

Quais os efeitos colaterais do protocolo de sepse no controle de antimicrobianos?

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PRINCÍPIOS DO CONTROLE

Fatos relevantes


- Aproximadamente 40% dos pacientes internados em hospitais brasileiros estão em uso de antimicrobianos.
 - *Dados preliminares/IRAS Brasil*
- As prescrições inadequadas de antimicrobianos podem superar 60%.
 - *Jones SR et al. Am J Med Sci 1977; 273: 79-85.*
 - *Hecker MT et al. Arch Intern Med 2003; 163:972-8.*
 - *Erbay A et al. J Hosp Infect. 2005; 59: 53-61.*
 - *Apisarnthanarak A et al. Infect Control Hosp Epidemiol 2006; 27: 416-20.*



Consequências do uso inadequado ou sub-ótimo




- Falha terapêutica.
- Eventos adversos graves.
- Diarréia por *Clostridium difficile*.
- Emergência de resistência microbiana.



Core Elements
of Hospital Antibiotic
Stewardship Programs

National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion



- **Leadership Commitment:** Dedicating necessary human, financial and information technology resources.
- **Accountability:** Appointing a single leader responsible for program outcomes. Experience with successful programs show that a physician leader is effective.
- **Drug Expertise:** Appointing a single pharmacist leader responsible for working to improve antibiotic use.
- **Action:** Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (i.e. “antibiotic time out” after 48 hours).
- **Tracking:** Monitoring antibiotic prescribing and resistance patterns.
- **Reporting:** Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff.
- **Education:** Educating clinicians about resistance and optimal prescribing.

Métodos usuais de controle...

- Reavaliação pela equipe clínica (“*antibiotic time outs*”).
- Auditoria prospectiva com *feedback* à equipe.
- Requerimento de autorização prévia.

PRIMÓRDIOS DA CAMPANHA

Factors predictive of inappropriateness in requests for parenteral antimicrobials for therapeutic purposes: A study in a small teaching hospital in Brazil

Scandinavian Journal of Infectious Diseases, 2011; 43: 528–535

GUSTAVO HIDEKI KAWANAMI¹ & CARLOS MAGNO CASTELO BRANCO FORTALEZA^{1,2}

Table I. Classification of parenteral antimicrobial requests according to the modified Kunin and Jones categories [25,26].

Category	Instances of prescription	%
Appropriate (A)	480	49.8
Probably appropriate (PA)	150	15.6
Unnecessary (U)	74	7.7
Excessive/redundant spectrum (E/R)	59	6.1
Insufficient spectrum (I)	45	4.7
Short duration or low dosing (S/L)	45	4.7
Long duration or high dosing (L/H)	99	10.3
Multiple errors (M)	11	1.1

Table IV. Factors predictive of inappropriateness in antimicrobial requests—multivariate analysis.

Predictors	OR (95% CI)	p-Value
Inappropriate prescription (in general)		
Patient in the intensive care unit	1.57 (1.11–2.23)	0.01
Prescription on weekends/holidays	1.67 (1.20–2.28)	0.002
Previous consultation with ID specialist	0.34 (0.24–0.50)	<0.001
Peritoneal infection	2.15 (1.27–3.65)	0.004
Urinary tract infection	1.89 (1.25–2.87)	0.01
Drug from penicillin class	2.12 (1.39–3.25)	0.001
Cephalosporin, 1 st generation	1.74 (1.01–3.00)	0.048
Combination therapy ^a	1.72 (1.15–2.57)	0.008
Unnecessary antimicrobial use		
Urinary tract infection	2.77 (1.51–5.11)	0.001
Peritoneal infection	4.31 (1.85–10.07)	0.001
Cephalosporin, 1 st generation	2.28 (1.05–4.91)	0.04
Previous consult with ID specialist	0.04 (0.01–0.26)	0.001
Excessive/redundant antimicrobial spectrum		
Age >60 y	0.39 (0.18–0.84)	0.02
Prescription on weekends/holidays	2.73 (1.34–5.55)	0.006
Combination therapy ^a	22.54 (7.78–65.30)	<0.001
Urinary tract infection	8.22 (3.05–22.5)	<0.001
Quinolone	0.65 (0.02–0.16)	<0.001
Aminoglycoside	0.16 (0.04–0.63)	0.008
Insufficient antimicrobial spectrum		
Patient in the intensive care unit	8.34 (2.55–27.31)	<0.001
Previous consult with ID specialist	0.14 (0.03–0.3)	0.01
Peritoneal infection	91.15 (17.88–464.63)	<0.001
Urinary tract infection	0.04 (0.00–0.54)	0.02

Analysis of vancomycin use and associated risk factors in a university teaching hospital: a prospective cohort study

Moacyr S Junior*, Luci Correa, Alexandre R Marra, Luis FA Camargo and Carlos AP Pereira

Table 5: Univariate analyses of risk factors for inappropriate vancomycin use, at the first 24 and 72 hours, according to the CDC criteria (HICPAC, 1995), in 557 patients in Sao Paulo Hospital between March and September 2002

Variables	Inappropriateness (24 h)		p	Inappropriateness (72 h)		p
	N(366)	%		N(373)	%	
Age						
< 60 years	264	(70.5)	0.001	266	(71.3)	0.002
≥ 60 years	102	(56.3)		107	(58.5)	
Unit						
Others	210	(71.3)	0.001	215	(73.4)	0.001
UCI/UCI ped	156	(59.7)		158	(60.1)	
Neutropenia						
Yes	9	(32.1)	0.001	8	(32.1)	0.001
No	357	(67.6)		365	(68.9)	
Central venous catheter						
Yes	221	(62.7)	0.04	226	(64.1)	0.049
No	145	(71.3)		147	(72.3)	
Central venous catheter						
< 2 weeks	125	(69.9)	0.003	127	(69.5)	0.002
≥ 2 weeks	96	(56.7)		99	(57.9)	

O QUE DIZ O GUIDELINE?

Surviving Sepsis Campaign

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

R. Phillip Dellinger, MD¹; Mitchell M. Levy, MD²; Andrew Rhodes, MB BS³; Djillali Annane, MD⁴; Herwig Gerlach, MD, PhD⁵; Steven M. Opal, MD⁶; Jonathan E. Sevransky, MD⁷; Charles L. Sprung, MD⁸; Ivor S. Douglas, MD⁹; Roman Jaeschke, MD¹⁰; Tiffany M. Osborn, MD, MPH¹¹; Mark E. Nunnally, MD¹²; Sean R. Townsend, MD¹³; Konrad Reinhart, MD¹⁴; Ruth M. Kleinpell, PhD, RN-CS¹⁵; Derek C. Angus, MD, MPH¹⁶; Clifford S. Deutschman, MD, MS¹⁷; Flavia R. Machado, MD, PhD¹⁸; Gordon D. Rubenfeld, MD¹⁹; Steven A. Webb, MB BS, PhD²⁰; Richard J. Beale, MB BS²¹; Jean-Louis Vincent, MD, PhD²²; Rui Moreno, MD, PhD²³; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

D. Antimicrobial Therapy

1. The administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) should be the goal of therapy. *Remark:* Although the weight of the evidence supports prompt administration of antibiotics following the recognition of severe sepsis and septic shock, the feasibility with which clinicians may achieve this ideal state has not been scientifically evaluated.

Apesar da forte recomendação de introdução de antimicrobianos na primeira hora de diagnóstico de sepse grave ou choque séptico, estudos indicam que essa ainda não é uma prática rotineira.

Levy MM et al. Crit Care Med 2010; 38: 367-74.

Sugere-se manter antimicrobianos estratégicos previamente preparados (ou seja, pré-diluídos) para infusão em emergência.

- 2a. We recommend that initial empiric anti-infective therapy include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis (grade 1B).

Considerar patógenos prováveis (sítio de infecção), história prévia de uso de antimicrobianos (evitar agentes recentemente utilizados).

MRSA e Bacilos Gram-negativos multidroga-resistentes são cada vez mais comuns na comunidade e em serviços de saúde. Sempre que houver possibilidade de envolvimento, terapia adequada deve ser instituída.

Considerar a possível necessidade de incluir terapia antifúngica (para candidemias), preferencialmente com fluconazol ou equinocandinas.

- 2a. We recommend that initial empiric anti-infective therapy include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis (grade 1B).

Não há margem para erro, uma vez que diversos estudos documentaram maior mortalidade em caso de instituição de terapia inadequada.

Pacientes devem receber terapia antimicrobiana de amplo espectro até que o agente etiológico seja identificado. **É verdade que o uso de antimicrobianos deve ser limitado para prevenir resistência, mas isso não deve se aplicar a esta população.**

No entanto, o deescalonamento deve ser realizado após resultados de culturas. **Colaboração com programas de controle de antimicrobianos é aconselhada.**

- 2a. We recommend that initial empiric anti-infective therapy include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis (grade 1B).
- 2b. The antimicrobial regimen should be reassessed daily for potential de-escalation to prevent the development of resistance, to reduce toxicity, and to reduce costs (grade 1B).
3. We suggest the use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who appeared septic, but have no subsequent evidence of infection (grade 2C).

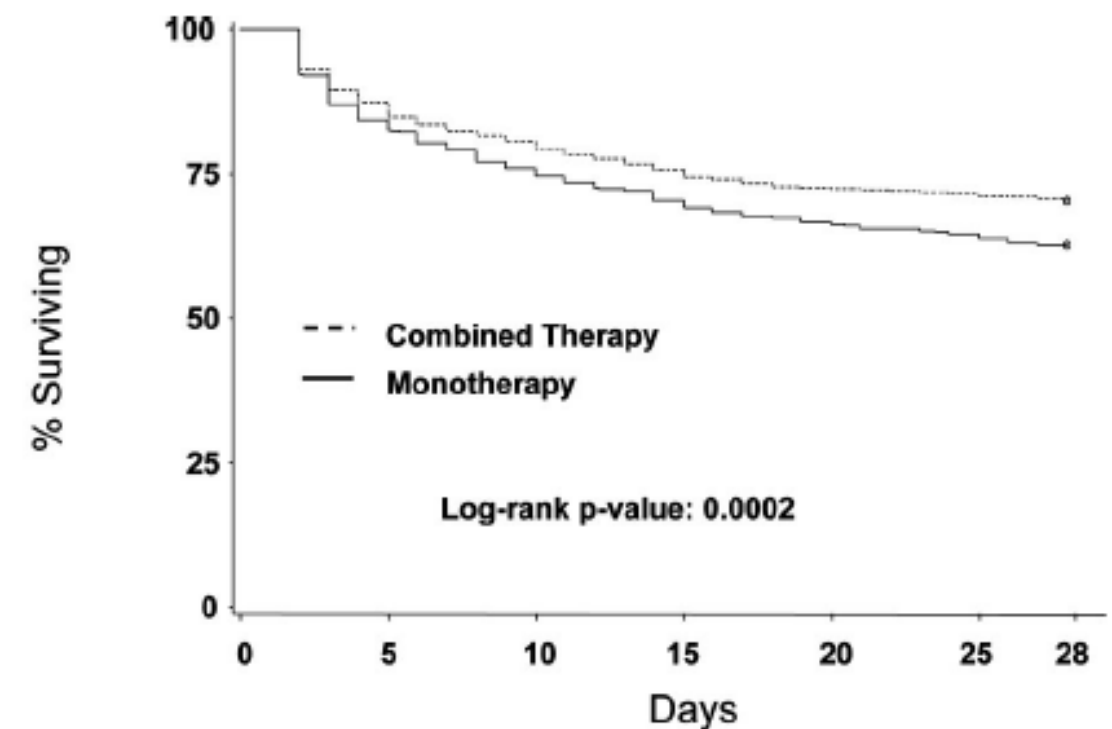
Utilização de resultados microbiológicos e biomarcadores para deescalonar ou descontinuar antimicrobianos.

- 4a. Empiric therapy should attempt to provide antimicrobial activity against the most likely pathogens based upon each patient's presenting illness and local patterns of infection. We suggest combination empiric therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp. (grade 2B). For selected patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is suggested for *P. aeruginosa* bacteremia (grade 2B). Similarly, a more complex combination of beta-lactam and a macrolide is suggested for patients with septic shock from bacteremic *Streptococcus pneumoniae* infections (grade 2B).

Terapia combinada para patógenos como *Acinetobacter*, *Pseudomonas* e pneumococos?

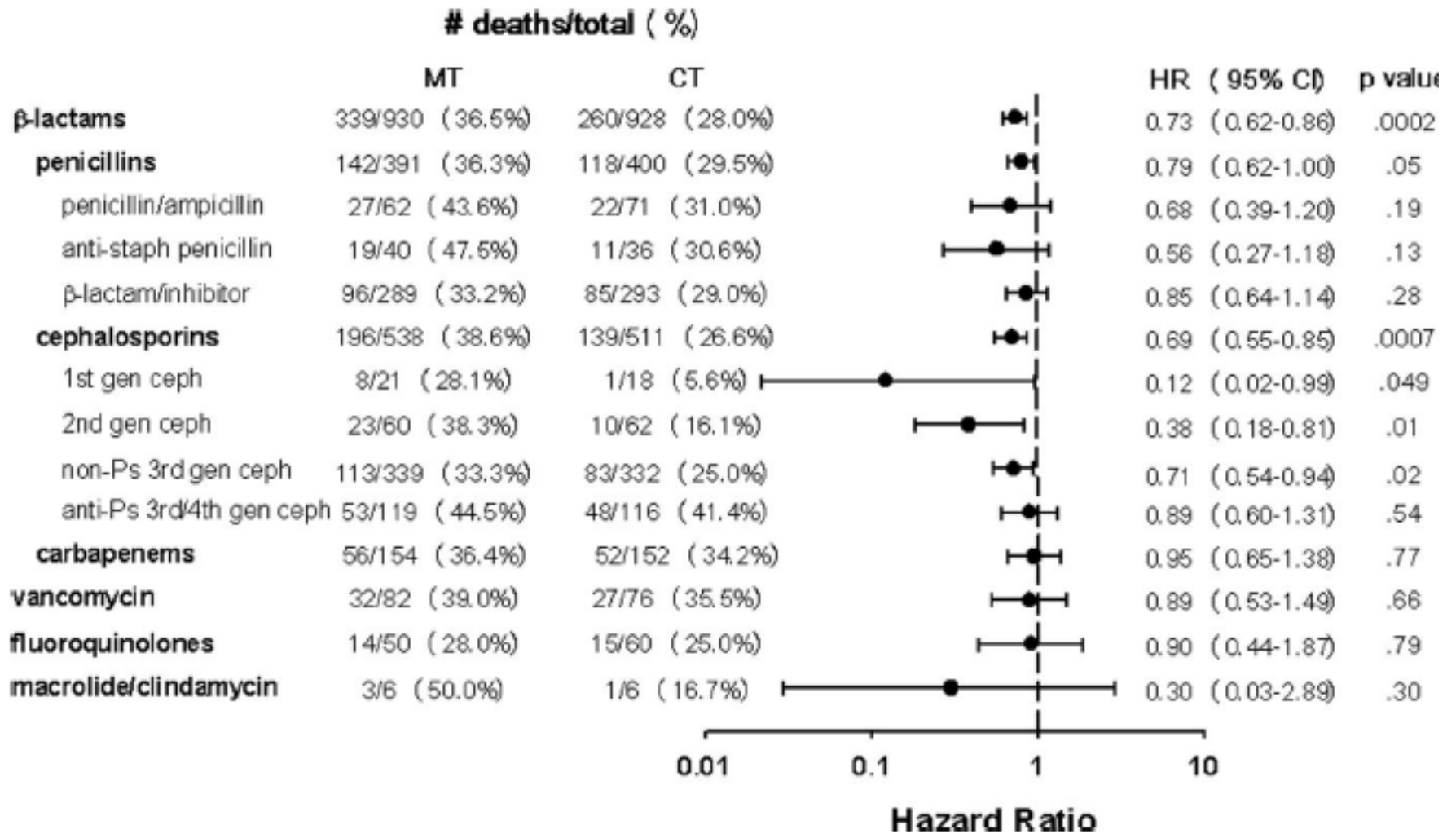
Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: A propensity-matched analysis*

Anand Kumar, MD; Ryan Zarychanski, MD; Bruce Light, MD; Joseph Parrillo, MD; Dennis Maki, MD; Dave Simon, MD; Denny Laporta, MD; Steve Lapinsky, MD; Paul Ellis, MD; Yazdan Mirzanejad, MD; Greg Martinka, MD; Sean Keenan, MD; Gordon Wood, MD; Yaseen Arabi, MD; Daniel Feinstein, MD; Aseem Kumar, PhD; Peter Dodek, MD; Laura Kravetsky, BSc; Steve Doucette, MSc; the Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group



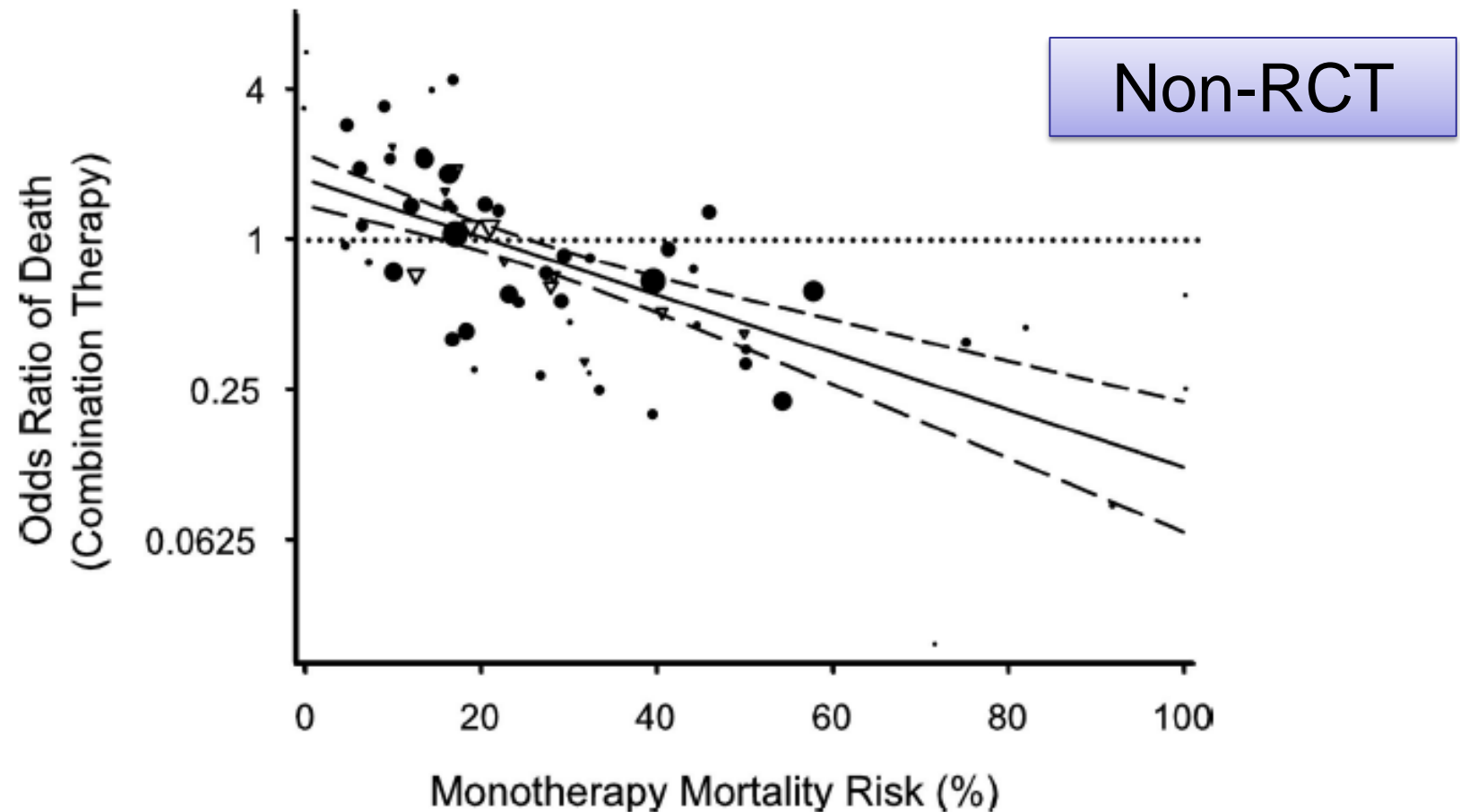
Combined Therapy	1223	1077	996	937	895	881	868
Monotherapy	1223	1046	939	867	826	801	779
Number at risk							

(Crit Care Med 2010; 38:1773–1785)



A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: A meta-analytic/meta-regression study

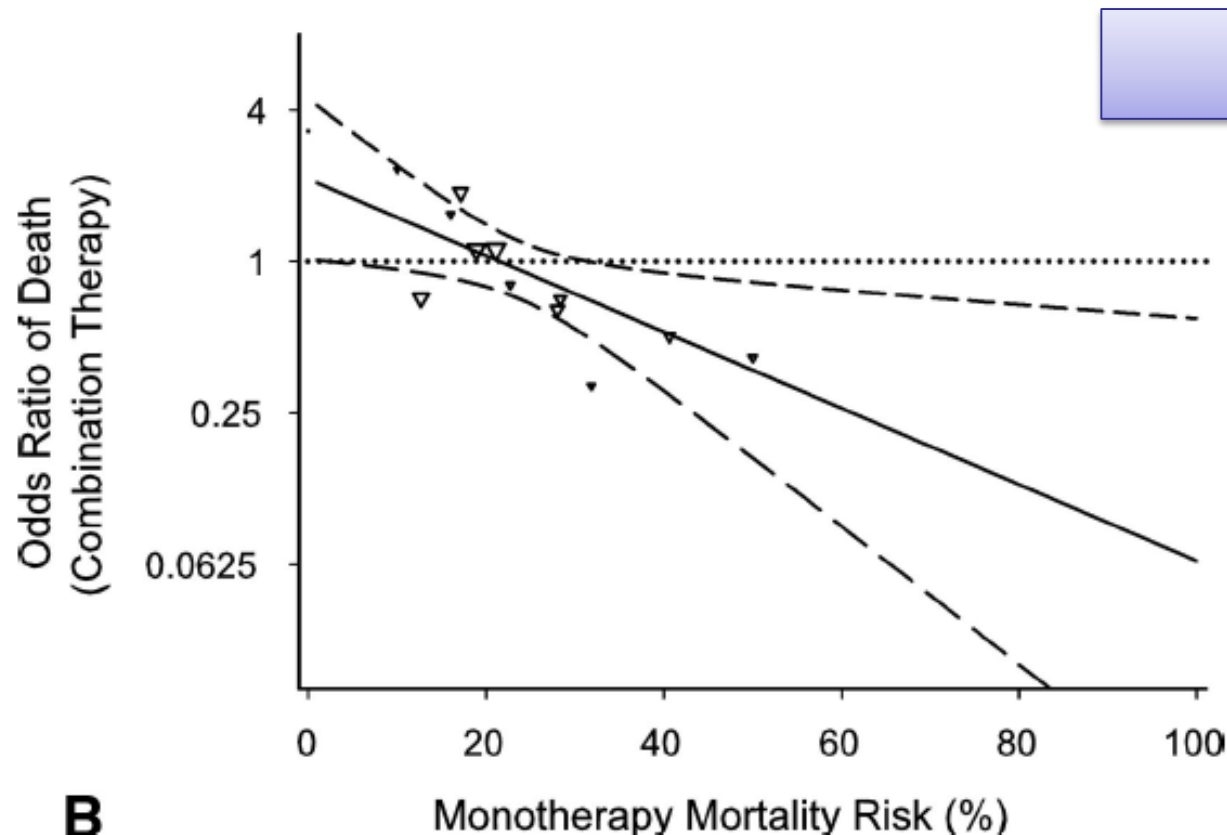
Anand Kumar, MD; Nasia Safdar, MD; Shravan Kethireddy, MD; Dan Chateau, PhD



(Crit Care Med 2010; 38:1651–1664)

A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: A meta-analytic/meta-regression study

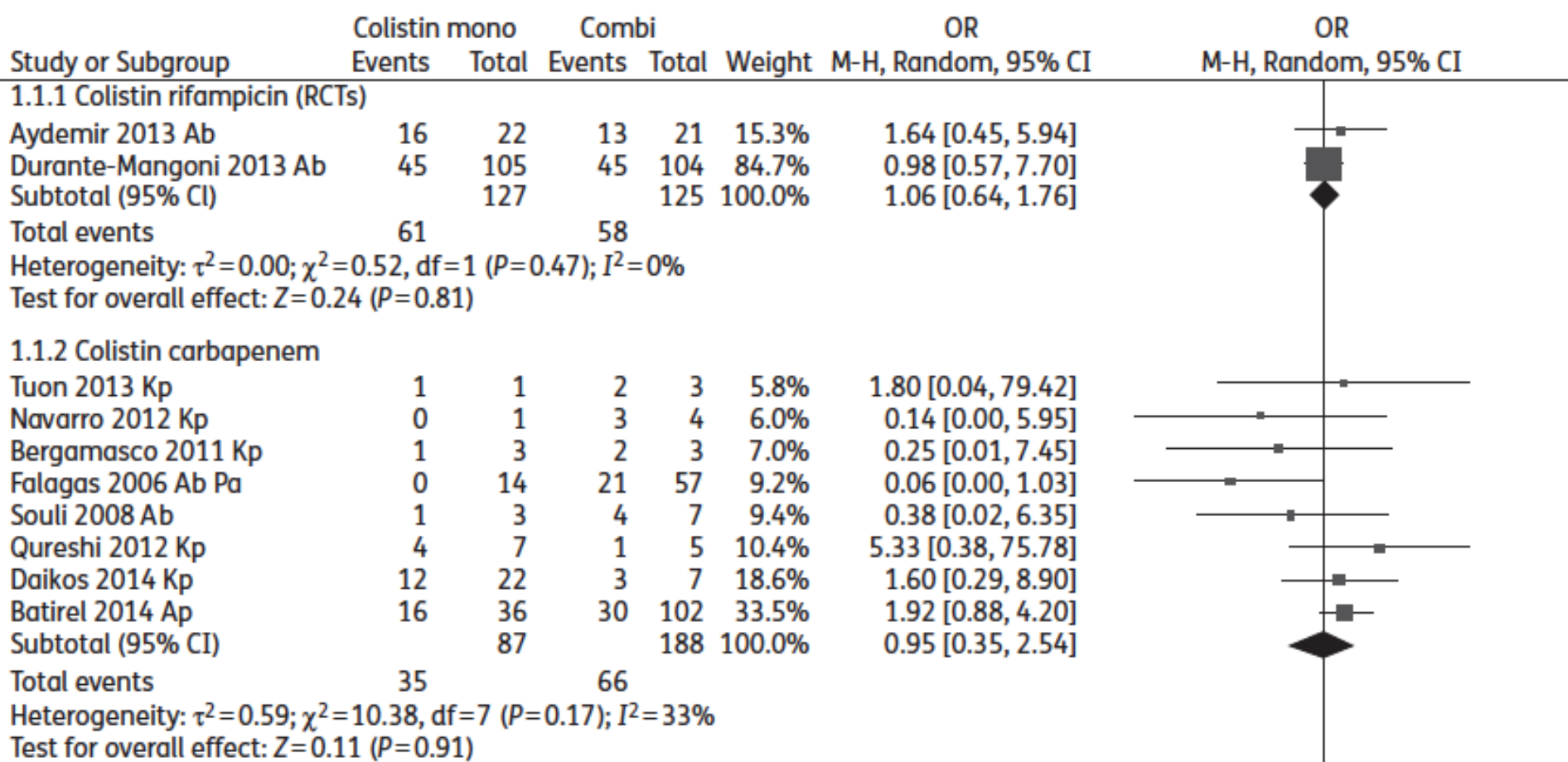
Anand Kumar, MD; Nasia Safdar, MD; Shravan Kethireddy, MD; Dan Chateau, PhD



(Crit Care Med 2010; 38:1651–1664)

Combination therapy for carbapenem-resistant Gram-negative bacteria

Mical Paul^{1*}, Yehuda Carmeli², Emanuele Durante-Mangoni³, Johan W. Mouton⁴, Evelina Tacconelli⁵, Ursula Theuretzbacher⁶, Cristina Mussini⁷ and Leonard Leibovici^{8,9}



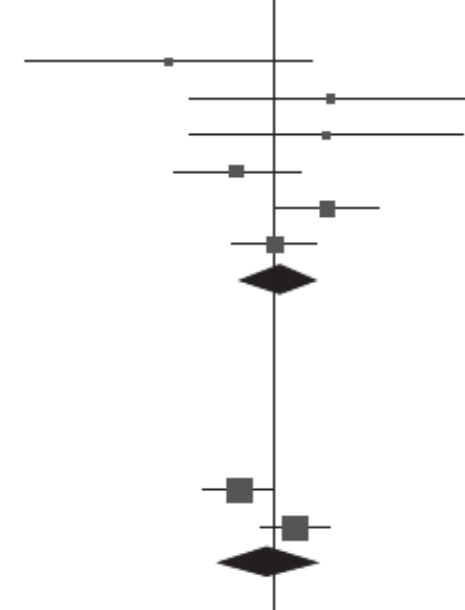
1.1.3 Colistin tigecycline

Navarro 2012 Kp	0	1	7	8	6.8%	0.07 [0.00, 2.56]
Bergamasco 2011 Kp	1	3	0	3	7.0%	4.20 [0.12, 151.97]
Qureshi 2012 Kp	4	7	0	1	7.3%	3.86 [0.12, 126.73]
Kontopidou 2013 Kp	6	26	4	9	21.7%	0.38 [0.08, 1.86]
Daikos 2014 Kp	12	22	5	21	26.2%	3.84 [1.04, 14.21]
Ku 2012 Ab	26	71	7	19	30.9%	0.99 [0.35, 2.83]
Subtotal (95% CI)		130		61	100.0%	1.16 [0.41, 3.27]

Total events 49 23
Heterogeneity: $\tau^2=0.61$; $\chi^2=8.50$, $df=5$ ($P=0.13$); $I^2=41\%$
Test for overall effect: $Z=0.29$ ($P=0.77$)

1.1.4 Colistin sulbactam

Kalin 2013 Ab	27	52	27	37	49.2%	0.40 [0.16, 0.99]
Batirel 2014 Ab	16	36	22	69	50.8%	1.71 [0.75, 3.92]
Subtotal (95% CI)		88		106	100.0%	0.84 [0.20, 3.47]
Total events	43		49			



A heterogeneidade dos estudos não permite uma conclusão definitiva a favor da terapia combinada

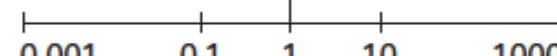
Daikos 2014 Kp	12	22	5	17	62.7%	2.88 [0.75, 10.99]
Subtotal (95% CI)		49		36	100.0%	2.63 [0.91, 7.58]

Total events 18 7
Heterogeneity: $\tau^2=0.00$; $\chi^2=0.05$, $df=1$ ($P=0.83$); $I^2=0\%$
Test for overall effect: $Z=1.79$ ($P=0.07$)

1.1.6 Mixed comparators

Simsek 2012 Ab	10	20	10	31	15.3%	2.10 [0.66, 6.67]
Tumbarello 2012 Ab	11	22	27	79	22.3%	1.93 [0.74, 5.01]
Daikos 2014 Ab	12	22	28	103	22.8%	3.21 [1.25, 8.27]
Batirel 2014 Ab	16	36	68	214	39.6%	1.72 [0.84, 3.52]
Subtotal (95% CI)		100		427	100.0%	2.10 [1.33, 3.29]

Total events 49 133
Heterogeneity: $\tau^2=0.00$; $\chi^2=1.11$, $df=3$ ($P=0.77$); $I^2=0\%$
Test for overall effect: $Z=3.21$ ($P=0.001$)



5. We suggest that the duration of therapy typically be 7 to 10 days if clinically indicated; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *S. aureus*; some fungal and viral infections, or immunologic deficiencies, including neutropenia (grade 2C).

Duração: 7 a 10 dias

6. We suggest that antiviral therapy be initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C).

Etiologia viral

7. We recommend that antimicrobial agents not be used in patients with severe inflammatory states determined to be of noninfectious cause (UG).

SIRS não infecciosa



IMPASSE?

É VIÁVEL O CONTROLE DE ANTIMICROBIANOS?

Evaluation of the Short-Term Effects of Antimicrobial Stewardship in the Intensive Care Unit at a Tertiary Hospital in China

Dapeng Hou^{1*}, Qiushi Wang¹, Cuihua Jiang¹, Cui Tian¹, Huaqing Li¹, Bo Ji^{2*}

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Characteristic	Before (n = 259)	After (n = 279)	P
Male/female	170/89	187/92	0.734
Age	53.10±19.43	54.59±18.07	0.357
APACHE II score	21.46±8.04	21.04±9.14	0.578
Primary diseases			0.998
Medical diseases	84	90	
Surgical diseases	80	86	
Trauma	95	103	
Infectious diseases/non-infectious	50/209	44/235	0.281
Transfer from Infectious department/General department	106/153	139/140	0.038
Antibiotic use before			0.011
Non	178(68.7%)	214(76.7%)	
Single	33(12.7%)	39(14.0%)	
Two	36(13.9%)	19(6.8%)	
Three	11(4.2%)	4(1.4%)	
More than three	1(0.4%)	3(1.1%)	
Glucocorticoid use before	19/240	19/260	0.812
With or without ventilator application	140/119	177/102	0.027
Ventilator days	3.38±3.54	3.30±5.29	0.867
ICU days (median)	2	2	0.148
All-cause death/survival	40/219	32/247	0.176
Death associated with infection/others	11/248	8/271	0.386

Impacto sobre consumo

Table 2. Changes of antimicrobial consumption (DDDs/100 patient/days) after the antimicrobial stewardship.

Antibiotics	ICU			Hospital-wide		
	Before	After	Change (%)	Before	After	Change (%)
Penicillins	2.72	0.27	−90.07	3.37	1.58	−53.12
Cephalosporins	53.65	63.17	+17.74	23.95	30.09	+25.64
Carbapenems	16.44	17.05	+3.71	0.48	0.45	−6.25
Other B-lactams	10.11	0.59	−94.16	12.29	3.75	−69.49
Aminoglycosides	0.47	0.00	—	0.15	0.06	−60.00
Tetracyclines	28.63	29.76	+3.95	0.85	0.81	−4.71
Macrolides	11.43	3.39	−70.34	5.01	3.58	−28.54
Glycopeptides	3.63	3.73	+2.75	0.11	0.09	−18.18
Quinolones	49.82	7.74	−84.46	14.32	3.40	−76.26
Imidazoles	14.63	10.61	−27.48	8.13	6.08	−25.22
Antifungal Agents	6.01	6.96	+15.81	0.43	0.34	−20.94
Others	0.11	0.14	+27.27	0.60	0.53	−11.67
Total	197.65	143.41	−27.44	69.69	50.76	−27.16

Impacto sobre resistência

Antibiotic	Enterobacteriaceae			Non-fermenting Gram-negative rods		
	Before	After	P	Before	After	P
Amikacin	82.6	44.7	0.004	88.6	81.4	0.356
Gentamycin	91.3	39.5	<0.001			
Ciprofloxacin	91.3	44.7	<0.001	91.4	84.7	0.525
Ofloxacin	91.3	42.1	<0.001			
Ceftriaxone	95.7	50.0	<0.001			
Ceftazidime	78.3	39.5	0.003	85.7	64.4	0.026
Cefepime	52.2	36.8	0.241	60.0	52.5	0.482
Imipenem	4.3	0	0.377	85.7	59.3	0.007
Piperacillin	87.0	57.9	0.018	80.0	72.9	0.438
Ampicillin/Sulbactam	56.5	42.1	0.275			
Tobramycin				94.3	79.7	0.054
Levofloxacin				88.6	81.4	0.356
Meropenem				88.6	62.7	0.007
Minocycline				11.4	23.7	0.143
Piperacillin/Tazobactam				77.1	66.1	0.258

Combination therapy	Before No.(%) of patients (n = 259)	After No.(%) of patients (n = 279)
Unused	6(2.3%)	14(5.0%)
Single antibiotic	53(20.5%)	220(78.9%)
Two antibiotics	192(74.1%)	45(16.1%)
Three antibiotics	8(3.1%)	0(0%)

Sim, é possível...

TRABALHAR COM INDICADORES DE QUALIDADE

Development of quality indicators for antimicrobial treatment in adults with sepsis

Caroline MA van den Bosch^{1*}, Marlies EIJL Hulscher², Stephanie Natsch³, Inge C Gyssens^{4,5,6}, Jan M Prins¹, Suzanne E Geerlings¹ and Dutch Sepsis QI expert panel

Methods: A RAND-modified, five step Delphi procedure was used. A multidisciplinary panel of 14 experts appraised and prioritized 40 key recommendations from within the Dutch national guideline on antimicrobial use for adult hospitalized patients with sepsis (www.swab.nl/guidelines). A procedure to select QIs relevant to clinical outcome, antimicrobial resistance and costs was performed using two rounds of questionnaires with a face-to-face consensus meeting between the rounds over a period of three months.

van den Bosch *et al.* *BMC Infectious Diseases* 2014, **14**:345
<http://www.biomedcentral.com/1471-2334/14/345>

Table 4 Final set of quality indicators to monitor antimicrobial use in hospitalized adult patients with sepsis

Indicator number from Table 3	Quality indicator	Numerator description	Denominator description
	All patients are: hospitalized adult patients with sepsis, severe sepsis or septic shock, where systemic antimicrobial therapy must be started	All patients are: hospitalized adult patients with sepsis, severe sepsis or septic shock, where systemic antimicrobial therapy must be started	All patients are: hospitalized adult patients with sepsis, severe sepsis or septic shock, where systemic antimicrobial therapy must be started
Number 1.	Antimicrobial therapy in adult patients with sepsis should be started intravenously.	Number of patients who started with empirical systemic antimicrobial therapy intravenously.	Total number of patients who started with empirical systemic antimicrobial therapy.
Number 2.	Antimicrobial therapy should be started as soon as possible, preferably within the first hour in adult patients with severe sepsis and septic shock.	Number of patients with severe sepsis or septic shock who started with empirical systemic antimicrobial therapy within the first hour after the clinical diagnosis.	Total number of patients with severe sepsis or septic shock, who started with empirical systemic antimicrobial therapy.
Number 3.	Before starting antimicrobial therapy, at least two sets of blood cultures and specimens for culture from suspected sites of infection should be taken.	Number of patients from whom at least 2 blood cultures and specimens for culture from suspected sites of infection were taken before empirical systemic antimicrobial therapy was started.	Total number of patients who started with empirical systemic antimicrobial therapy.
Number 45.	Empiric systemic antimicrobial therapy should be changed to pathogen-directed therapy if culture results become available.	Number of patients with a positive culture and empirical systemic antimicrobial therapy, which was changed to pathogen-directed therapy after the results became available.	Total number of patients with empirical systemic antimicrobial therapy whose culture became positive.
Number 43 and number 42.	Empiric systemic antimicrobial therapy (only choice of antimicrobial agent) should be prescribed according to the national guideline. The local guidelines should correspond to the national guideline, but should deviate based on local resistance patterns.	<p>Number of patients who started with empirical systemic antimicrobial therapy according to the national guideline.</p> <p>Number of hospitals with a local guideline that corresponds with the national guideline or only deviates based on local resistance patterns.</p>	<p>Total number of patients who started with empirical systemic antimicrobial therapy (only choice of antimicrobial agent).</p> <p>Total number of hospitals with a local guideline.</p>

Comentários finais

- A relação entre uso e resistência a antimicrobianos é consistente.
- No entanto, o foco do programa de controle de antimicrobianos deve ser principalmente a instituição de terapêutica apropriada.
- Ainda assim, a proximidade entre emergencistas, intensivistas e infectologistas tem a possibilidade de, ao mesmo tempo, promover terapêutica apropriada e evitar o emprego abusivo de antimicrobianos.



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