed BSI (7.8%)**
- 572 controls without a documented infection during their hospitalization were selected

	OR (95% CI)	P-value	Risk score point
Admission to ICU	1.65 (1.05-2.59)	0.03	2
Invasive abdominal procedures	1.87 (1.16-3.04)	0.01	3
Chemotherapy/radiation therapy	3.07 (1.78-5.29)	<0.0001	4
Colonization at site besides stool (risk per each additional site)	3.37 (2.56- 4.43)	<0.0001	5 per site

Increased relative abundance of carbapenemase-producing Klebsiella pneumoniae within the gut microbiota is associated with risk of bloodstream infection in long-term acute care hospital patients. *Shimasaki T et al Clin Infect Dis. 2018 Sep 18.*

ROC curve analysis of the relation between relative abundance of KPC-Kp and subsequent KPC-Kp BSI



VENTILATOR ASSOCIATED PNEUMONIA

TOOLS FOR A TREATMENT DECISION-MAKING PROCESS

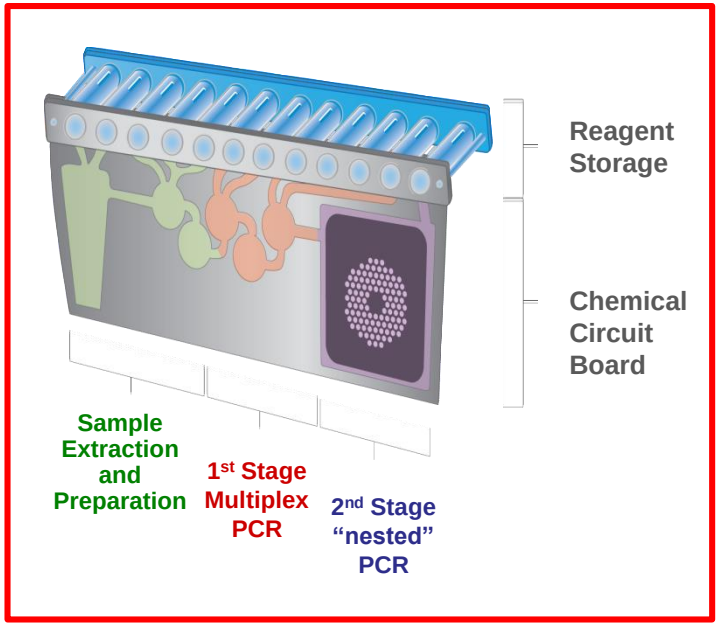
- COMORBIDITIES
- CPIS SCORE
- TIMING FROM INTUBATION
- TIMING FROM HOSPITAL ADMISSION
- BAL SURVEILLANCE CULTURES
- LOCAL EPIDEMIOLOGY KNOWLEDGE

- COLONIZATION STATUS

- **FAST MICROBIOLOGY**

BioFire FilmArray
Advanced Syndromic Screening for the Diagnosis of Infections

- PCR-based device integrates sample preparation, amplification, detection and analysis into one simple system that requires 2 min of hands-on time and has a total run time of about 1 hour



Rapid Detection of Methicillin-Resistant *Staphylococcus aureus* in BAL. A Pilot Randomized Controlled Trial *Paonessa JR et al, Chest 2019; 155:999-1007*

A prospective, unblinded, randomized clinical trial to assess the effect of antibiotic management made on the basis of rapid diagnostic testing compared with usual care. The clinical trial randomized 45 patients: 22 to antibiotic management made on the basis of RDT and 23 to usual care.

Outcome	RPCR Group (n = 22)	Usual Care (n = 23)	*P*
Initial anti-MRSA treatment, h[a,b]	32 (22-48)	72 (50-113)	<.001
28-d total anti-MRSA treatment, h[a]	46 (24-73)	122 (66-219)	<.001
Duration of mechanical ventilation, h[a]	132 (54-209)	158 (44-464)	.44
ICU length of stay, d[a]	6 (5-14)	8 (6-26)	.19
Hospital length of stay, d[a]	15 (10-24)	29 (12-44)	.07
Any adverse event, No. (%)	13 (59.1)	17 (73.9)	.29
Acute renal failure	4 (18.2)	5 (21.7)	1.00
Thrombocytopenia	5 (22.7)	6 (26.1)	.79
Nosocomial infection	8 (36.4)	12 (52.2)	.29
In-hospital mortality	3 (13.6)	9 (39.1)	.05

Antimicrobial Stewardship Mission

Contain antimicrobial exposures and resultant ecological damage without undermining the clinical outcome

SHORTENING THE DURATION OF TREATMENT

"One patients exposed to antibiotics for 10 days is far worse than 5 patients exposed for 2 days each"