

Resistência à polimixina.. Possível prevenir?

Não....?

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0934-9723/88/06 0713-08 \$ 3.00/0

Antibiotic Uptake into Gram-Negative Bacteria

R. E. W. Hancock*, A. Bell

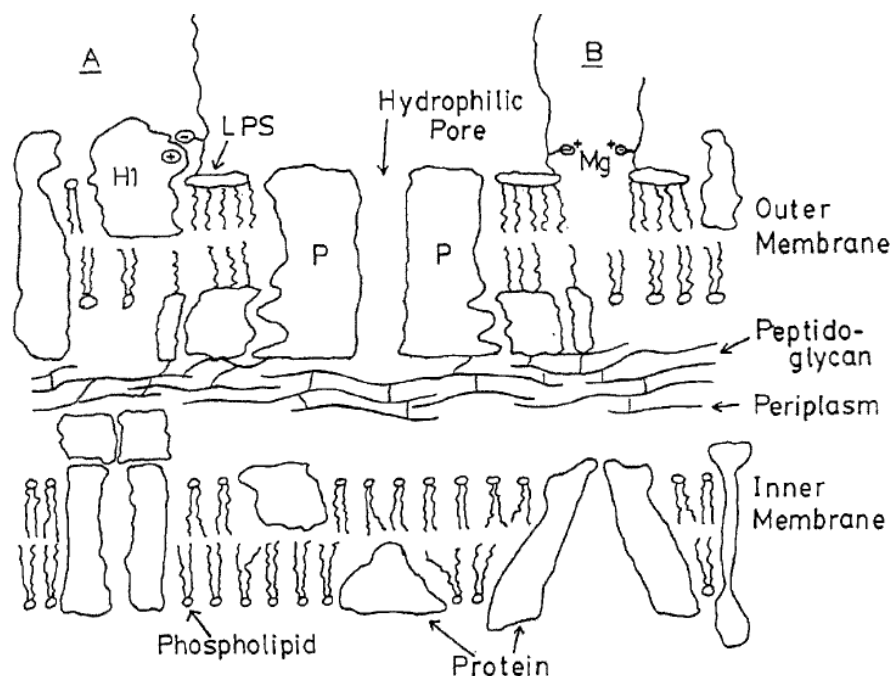
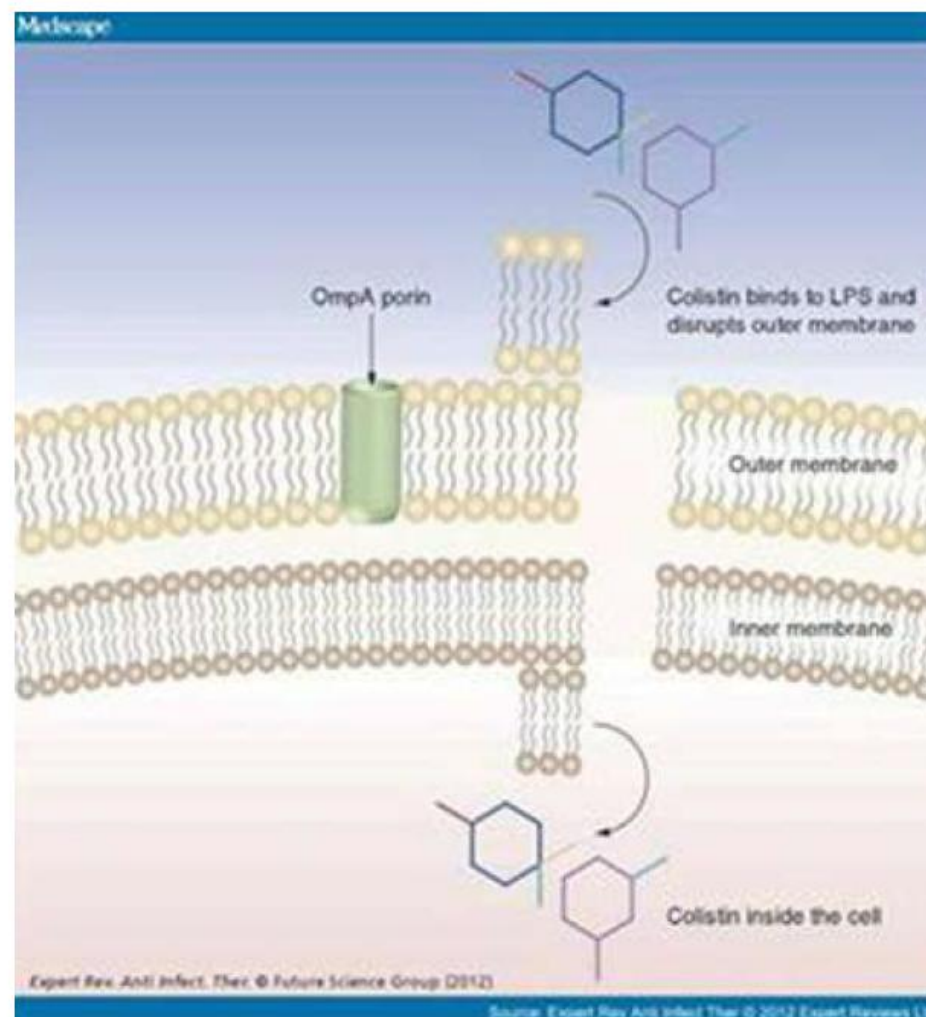


Figure 1: Schematic representation of a cross section of the cell envelope of gram-negative bacteria. P = porin protein involved in uptake of hydrophilic antibiotics, LPS = lipopolysaccharide. HI = other membrane protein. A represents sites at which self-promoted uptake is blocked by protein HI in *Pseudomonas aeruginosa* (see text). B represents sites at which polycations and chelators can displace divalent cations from LPS, resulting in self-promoted uptake. Alteration in the nature of the B sites (e.g. reduction in the affinity of LPS for divalent cations) might result in a non-porin pathway of uptake for antibiotics that are not polycations (including hydrophobic antibiotics).

MECANISMO DE AÇÃO DE POLIMIXINAS

- Ação antimicrobiana direta por meio da interação eletrostática entre o ácido diaminobutírico (Dab) carregado + e os grupos fosfato do lipídio A (componente do LPS) carregados –
- Deslocamento dos íons de Mg^{2+} e Ca^{2+} que pertencem ligação cruzada entre a molécula de LPS e rompimento de ambas as membranas
- Esta interação acarreta a passagem da polimixina nas membranas seguida pela morte celular por mecanismos pouco conhecidos



Resistência à polimixina x bactérias

Mecanismos de resistência	Bactérias
<ul style="list-style-type: none"> Alteração na LPS 	<i>Escherichia coli</i> , <i>Salmonella</i> , <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter baumannii</i>
<ul style="list-style-type: none"> Mutações nos genes <i>pmr A</i> e <i>pmr B</i> e duas proteínas do componente de sinalização 	<i>A. baumannii</i>
<ul style="list-style-type: none"> Mutações em <i>lpxA</i> , <i>lpxC</i> e <i>lpxD</i> induzindo perda do componente lipideo A do lipopossacarideo 	<i>A. baumannii</i>
<ul style="list-style-type: none"> Papel do OprH, uma proteína de membrana alterada 	<i>Pseudomonas aeruginosa</i>
<ul style="list-style-type: none"> Mudanças na carga da superfície LPS induzidas pelo locus regulatório <i>pmrA</i> e <i>phoP</i> 	<i>Enterobacteriaceae</i>
<ul style="list-style-type: none"> Resistência por mutação nos genes <i>pmrA</i> e <i>PmrB</i> 	<i>Salmonella</i>

Biswas S. Expert Rev Anti Infect Ther 2012;10(8):917

TIPOS DE RESISTÊNCIA- POLIMIXINAS

■ Adaptativa

- Fenômeno autorregulado caracterizado pela indução rápida de resistência na presença do ATB e a reversão na sua ausência.
- Sem a manutenção do efeito do ATB, a resistência é instável.
- Na manutenção da droga a resistência é ampliada e prolongada
- Ex. mediação de sistemas regulatórios, ex. ParR-ParS

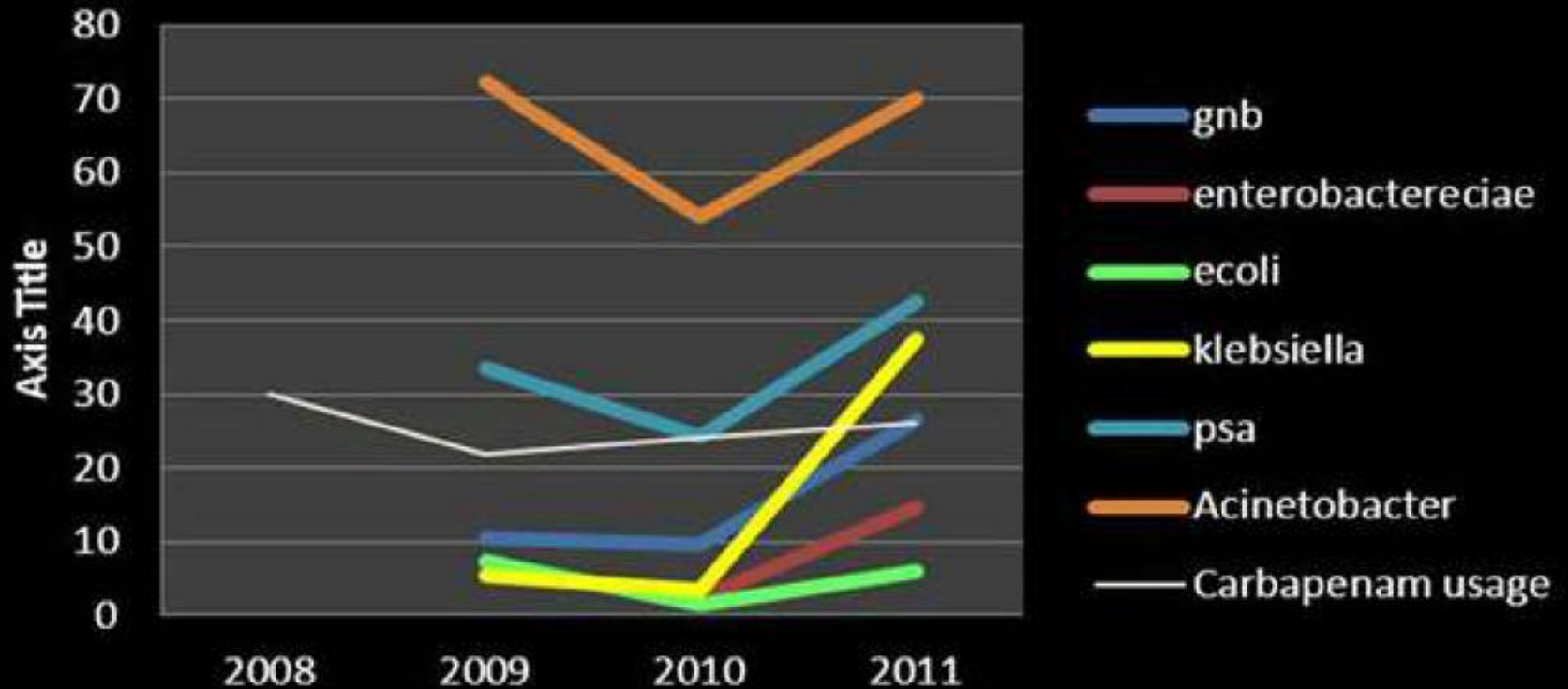
■ Adquirida (mutacional)

- Resistência genética que é estável e surge com a mutação cromossomal ou aquisição de um elemento genético
- Ex. *Klebsiella pneumoniae* → mudanças na carga da superfície LPS induzidas pelo locus regulatório *pmrA* e *phoP*

■ Heteroresistência

- Presença de uma subpopulação de microrganismos que apresentam resistência à polimixina dentro de uma população considerada como sensível nos métodos convencionais de sensibilidade aos ATM
- A subpopulação resistente a polimixina permanece resistente após passagens em meios livres da droga
- A relevância clínica é desconhecida
- O uso de terapia combinada poderia reduzir a probabilidade de selecionar subpopulações resistentes

Carbapenem resistance trend of Gram negative bacteriaemic isolates



Abdhul Ghafur, Appolo Hospital, Chennai, India
 2nd ICPIC, 25 to 28 June 2013, Geneva, Switzerland

High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality

Abstract

Carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) is becoming a common cause of healthcare-associated infection in Italy, with high morbidity and mortality. Prevalent CR-KP clones and resistance mechanisms vary between regions and over time. Therapeutic approaches and their impact on mortality have to be investigated. We performed a prospective study of patients with CR-KP isolation, hospitalized in nine hospitals of Rome, Italy, from December 2010 to May 2011, to describe the molecular epidemiology, antibiotic treatment and risk factors for mortality. Overall, 97 patients (60% male, median age 69 years) were enrolled. Strains producing *bla*KPC-3 were identified in 89 patients, *bla*VIM in three patients and *bla*CTX-M-15 plus porin defects in the remaining five patients. Inter-hospital spread of two major clones, ST512 and ST258, was found. Overall, 36.1% and 20.4% of strains were also resistant to colistin and tigecycline, respectively. Infection was diagnosed in 91 patients who received appropriate antibiotic treatment, combination therapy and removal of the infectious source in 73.6%, 59.3% and 28.5% of cases, respectively. Overall, 23 different antibiotic regimens were prescribed. In-hospital mortality was 25.8%. Multivariate analysis adjusted for appropriate treatment, combination therapy and infectious-source removal, showed that Charlson comorbidity score, intensive-care unit onset of infection, bacteraemia and infection due to a colistin-resistant CR-KP strain were independent risk factors for mortality. The spread of clones producing *K. pneumoniae* carbapenemases, mainly ST258, is currently the major cause of CR-KP infection in central Italy. We observed a high rate of resistance to colistin that is independently associated with worse outcome.

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10.1111/1469-0691.12070

ROSSI, F.

Colistimethato sódio e marca distintas

	Colomycin injection	Coly-Mycin M Parenteral
Manufacturer	Dumex-Alpha A/S, Copenhagen, Denmark	Parkdale Pharmaceuticals, Rochester, MN, USA
Main distributors	Pharmax Limited, Bexley, Kent, UK; Forest Laboratories UK Ltd, Bexley, Kent, UK	Monarch Pharmaceuticals, Inc, Bristol, TN, USA; Link Pharmaceuticals (Australia/New Zealand), Avalon Beach, NSW, Australia (since July, 2005; Pfizer Australia, before July, 2005)
Labelled content per vial	500 000, 1 000 000 or 2 000 000 IU; about 12 500 units/mg	150 mg colistin base activity
Mass of colistimethate sodium dry powder per vial	40 mg, 80 mg, or 160 mg	About 400 mg
Appearance	Creamy-white powder	White to slightly yellow lyophilised cake
Recommended dose*	<p>≤60 kg bodyweight: 50 000 IU–75 000 IU/kg per day in three divided doses, equivalent to 4–6 mg/kg per day colistimethate sodium</p> <p>>60 kg bodyweight: 1–2 million IU three times a day, equivalent to 80–160 mg colistimethate sodium three times per day</p>	2.5–5.0 mg/kg per day colistin base activity in two to four doses, equivalent to about 6.67–13.3 mg/kg per day colistimethate sodium
Product-recommended upper limit dose for a 60 kg patient*	480 mg of colistimethate sodium per day	800 mg of colistimethate sodium per day
*For patients with normal renal function.		
Table 1: Comparison of the two major types of colistimethate sodium parenteral products		

Promixin®

Colistimetato sódico 1.000.000 UI

Pó estéril para injeção e nebulização.

USO INTRAVENOSO E INALATÓRIO
"USO ADULTO e PEDIÁTRICO."

APRESENTAÇÃO

Caixa com 30 frascos-ampola.

COMPOSIÇÃO:

Princípio Ativo: Colistimetato Sódico aproximadamente 1.000.000 UI.

EQUIVALÊNCIA DO COLISTIMETATO SÓDICO ENTRE UI E MG:

1.000.000 UI equivalem aproximadamente a 80 mg de colistimetato sódico.
1 mg equivale aproximadamente 12.740 UI.

Portanto, 1 frasco de PROMIXIN contém aproximadamente 1.000.000 UI.

PROMIXIN é um antibiótico, e sua ação se dá combatendo infecções de diversas origens. Pode ser intravenosa ou utilizado para nebulização (administração por via inalatória).

Observar o prazo de validade no rótulo, que é de 2 anos após a data de fabricação. Não utilizar medicamento de validade esteja vencido.

Informar o médico a ocorrência de gravidez ou lactação antes de iniciar o tratamento sem o conhecimento do médico. Informar o médico se estiver amamentando.

Informe seu médico e/ou ao pessoal hospitalar o aparecimento de efeitos adversos, como rubor facial, tonturas, urticárias, coceira ou falta de ar.

"TODO MEDICAMENTO DEVE SER MANTIDO FORA DO ALCHEQUE DO PACIENTE"

Manter o medicamento fora do alcance das crianças e sob supervisão hospitalar sobre qualquer uso.

Função renal prejudicada aumenta a possibilidade de aprisionamento e bloqueio neuromuscular. Isto se dá geralmente devido a falhas em seguir as recomendações de dosagem ou a administração de doses excessivas. Quando ocorrer bloqueio neuromuscular, a redução da dose em pacientes com comprometimento renal podem levar a efeitos adversos. Estas manifestações de neurotoxicidade são reversíveis após a interrupção da administração.

Altas concentrações séricas de colistimetato sódico, as quais podem ser a redução da dose em pacientes com comprometimento renal podem levar a efeitos adversos. Estas manifestações de neurotoxicidade são reversíveis após a interrupção da administração.

Agentes curarizantes ou outros antibióticos que possuem efeitos neurotóxicos podem potencializar os efeitos de neurotoxicidade. A redução da dose pode melhorar estes sintomas. Os efeitos de neurotoxicidade são reversíveis após a interrupção da administração.

Pode ocorrer exacerbação dos sintomas de reações adversas como: fraqueza muscular e insuficiência renal. Não há antídotos disponíveis para o tratamento da superdosagem e a eliminação do colistimetato sódico é prolongada.

Para os casos de superdosagem, recomenda-se a suspensão da administração e a substituição da terapia antimicrobiana.

"USO RESTRITO A HOSPITAIS"
Lote, data de fabricação e prazo de validade: vide cartucho e rótulos.

Fabricado por:
Xellia Pharmaceuticals ApS
Dalslandsgad, 11 - Copenhagen S
DK 2300 Dinamarca

Para:
Profile P
Chichester
PO20 2F
Inglaterra
Philips G

Importado e distribuído no Brasil por:
OPEM REPRESENTAÇÃO IMPORTADORA EXPORTADORA E
Rua Frei Caneca, 356 - São Paulo - SP
CNPJ: 38.909.503/0001-57
Resp. Téc.: Joyce Ap. Pires Bueno Tonelli Porto - CRF-SP 38.
MS: 1.2748.0028.003-4
SAC: 0800-774-0119

COLIS-TEK

colistimetato de sódio

Pó Liófilo Injetável

Para Uso Intravenoso ou Intramuscular

USO ADULTO e PEDIÁTRICO.

APRESENTAÇÃO

Caixa com 1 frasco-ampola

COMPOSIÇÃO

Cada frasco-ampola contém:

346 mg de colistimetato de sódio equivalente a 150 mg de colistina base.

1mg de colistimetato de sódio corresponde aproximadamente a 12.740 UI

346 mg de colistimetato de sódio corresponde aproximadamente a 4.408.040 UI

ATENÇÃO: ESTE PRODUTO É RESTRITO AO USO HOSPITALAR. AS INFORMAÇÕES DESTINAM-SE AOS PACIENTES QUE ADQUIRAM O PRODUTO PARA USO EM SITUAÇÕES DE EMERGÊNCIA, ACOMPANHADAS OU AO PESSOAL DA ÁREA HOSPITALAR QUE TRABALHE COM O PRODUTO E/OU ORIENTAÇÃO AO PACIENTE.

Fabricado por:

Hikma Itália S.p.A.

Viale Certosa, 10 - 27100 Pavia - Itália

Importado e distribuído no Brasil por:

OPEM REPRESENTAÇÃO IMPORTADORA EXPORTADORA E DISTRIBUIDORA

Rua Frei Caneca 356 - Consolação - São Paulo - SP CEP: 01307-000

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Resp. Téc: Joyce Ap. Pires Bueno Tonelli Porto - CRF-SP 38.678

MS 1.2748.0023

SAC 0800-774-0119

ROSSI,F.

CMS (sal de sódio) x Colsitin (sal de sulafato)

- CMS  METABOLIZADO EM VÁRIOS COMPOSTOS E Colisitim...
- CMS excreção renal (secreção tubular renal)
- Colsitin (reabsorção renal)
- DOSES:
- UI X mg X CBAmg

PK colistina

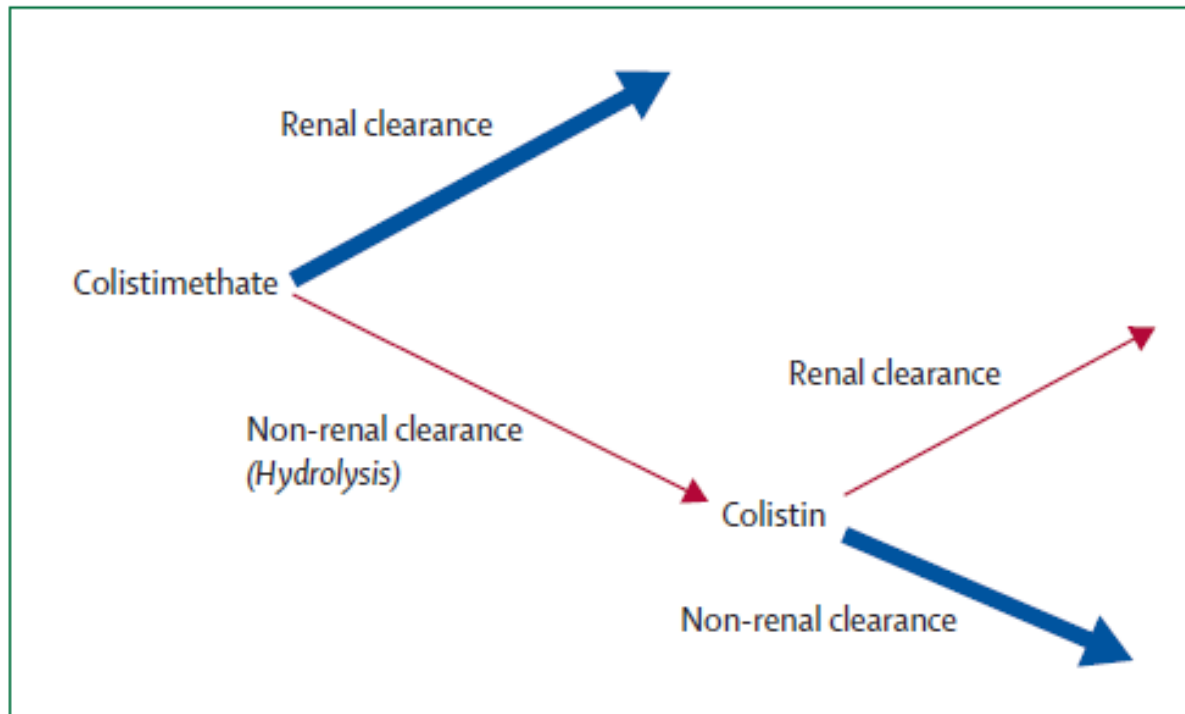


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

Colistin therapy for microbiologically documented multidrug-resistant Gram-negative bacterial infections: a retrospective cohort study of 258 patients

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EFICIÁCIA:...Local da
infecção,patógeno,dose,
Monoterapia x combinado

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Ventilator-associated pneumonia

Critical illness

Risk factors

Prognosis

Case series

ABSTRACT

It is unclear whether the effectiveness of polymyxins depends on the site of infection, the responsible pathogen, dosage, and monotherapy vs. combination therapy. We investigated colistin therapy in a large, retrospective, single-centre, cohort study. Primary analysis outcomes were infection outcome, survival and nephrotoxicity. Over a 7-year period (October 2000 to October 2007), 258 patients received intravenous (i.v.) colistin for at least 72 h for microbiologically documented multidrug-resistant Gram-negative bacterial infections, comprising 170 (65.9%) *Acinetobacter baumannii*, 68 (26.4%) *Pseudomonas aeruginosa*, 18 (7.0%) *Klebsiella pneumoniae*, 1 (0.4%) *Stenotrophomonas maltophilia* and 1 (0.4%) *Enterobacter cloacae*. Cure of infection occurred in 79.1% of patients, nephrotoxicity in 10% and hospital survival in 65.1%. In the multivariate analysis, independent predictors of survival were colistin average daily dose [adjusted odds ratio (aOR)= 1.22, 95% confidence interval (CI) 1.05–1.42] and cure of infection (aOR= 9, 95% CI 3.6–23.1), whilst the proportion of creatinine change (aOR= 0.21, 95% CI 0.1–0.45), Acute Physiology and Chronic Health Evaluation (APACHE) II score (aOR= 0.89, 95% CI 0.84–0.95) and haematological disease (aOR= 0.23, 95% CI 0.08–0.66) were associated with mortality. Effectiveness of colistin was not dependent on the type of pathogen. No independent predictors for nephrotoxicity were observed. The findings of the largest cohort study to date on i.v. colistin show that colistin is a valuable antibiotic with acceptable nephrotoxicity and considerable effectiveness that depends on the daily dosage and infection site.

REVIEW OF THERAPEUTICS


Colistin: Understanding and Applying Recent Pharmacokinetic Advances

Colistin, the most widely used polymyxin antibiotic, was originally introduced in the late 1950s before the establishment of the present-day drug approval process. Originally shelved due to toxicity concerns, colistin, in the form of its inactive prodrug colistin methanesulfonate, has undergone a renaissance in the past 15 years. Unfortunately, this is not because of an improved adverse-effect profile but because colistin is among the only remaining antibiotics with activity against multidrug-resistant gram-negative bacilli. Pharmacokinetic and pharmacodynamic data are limited to guide the appropriate use of colistin; however, important advances have occurred over the past 5 years. Since its reintroduction, published reports regarding colistin have produced discordant results in terms of both efficacy and safety. Because the efficacy and toxicity of colistin are dose dependent, the impact of discordant dosing recommendations cannot be understated. This review highlights the issues leading to differing and often conflicting dosing recommendations, reviews the recent pharmacokinetic advances, and provides recommendations for the optimal use of colistin.

KEY WORDS colistin, colistimethate, polymyxins, pharmacokinetics, pharmacodynamics.

(Pharmacotherapy 2014;**(**):**-**) doi: 10.1002/phar.1484

- Conclusão: 1
- Mesmo com concentrações máximas previstas..o nível sérico pode ser baixo e o breakpoint de 2 mcg/ml pode não ser adequado....



understanding of colistin PK. Three extremely important advances came from these data. First, the authors showed that predicted maximum serum concentrations, even with this dosage, which was above the upper limit of the European package insert dosage range recommendation,

would be 0.6 µg/ml with the first dose and 2.3 µg/ml at steady state. When protein binding of ~60% is taken into account,^{11, 12} these numbers for the first time brought into serious question the appropriateness of the current susceptibility breakpoint for colistin 2 µg/ml.¹³

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Jessica K. Ortwein,¹ Keith S. Kaye,^{2,3} Jian Li,⁴ and Jason M. Pogue^{3,5*}

¹Department of Pharmacy Services, Parkland Health and Hospital System, Dallas, Texas; ²Department of Internal Medicine, Division of Infectious Diseases, Detroit Medical Center, Detroit, Michigan; ³Wayne State University School of Medicine, Detroit, Michigan; ⁴Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia; ⁵Department of Pharmacy Services, Sinai-Grace Hospital, Detroit Medical Center, Detroit, Michigan

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(Pharmacotherapy 2014;•••(**):••-••) doi: 10.1002/phar.1484

Conclusão: 2

- Meia-vida longa ..necessidade de Loading dose..

Second, the half-life of colistin was determined to be 14.4 hours showing that without a loading dose it would take ~60 hours for colistin to reach steady state.

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- Conclusão: 3

concerning, the authors showed that hydrolysis of CMS to active colistin in critically ill patients was slow, with maximum concentrations occurring ~7 hours after the dose.

Pacientes criticos...

Hidrólise lenta...

Baixas
concentrações...

What Are the Important Lessons Learned from These Newer Pharmacokinetic Data?

- Concentração ideal: 2,5 mcg/ml
- Pacientes com função renal normal e obesos..com baixas concentrações...

The current clinical PK and animal PK/PD findings, when taken together, suggest that the susceptibility breakpoints for colistin warrant revisiting due to practical limitations in achieving adequate in vivo colistin exposure and are a primary reason why many experts recommend the use of combination therapy.

REVIEW OF THERAPEUTICS

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Key Words: colistin, colistin methate, polymyxins, pharmacokinetics, pharmacodynamics. (Pharmacotherapy 2014;34(11):1484-1494) doi: 10.1002/phar.1484

Baixa exposição à colsitina

Doses x concentrações....

When determining what to do, in the end, we need to come back to the important finding that even with the most aggressive of these dosing regimens, our likely obtainable colistin concentrations are relatively low and likely to result in bacteriostatic effects. When these relatively low exposures are combined with the known heteroresistance to colistin in multidrug-resistant gram-negative bacilli^{25–27} and the impressive synergy seen in vitro, the role of combination therapy with other active or synergistic agents becomes increasingly important. Because the

Targets de PK/PD difíceis de atingir...

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are presented in Table 2. A target AUC:MIC ratio of ≥ 60 has been suggested for colistin,¹⁸ which is difficult to achieve with current dosing recommendations for isolates with MICs $> 0.5 \mu\text{g/ml}$, a factor significantly compounded by the significant differences in MIC obtained by testing method, as shown in Table 2.

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Mutant prevention concentrations of colistin for *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* clinical isolates

Myung-Jin Choi and Kwan Soo Ko*

resistant mutants can be easily selected *in vitro*.⁹ The recommended dose regimen of colistin methanesulphonate of approximately 4–6 mg/kg/day lies within the MSW,⁹ which may be linked to the generation of colistin resistance. Since the use of

Mutant prevention concentrations of colistin for *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* clinical isolates

Myung-Jin Choi and Kwan Soo Ko*

This suggests that colistin treatment can provoke genetic mutations related to resistance as a mutagen within a short period in addition to the selection of resistant subpopulations. In short, colistin resistance may occur very easily during drug use.

These findings suggest the possibility of the rapid emergence and spread of colistin resistance by a single mutation. Thus, combination therapy for colistin treatment of non-fermenter and Enterobacteriaceae infections would be necessary to prevent or slow the emergence of colistin resistance.

Polymyxin use as a risk factor for colonization or infection with polymyxin-resistant *Acinetobacter baumannii* after liver transplantation

Results. We evaluated 65 patients submitted to LT, among whom PRAB was isolated in 7, 4 of whom developed infection. The MICs for polymyxin E ranged from 16 to 128 mg/mL. All patients with PRAB required dialysis. The median time of polymyxin use before PRAB isolation was 21 days. These 4 included 1 case of primary bloodstream infection (BSI), which was treated with the carbapenem-polymyxin combination; 1 case of surgical site infection, which was treated with gentamicin, polymyxin, ampicillin-sulbactam, and tigecycline; and 2 cases of pneumonia, treated with the combination of carbapenem-polymyxin. In the case of BSI and in 1 of the cases of pneumonia, the treatment was considered successful. Mortality was 71% among the cases, compared with 33% among the non-cases.

M.P. Freire, I.M. Van Der Heijden, G.V.B. do Prado, L.S. Cavalcante, I. Boszczowski, P.R. Bonazzi, F. Rossi, T. Guimarães, L.A.C. D'Albuquerque, S.F. Costa, E. Abdala. Polymyxin use as a risk factor for colonization or infection with polymyxin-resistant *Acinetobacter baumannii* after liver transplantation. *Transpl Infect Dis* 2014; **16**: 369–378. All rights reserved

PFGE...

Freire et al: *A. baumannii* in liver transplantation

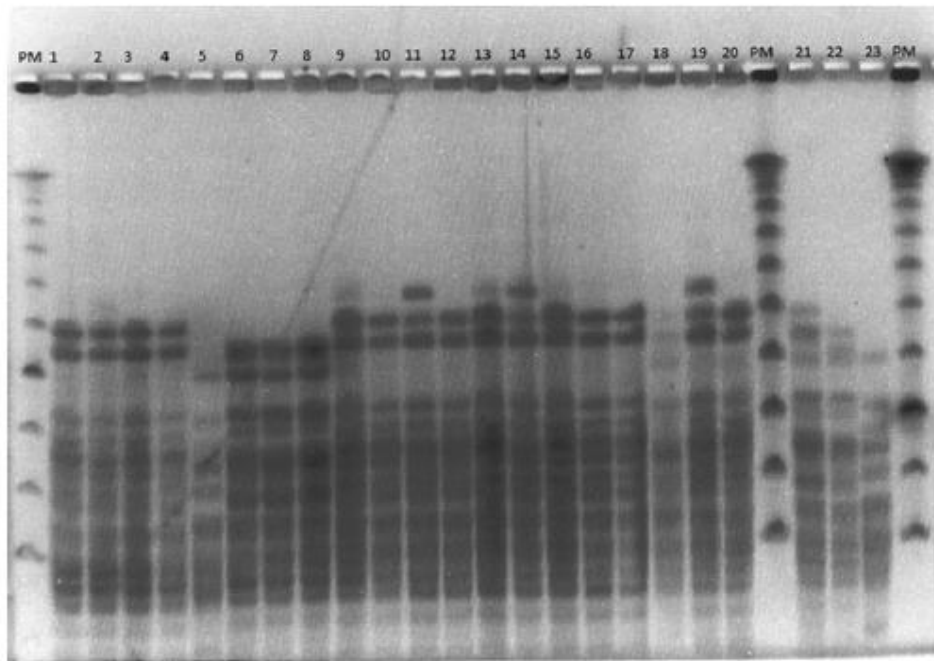


Fig. 2. Pulse-field gel electrophoresis of *Acinetobacter baumannii* strains isolated from 7 patients. Polymyxin-resistant *A. baumannii* (PRAB) in lanes 1 and 2, Case 4; lanes 3–5, Case 3; lanes 6–8, Case 1; lane 9, Case 6; lanes 10–13, Case 7; lanes 14–19, Case 2; and lane 20, Case 5. Carbapenem-resistant *A. baumannii* is shown in lane 21, Case 4; lane 22, Case 5; and lane 23, Case 3.

KPC colistina R

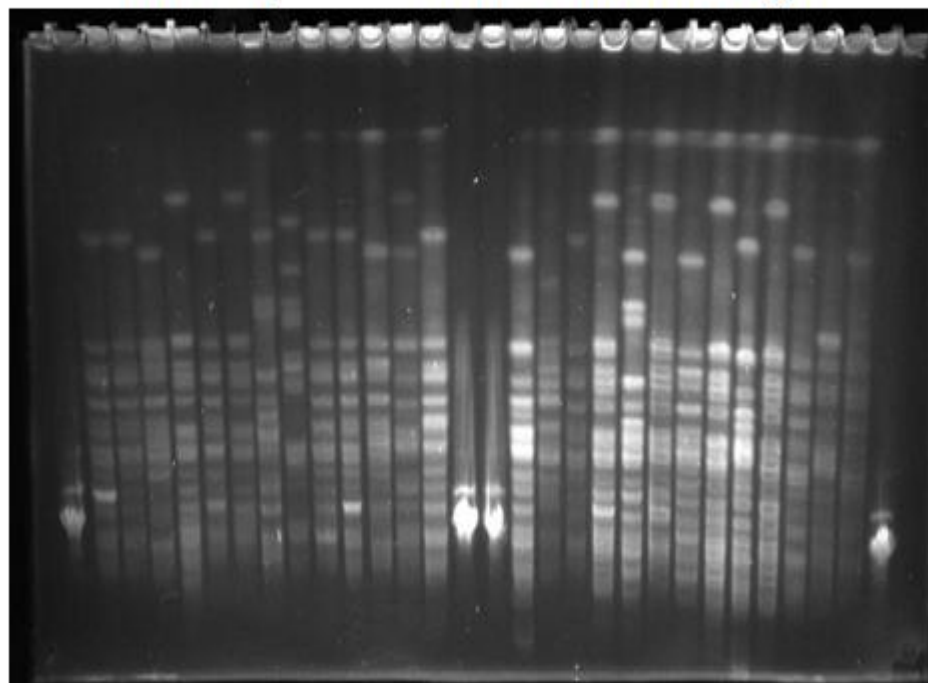
Lab. Microbiologia(HC- FMUSP)

Lim 54

PFGE	PACIENTE	RGHC	MATERIAL	CLÍNICA	DATA DE COLETA
1	MJCF	2981237i	liq. Ascítico	U2CC	04/06/2013
2	CFT	2165121d	liq. Ascítico	U1CH	09/02/2013
3	ACS	14044349a	coleção	UARR	13/06/2013
4	LAM	2261014J	sangue	A1MH	09/06/2012
5	FAM	14061819D	ferida operat.	UMIN	03/09/2013
6	AD	14024671X	sangue	ETMO	01/01/2013
7	FRM	6068185H	liq. Ascítico	U1CH	16/10/2012
8	EQS	2789369a	sangue	A1PS	02/02/2013
9	CMA	14027373f	liq Ascítico	U2CC	09/06/2013
10	ASRM	13810145c	sangue	E1CH	29/09/2013
11	RNRG	13960286d	sangue	ETMO	03/10/2012
12	ASEF	14066766d	coleção	UARR	19/12/2013
13	MOF	14038020c	liq abdominal	UP4C	12/01/2013
14	MSS	13826176a	sangue	UARR	24/09/2012
15	FSC	13980120i	sangue	UQUE	06/10/2011
16	JLG	13983246k	sangue	U1CC	14/02/2013
17	CCMS	13956316h	coleção	EUTR	24/06/2012
18	DANB	13965454d	liq peritoneal	U1CH	27/10/2011
19	ZSRP	13980030j	liq. ascítico	EUCH	09/11/2011
20	EMFA	13947469i	sangue	ETMO	20/01/2011
21	RMVS	14049649h	sangue	UP4M	22/05/2013
22	MSV	13926892h	sangue	E1CH	06/01/2011
23	PLS	13966841k	sangue	UMIN	19/07/2011
24	MPC	3128179d	sangue	UMIN	09/08/2013
25	MON	13485339j	sangue	UP4M	21/10/2013
26	JSC	14063435k	partes moles	EP509	11/09/2013

KPC colistina R (HC- FMUSP)

Lim 54/ Lab. Microbiologia

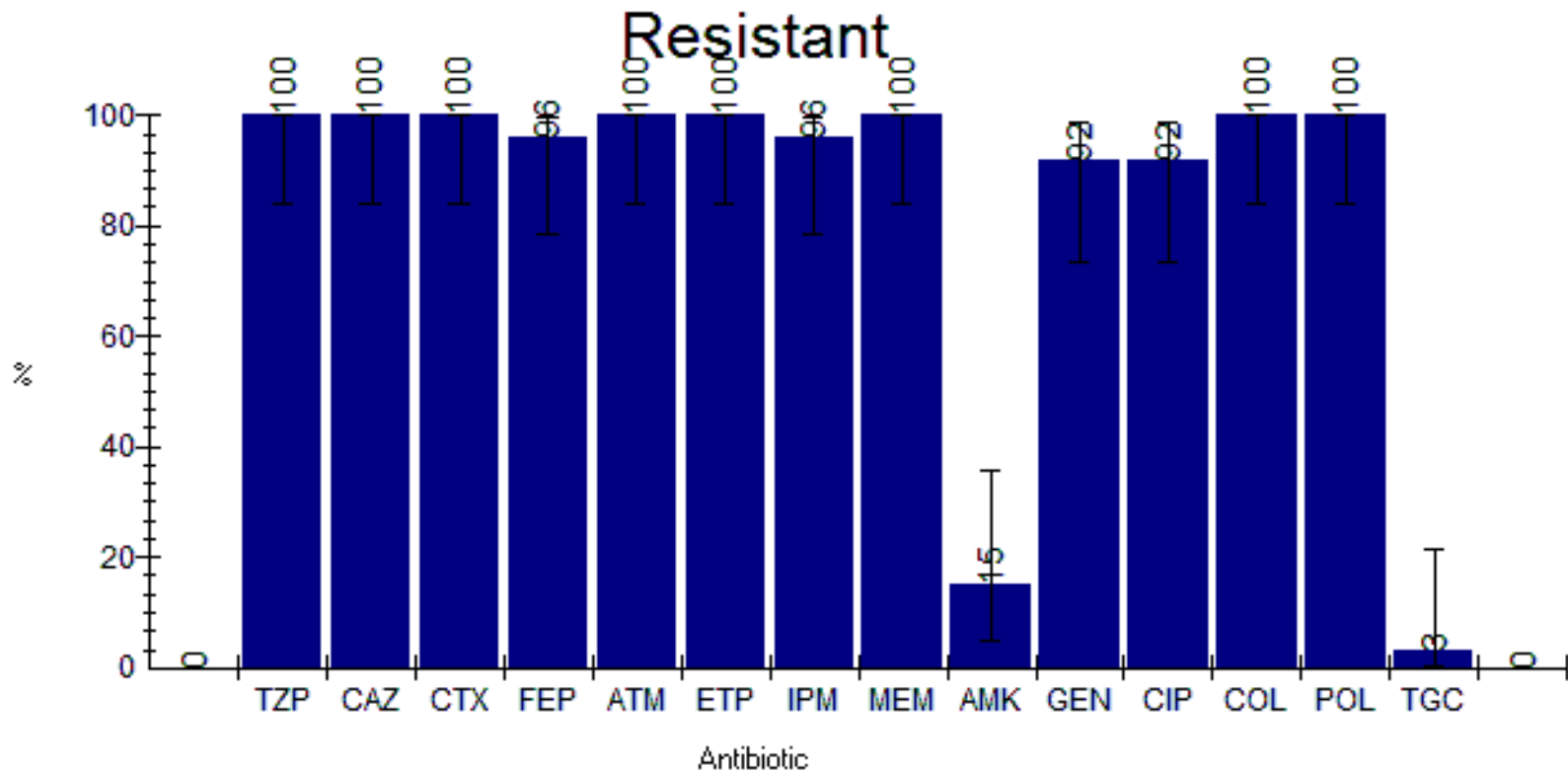


Percentual de Resistência-HC-FMUSP

KPC+ R a coistina

microdiluição

(N-26)



REVIEW OF THERAPEUTICS

Susceptibility Testing of the Polymyxins: Where Are We Now?

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¹Department of Pathology and Laboratory Medicine, University of California, Los Angeles, California; ²Clinical Microbiology, UCLA Health System, Los Angeles, California

Antimicrobial susceptibility testing for the polymyxins—colistin and polymyxin B—is fraught with technical challenges. Key among these is the propensity of the polymyxins to adsorb to polystyrene, a material often used for in vitro minimum inhibitory concentration testing devices. This effect may be mitigated by the addition of a surfactant such as polysorbate 80; however, concern exists that polysorbate 80 may act synergistically with the polymyxins and artificially lower minimum inhibitory concentrations. Furthermore, the polymyxins diffuse poorly through agar, compromising the performance of both disk diffusion and Etest methods. Very few peer-reviewed studies have investigated in vitro susceptibility test methods for the polymyxins, and it is clear that an in vitro test that reliably predicts the activity of the polymyxins in vivo has yet to be defined. This review describes the methods available and challenges associated with susceptibility testing of colistin and polymyxin B and discusses the current breakpoints for both agents.

KEY WORDS polymyxins, susceptibility testing, broth microdilution.
(Pharmacotherapy 2014;**(**):**-**) doi: 10.1002/phar.1505

Teste de sensibilidade com Tween 80?

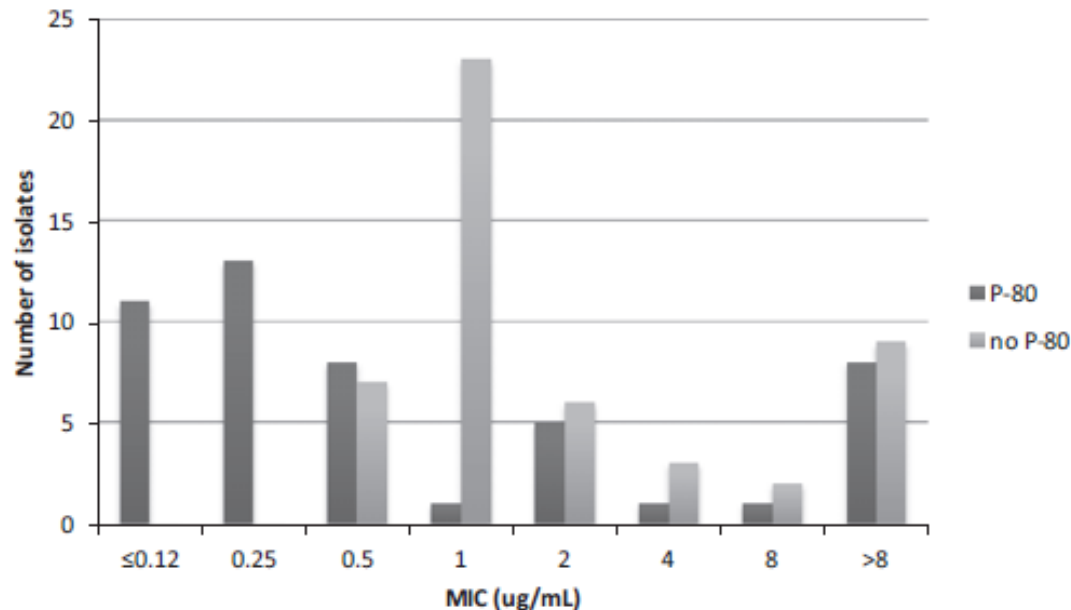


Figure 1. Broth microdilution minimum inhibitory concentrations (MICs), tested with and without the addition of 0.002% polysorbate 80, for 50 multidrug-resistant clinical isolates of gram-negative bacilli (data adapted from reference 10).

Breakpoints

Table 1. 2014 CLSI and EUCAST MIC Breakpoints for Colistin

Organism	CLSI Breakpoints (µg/ml) ^a			EUCAST Breakpoints (µg/ml) ^b		
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
<i>Enterobacteriaceae</i>	–	–	–	≤ 2	–	> 2
<i>Acinetobacter</i>	≤ 2	–	≥ 4	≤ 2	–	> 2
<i>Pseudomonas</i> species	≤ 2	4	≥ 8	≤ 4	–	> 4
Other non- <i>Enterobacteriaceae</i> gram-negative bacilli	≤ 2	4	≥ 8	–	–	–

CLSI = Clinical and Laboratory and Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing; MIC = minimum inhibitory concentration.

^aCLSI breakpoints include polymyxin B, which are the same as those for colistin.

^bThe British Society for Antimicrobial Chemotherapy breakpoints are the same as those published by EUCAST.

PK/PD PODE VARIAR COM O MÉTODO DA DETERMINAÇÃO DO MIC

4

PHARMACOTHERAPY Volume **, Number **, 2014

Table 2. Comparison of Colistin AUC:MIC Ratio Results Using Four Different MIC Methods

Organism	MIC Method	Colistin AUC:MIC Ratio	Interquartile Range	Range
<i>Acinetobacter baumannii</i> (n=10)	BMD with P-80	452.1	10.3–1000	3.8–1000
	BMD without P-80	35.6	6.5–60.00	3.8–1000
	Agar Dilution	76.5	13.1–120	3.8–120
	Etest	62.0	32.5–80	20–120
<i>Klebsiella pneumoniae</i> (n=13)	BMD with P-80	502.0	3.8–1000	3.8–1000
	BMD without P-80	63.8	3.8–120	3.8–120
	Agar Dilution	414.9	3.8–1000	3.8–1000
	Etest	74.00	7.5–120	5–157
<i>Pseudomonas aeruginosa</i> (n=21)	BMD with P-80	180.4	60–240	15–952
	BMD without P-80	46.3	30–60	3.8–60
	Agar Dilution	58.6	30–60	15–120
	Etest	76.7	30–80	15–240

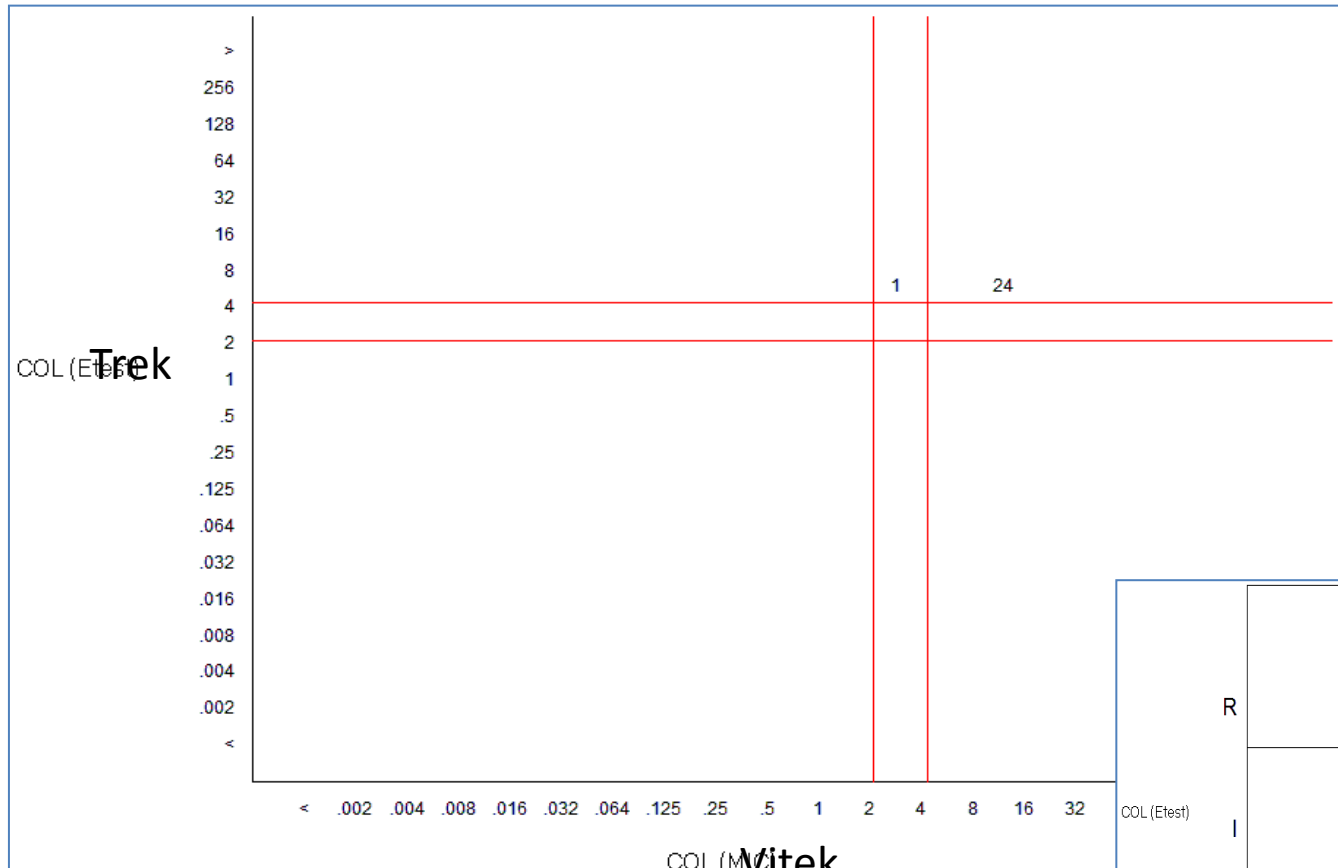
AUC:MIC = area under the concentration-time curve to minimum inhibitory concentration ratio; BMD = broth microdilution; P-80 = polysorbate 80.

Analise Laboratorial dos isolados colistina resistente

- 26 K.pneumoniae resistente a colistina pelo Vitek 2 foram submetidas a microdiluição (painel GNX2F - Sensititre)
- A concordância da colistina foi de 96%, com 4% de erro menor.
- Houve concordância de 100% entre colistina e polimixina na microdiluição.

Colistina (Vitek2 x Microdiluição-TREK)

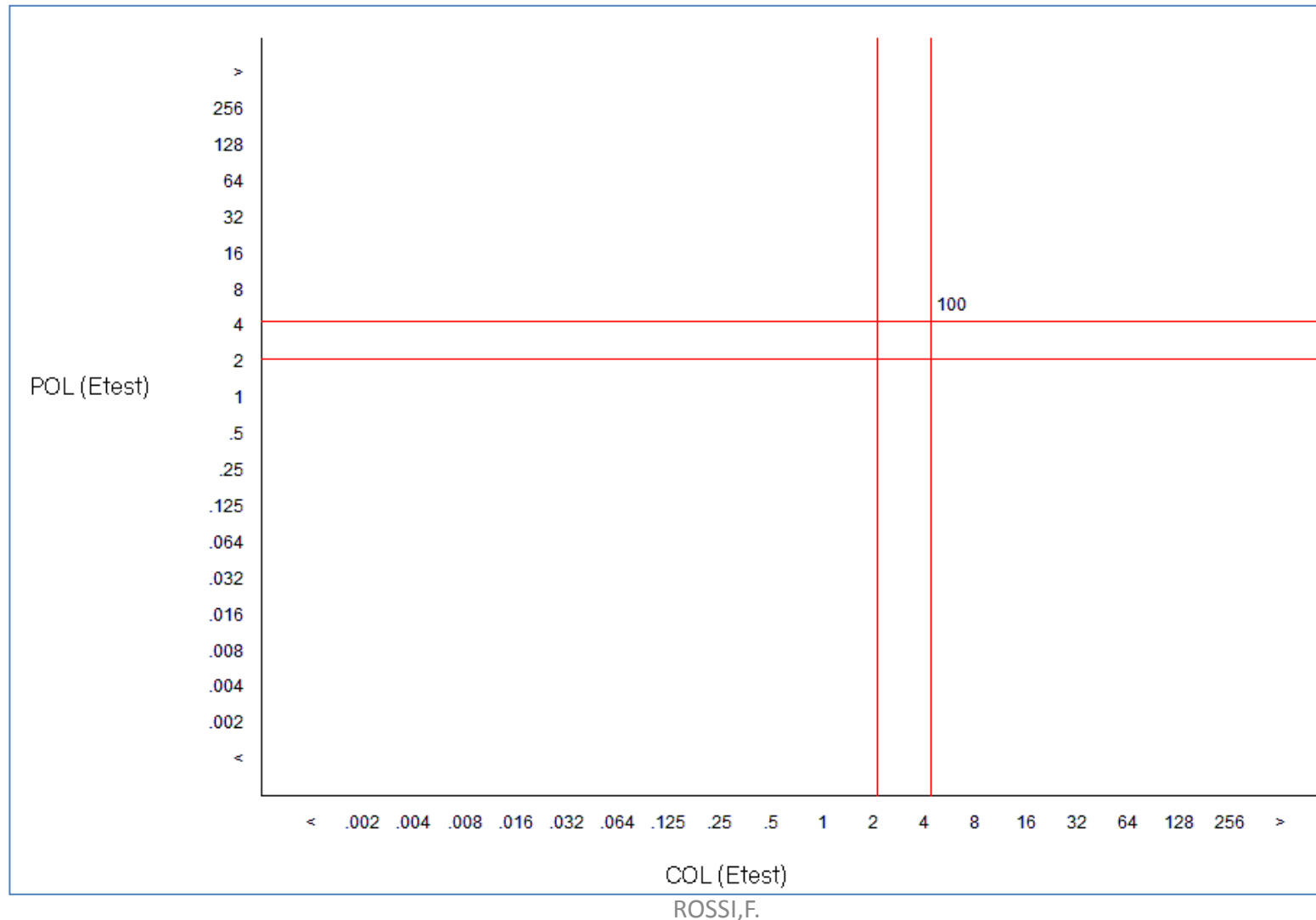
N-25



R		4%	96%
I			
S			
	S	I	R
	COL (MIC)		

ROSSI,F.

Colistina versus Polimixina B pela microdiluição. Concordância de 100%



Polymyxin B for the treatment of multidrug-resistant pathogens: a critical review

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Polymyxins have re-emerged in clinical practice owing to the dry antibiotic development pipeline and worldwide increasing prevalence of nosocomial infections caused by multidrug-resistant (MDR) Gram-negative bacteria. Polymyxin B and colistin (polymyxin E) have been ultimately considered as the last-resort treatment of such infections. Microbiological, pharmacokinetic, pharmacodynamic and clinical data available for polymyxin B are reviewed in this paper. Polymyxin B has rapid *in vitro* bactericidal activity against major MDR Gram-negative bacteria, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*. Acquired resistance to this agent is still rare among these pathogens. However, optimized dosage regimens are not known yet. Good clinical outcomes have been observed in the majority of the patients treated with intravenous polymyxin B in recent studies. However, these studies failed to provide definitive conclusions due to limitations of study design and additional clinical trials are required. Although combination therapy may be an attractive option based on some currently available *in vitro* data, clinical data supporting such recommendations are lacking. Since polymyxins will be increasingly used for the treatment of infections caused by MDR bacteria, clinical pharmacokinetic, pharmacodynamic and toxicodynamic studies underpinning the optimal use of these drugs are urgently required.

REVIEW OF THERAPEUTICS

To B or Not to B, That Is the Question: Is It Time to Replace Colistin With Polymyxin B?

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¹Department of Pharmaceutical Services, University of California Los Angeles, Los Angeles, California;

²Department of Pharmacy Practice, University of Illinois, Chicago, Illinois

The polymyxins—colistin and polymyxin B—are an increasingly important part of the antimicrobial arsenal given the rising rate of infections due to multidrug-resistant gram-negative bacteria. Although the drugs have been available since the 1950s, only recently have pharmacokinetic and pharmacodynamic data been available to guide appropriate use of these drugs. Far more data and global clinical experience exist for colistin, available as the prodrug colistimethate sodium (CMS), compared with polymyxin B. Concerns raised about variability in the ability to achieve therapeutic drug concentrations when dosing CMS have led many clinicians to desire a more pharmacokinetically reliable product. The pharmacokinetic and pharmacodynamic advantages of polymyxin B compared with CMS are compelling, but clinical experience has not consistently corroborated these data. Prospective, comparative data evaluating both drugs in combination with other antimicrobials as well as comparing polymyxin B and CMS directly will inform optimal use of each drug. Some of these investigations are currently under way. In the meantime, based on current data, both drugs appear to be appropriate for use in the clinical setting.

KEY WORDS colistin, polymyxin B, pharmacology, therapeutic use.

(Pharmacotherapy 2014;44(11):1111-1118) doi: 10.1002/phar.1510

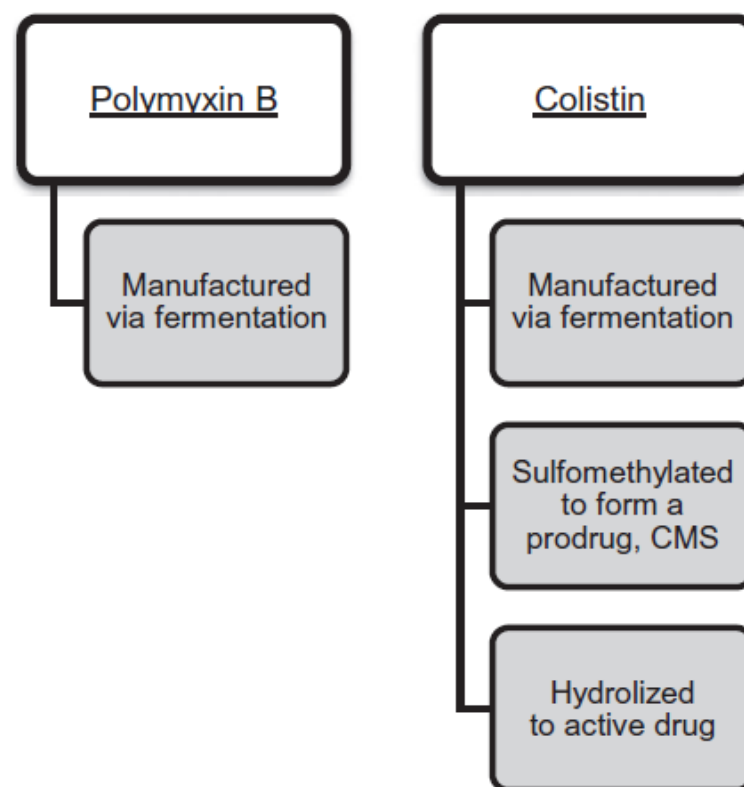
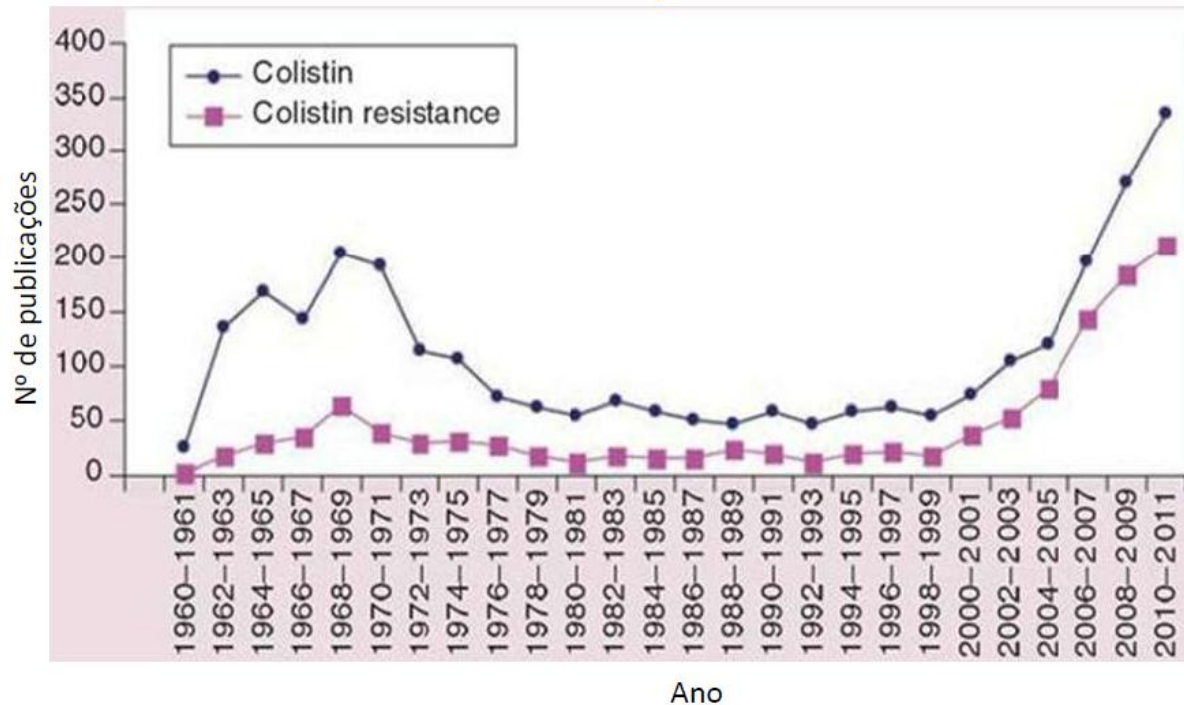


Figure 1. Comparison of manufacturing and processing of Polymyxin B and Colistin.

Resistência a polimixina



Número de publicações encontradas no PubMed de 1960 a 2011 usando os termos colistin ou colistin resistance

Biswas S. Expert Review of Anti-infective Therapy 2012;10(8):917

POLIMIXINAS

- Aumento significativo do uso
- Mecanismo de ação complexo
- Mecanismos de resistência complexo
- Heteroresistência selecionando MICs mais elevados
- Janela de Seleção de Mutação (MSW) alta
- Doses e apresentações comerciais (confusas)
- Farmacocinética/Farmacodinâmica (Targets ?)
- Teste de Sensibilidade (Tween? Breakpoints..?)
- Dados temporais de Resistência e Realidade no Brasil...
- Conclusão?

Conclusão... Não!!!

Espero que o Alexandre esteja certo...

Mas até agora não me convenci...

A Resistência às polimixinas vai continuar...

E precisa urgente de ação integrada!!!

Obrigada!!!