Treatment of extremely drug resistant gram-negative organisms

Paul Ananth Tambyah

With thanks to
Dr Hsu Li Yang

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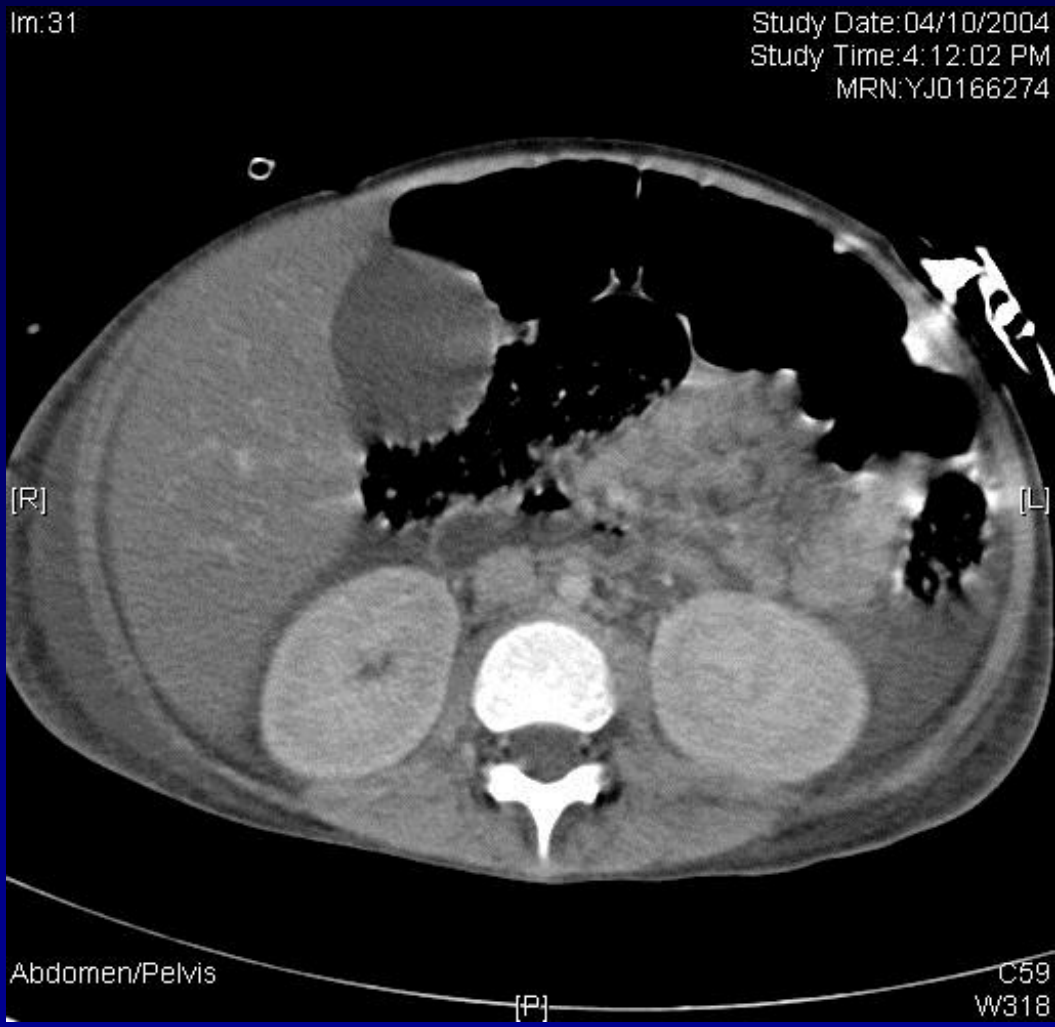
NUS National University of Singapore

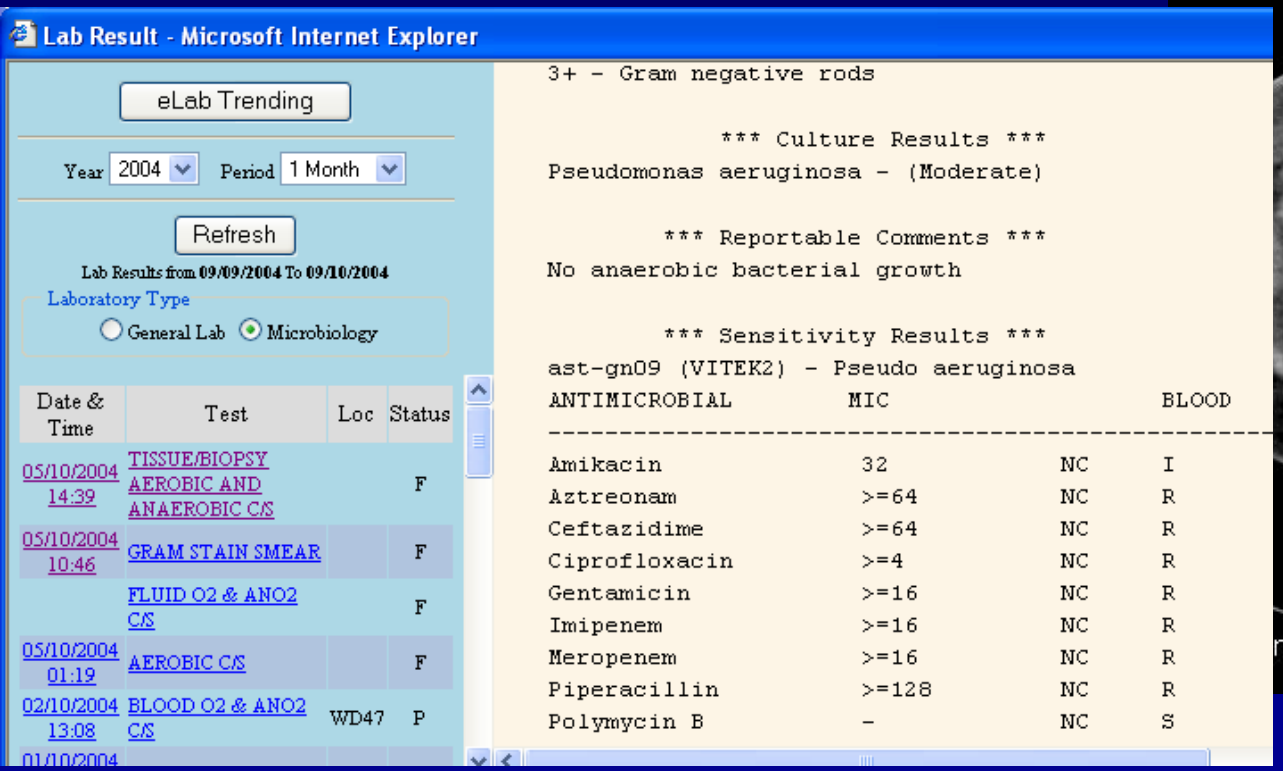
An unfortunate young man

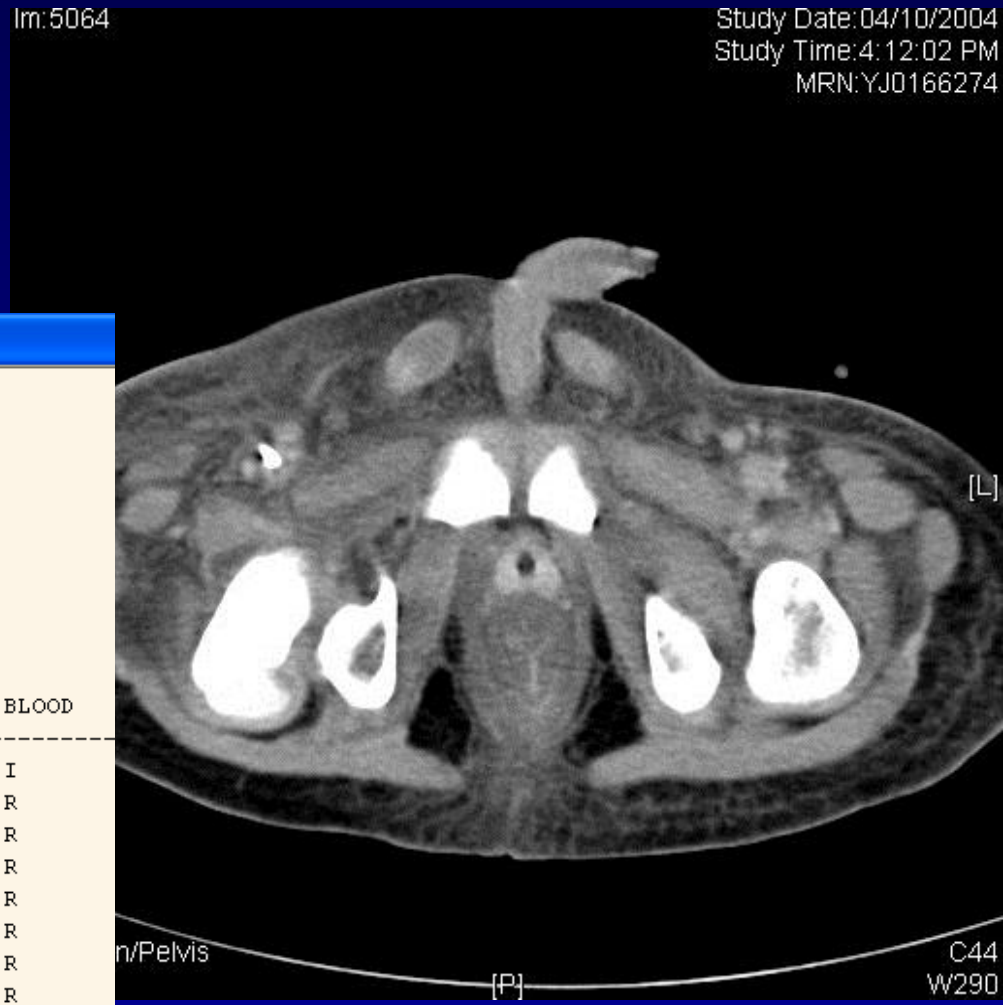
- 7 year old boy with AML M2, finishing chemotherapy in remission
- Admitted with neutropenic sepsis
- Stool *C.diff* toxin positive
- Blood culture positive
- Hickmann removed
- Abdominal pain



An unfortunate young man

- Developed blisters in groin
- Blood cultures persistently positive
- Debrided in ICU

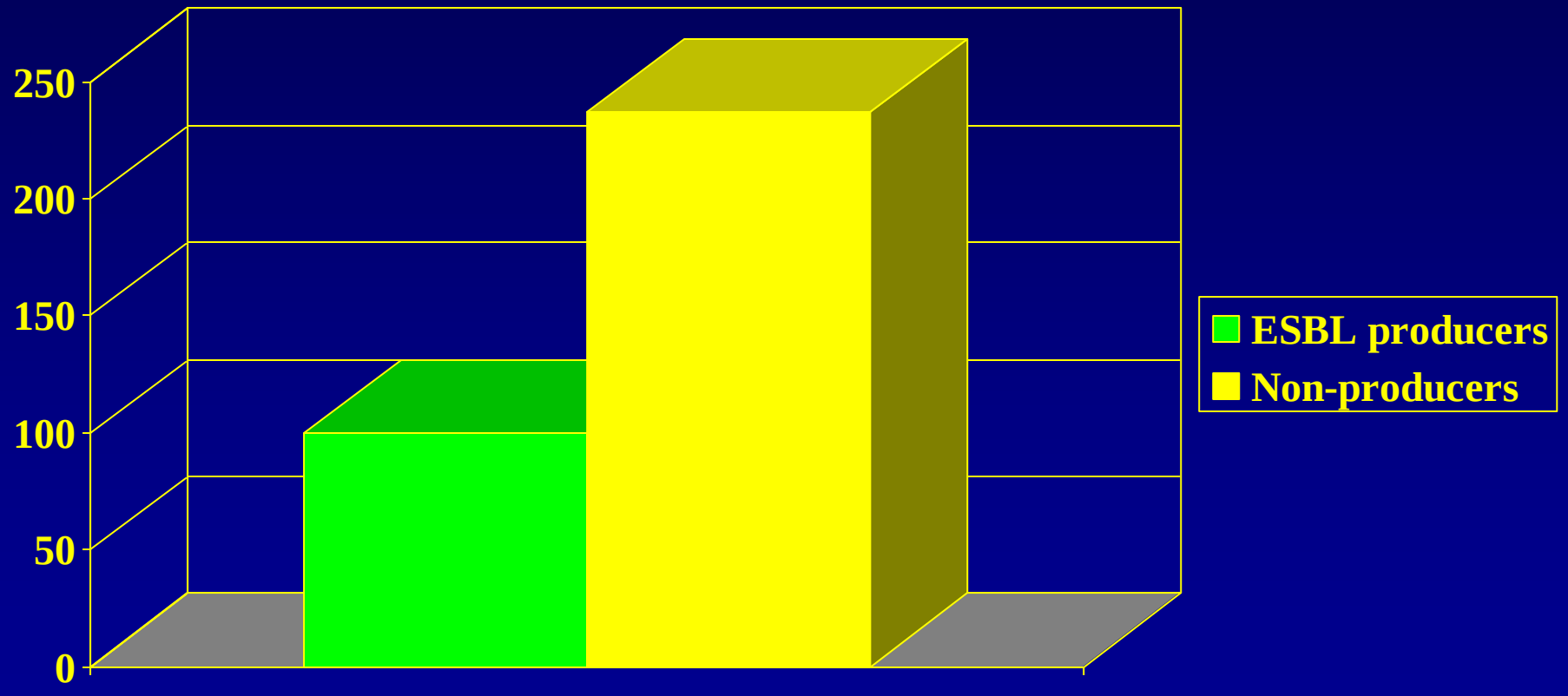




First ESBL SSI - 1992

- "One new strain of Klebsiella spp. which ifrst appeared in February 1990 which was resistant to ampicillin, piperacillin, augmentin, unasyn, aztreonam, co-trimoxazole, amikacin, gentamicin, cephalexin, cefotaxime, ceftriaxone, cefoperazone and ceftazidime"
  - *Esuvaranathan K, Kuan YF, Kumarasinghe G, Bassett DCJ, Rauff A. J Hosp Infect 1992;21:231-40*

ESBL production in Gram-negative bacilli causing Surgical site infections



Kumarasinghe, Tambyah, Chow, Liew, 1st APSIC 1999

Singapore Data

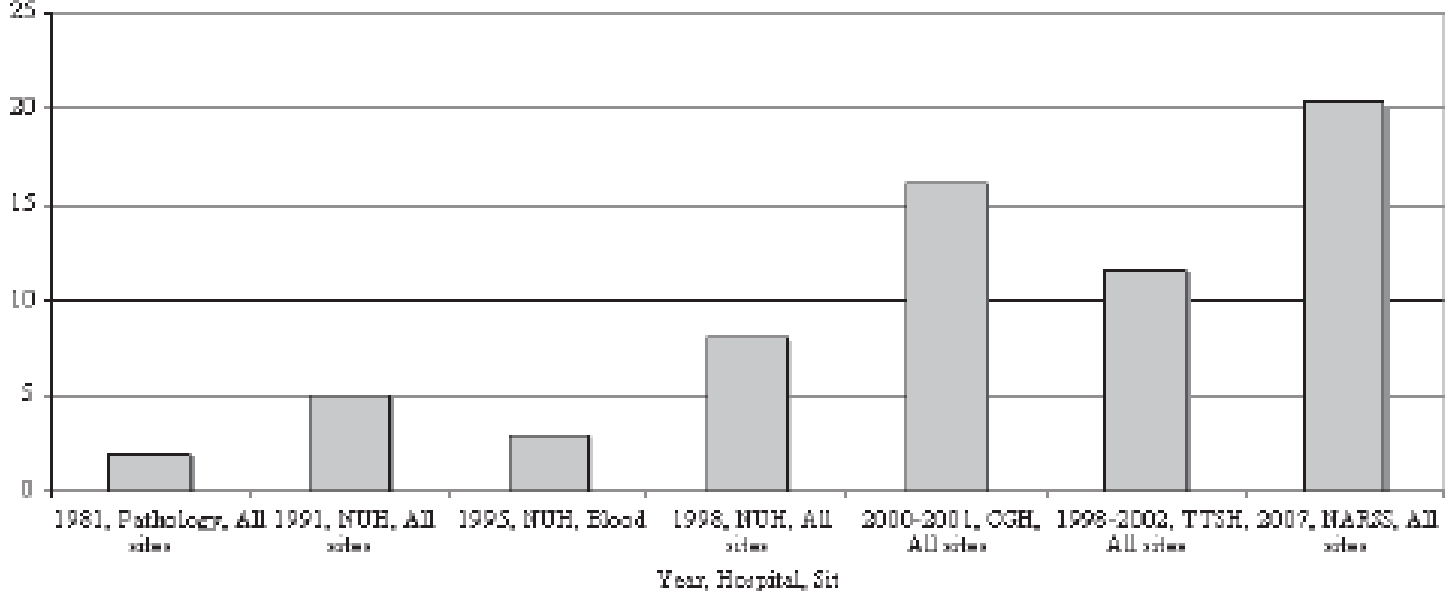


Fig. 2. Percentage of *E. coli* resistant to extended-spectrum cephalosporins.

Not just NUH
All across Singapore

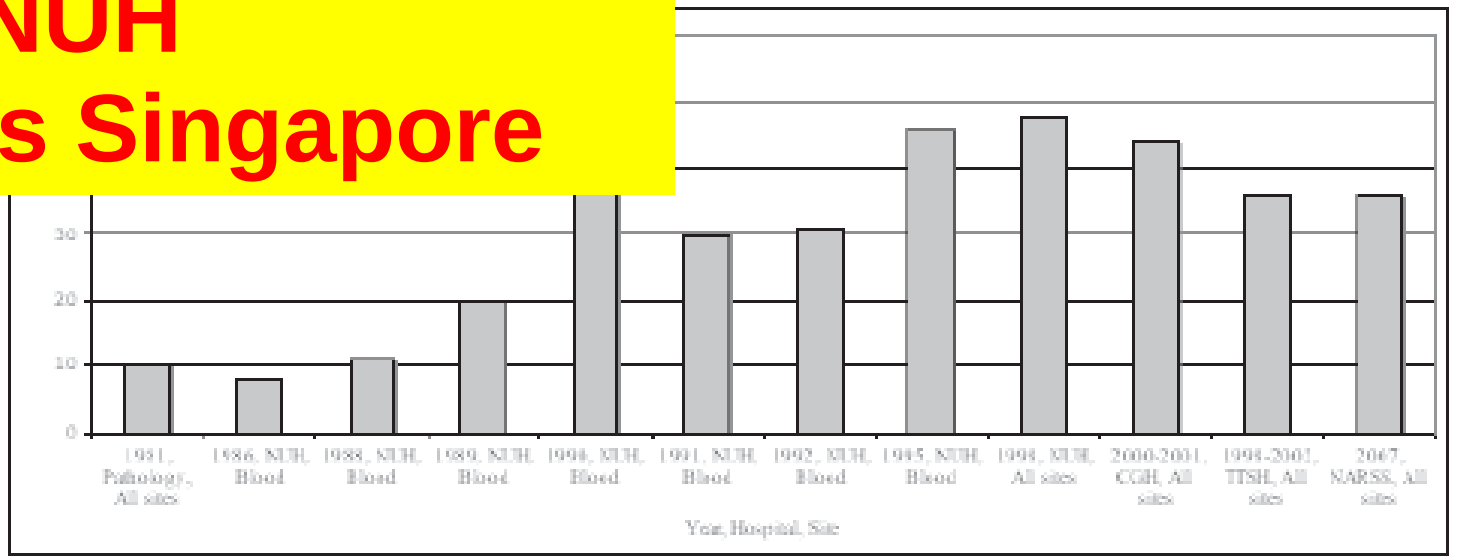


Fig. 3. Percentage of *Klebsiella* spp. resistant to extended-spectrum cephalosporins.

Koh TH
Ann Acad Med Sing
2008;37:847-54

Multiresistant Gram-negative infections: a global perspective

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Current Opinion in Infectious Diseases 2010, 23:546–553

Purpose of review

Multiresistant Gram-negative infections are an increasing problem in hospitals and healthcare facilities worldwide. While much attention has been paid to Gram-positive pathogens such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* lately, the importance of Gram-negative nosocomial infections has also been recognized globally.

Recent findings

Recent reports have described the spread of carbapenemase-producing *Klebsiella pneumoniae* across North America. In addition, many strains of *Pseudomonas* and *Acinetobacter* in Asia are resistant to all known antibiotics. The global epidemiology of multiresistant Gram-negative pathogens seems to vary by continent. There are very few existing agents which can be used for these pathogens and there are limited options on the horizon. This limited therapeutic armamentarium has been an impetus for novel approaches including combination therapies and increased attention to infection control and prevention efforts.

Summary

Clinicians need to be aware of the rising problem of resistance in nosocomial and community-acquired Gram-negative pathogens. Novel agents are urgently needed to combat these infections and innovative infection control strategies need to be devised to protect our vulnerable patients.

Keywords

antibiotic resistance, beta-lactamase, Gram-negative infection, nosocomial

Curr Opin Infect Dis 23:546–553

0951-7375

Table 1 Resistance profiles (% susceptible) of Gram-negative organisms from the United States, Europe and Asia-Pacific

MYSTIC[a]: United States 2008 [62•]

	Meropenem	Imipenem	Ertapenem	Ceftriaxone	Ceftazadime	Cefipime	Piperacillin/ tazobactam	Ciprofloxacin	Tobramycin
Enterobacteriacae (total)	97.3	97.4	96.6	88.0	88.9	95.3	89.3	80.5	88.4
E. coli	98.6	98.6	98.2	89.3	92.6	94.5	93.6	68.2	84.8
Klebsiella sp.	94.2	94.5	93.5	87.3	86.3	93.0	85.6	84.1	85.1
P. aeruginosa	85.4	79.5		8.9	85.6	86.6	90.2	77.0	89.1
Acinetobacter sp.	45.7	52.0		11.8	31.5	31.5	34.6	32.3	59.1

MYSTIC[b]: Europe 2007 [63•]

	Meropenem	Imipenem	Ceftazadime	Piperacillin/ tazobactam	Ciprofloxacin	Gentamicin	Tobramycin
E. coli	99.9	100	88.1	91.4	79.4	90.1	84.2
Klebsiella sp.	99.6	100	75.8	71.0	84.0	79.7	74.9
P. aeruginosa	79.2	70.5	69.1	79.4	70.1	62.3	74.2
Acinetobacter sp.	84.3	83.3	54.9	42.2	44.1	67.1	69.2

TEST[c]: Asia/Pacific rim, Europe 2004–2007 [74•]

	Imipenem	Ceftriaxone	Ceftazadime	Cefipime	Piperacillin/ tazobactam	Levofloxacin	Amikacin	Minocycline	Tigecycline
E. coli	100	79.4	89.7	89.5	93.6	67.6	98.1	75.5	100
ESBL *E. coli*	100	4.6	60.9	47.1	88.5	19.5	95.5	72.4	100
Klebsiella sp.	99.0	76.4	79.0	85.6	87.7	83.5	92.7	82.1	96.5
ESBL *Klebsiella* sp.	100	21.4	30.4	50.9	65.2	50.9	75.9	59.8	93.7
P. aeruginosa	82.0	-	75.8	74.5	87.6	68.1	89.2	7.8	–
Acinetobacter sp.	66.2	33.3	50.4	54.2	55.3	60.4	67.1	90.8	–
MDR *Acinetobacter* sp.	20.2	0.7	0.7	3.3	4.6	15.0	22.9	75.8	–

[a]Meropenem Yearly Susceptibility Test Information Collection. 27 289 bacterial isolates obtained from serious clinical infections in hospitalized patients from 15 medical centers within the United States.
[b]Five thousand and eight clinical significant bacterial isolates obtained from blood culture, sputum, urine, cerebrospinal fluid and wound swabs from 28 centers throughout Europe.
[c]Tigecycline Evaluation and Surveillance Trial. 3596 bacterial isolates obtained from blood, respiratory tract, urine, skin, wound and fluids from 31 medical centers from 9 countries in the Asia-Pacific rim. ESBL, extended spectrum β-lactamase; MDR, multidrug-resistant.

Big regional differences

Table 2
Percentage of organisms expressing an ESBL phenotype in the SENTRY Antimicrobial Surveillance Program in the Asia-Pacific region, 1998–2002

Organism, country, or region (number of isolates tested)	No. (%) of isolates with presumptive ESBL phenotype				No. (%) of isolates with confirmed ESBL phenotype			
	All substrates[a]	Ceftazidime[b]	Ceftriaxone[b]	Aztreonam[b]	All substrates[c]	Ceftazidime[b]	Ceftriaxone[b]	Aztreonam[b]
K. pneumoniae								
Australia (328)	15 (4.6)	15 (100)	13 (86.7)	11 (73.3)	12 (3.7)	12 (100)	12 (100)	11 (91.7)
China (75)	28 (37.3)	26 (92.9)	25 (89.3)	28 (100)	23 (30.7)	21 (91.3)	23 (100)	23 (100)
Hong Kong (224)	37 (16.5)	34 (91.9)	30 (81.1)	33 (89.2)	26 (11.6)	23 (88.5)	24 (92.3)	24 (92.3)
Japan (210)	23 (11.0)	19 (82.6)	21 (91.3)	21 (91.3)	21 (10.0)	17 (81.0)	21 (100)	21 (100)
Philippines (319)	89 (27.9)	89 (100)	82 (92.1)	85 (95.5)	70 (21.9)	70 (100)	67 (95.7)	67 (95.7)
Singapore (225)	82 (36.4)	80 (97.6)	81 (98.8)	79 (96.3)	80 (35.6)	78 (97.5)	80 (100)	78 (97.5)
South Africa (135)	40 (29.6)	38 (95.0)	38 (95.0)	36 (90.0)	38 (28.1)	36 (94.7)	38 (100)	36 (94.7)
Taiwan (222)	36 (16.2)	31 (86.1)	34 (94.4)	33 (91.7)	30 (13.5)	25 (83.3)	28 (93.3)	27 (90.0)
Overall (1738)	350 (20.1)	332 (94.9)	324 (92.6)	326 (93.1)	300 (17.3)	282 (94.0)	293 (97.7)	287 (95.7)
E. coli								
Australia (1311)	21 (1.6)	17 (81.0)	10 (47.6)	19 (90.5)	6 (0.5)	5 (83.3)	6 (100)	6 (100)
China (163)	51 (31.3)	42 (82.4)	43 (84.3)	48 (94.1)	40 (24.5)	33 (82.5)	37 (92.5)	37 (92.5)
Hong Kong (608)	106 (17.4)	75 (70.8)	90 (84.9)	102 (96.2)	87 (14.3)	57 (65.5)	86 (98.9)	85 (97.7)
Japan (337)	22 (6.5)	17 (77.3)	12 (54.5)	22 (100)	8 (2.4)	8 (100)	8 (100)	8 (100)
Philippines (338)	44 (13.0)	42 (95.5)	22 (50.0)	35 (79.5)	17 (5.0)	15 (88.2)	17 (100)	17 (100)
Singapore (318)	39 (12.3)	32 (82.1)	37 (94.9)	39 (100)	36 (11.3)	30 (83.3)	35 (97.2)	36 (100)
South Africa (261)	5 (1.9)	4 (80.0)	5 (100)	4 (80.0)	4 (1.5)	3 (75.0)	4 (100)	3 (75.0)
Taiwan (319)	3							4)
Overall (3655)	32							8)
K. oxytoca								

High rates in SG, CN, SA

Superbug NDM-1 To Kill Millions Unless New Antibiotics Found

London : United Kingdom | Aug 11, 2010

BY INVIGILATOR

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BACK 1 of 4 NE

Fears new superbug could go global

0:00 / 1:44

Superbug resistant to all known antibiotics could go global and

"The potential for wider international spread and for N endemic worldwide, are clear and frightening."- Lance Diseases

A lot of recent Media hype about NDM-1

Superbug

Antibiotic resistance. The things we do to make it worse. And anything else I find interesting.

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PROFILE

Maryn McKenna

Maryn McKenna is an award-

SUPERBUG has been featured

20 AUGUST 2010

NDM-1: The World Health Organization warns governments

The World Health Organization released a statement this afternoon, prompted by news of the NDM-1 multi-resistance gene. It's worth taking a look: The agency recommends that countries around the world pay serious attention to the emergence of this resistance factor.

WHO calls for broad action within countries, from **hospital infection-control and antibiotic-stewardship programs**, to **increased surveillance for the emergence of resistance**, to **legislative control of over-the-counter sales**. Those sound like (and are) minimal and rational suggestions — but they have the potential to be quite controversial in some countries, from India where OTC antibiotic purchases are a major economic sector, to the US where best practices for hospital control of resistant organisms continue to be, umm, vociferously debated.

The WHO says:

icrobial resistance
scribers and
d diagnostic
ties, as well as
rofessional

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SEP 15, 2010 by R. C. Camphausen - 1 comment

Super-bug NDM-1 keeps spreading yet without new fatalities

hindustantimes
Tue,21 Sep 2010
north india

Even reached Singapore!

new delhi

'Superbug more hype than substance

HT Correspondent, Hindustan Times
Email Author
New Delhi, August 14, 2010

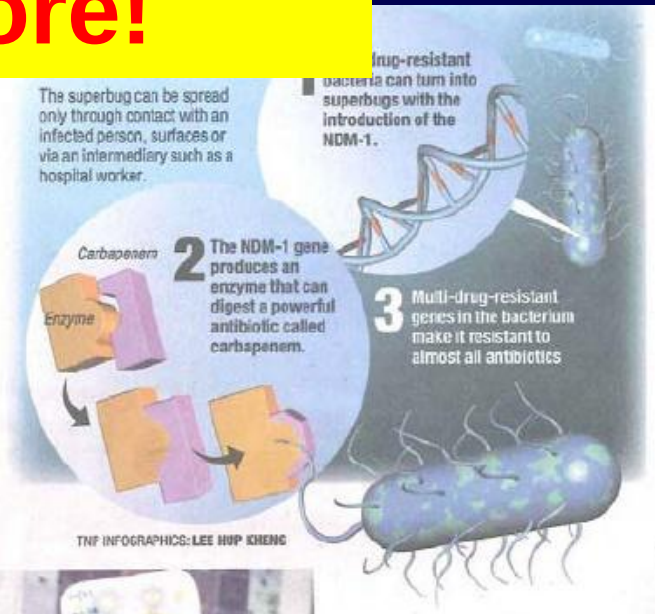
India superbug study author Karthikeyan Kumarasamy has backtracke
was not as big as it was being made out to be. "It's all hype and not as
the NDM-1 is not that big as, say, H1NI (swine flu)," said the 32-year-ol
Dr A.L. Mudaliar Postgraduate Institut
He also said the study's conclusion th
was speculative at best, underscoring
the study was motivated and prejudic

"The conclusion that the bacteria was
hypothetical. Unless we analyse samp
trace its origin, we can only speculate

The study alleged that people travelli
because of medical tourism — were t
superbug called New Delhi metallo-be
antibiotics used to treat other superbu
Staphyloccus aureus (MRSA), are ineffective.

Singapore on alert for gene that creates superbugs

Mutated bacteria are resistant to most powerful antibiotics available



REPORT: CHAI HUNG YIN
chaihyn@sph.com.sg

THERE is a new gene that could turn any bacteria into a superbug that is resistant to even the most powerful antibiotics.

Fifty Britons have already been infected, many of whom had returned to the UK after undergoing surgery in India or Pakistan.

And earlier this month, a Belgian man became the first known fatality.

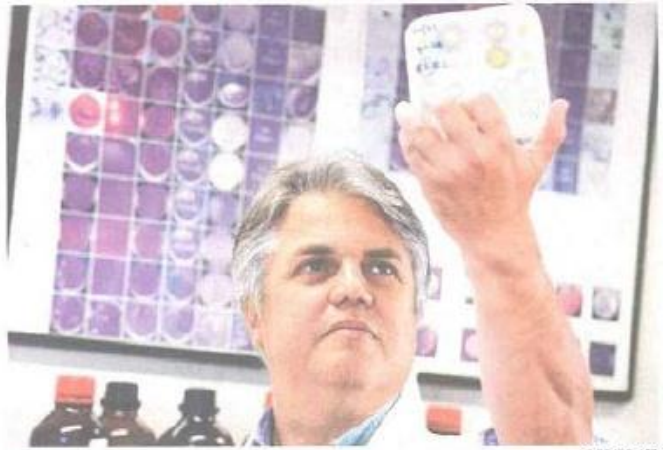
The unnamed man had been hospitalised in Pakistan for a leg injury after a car accident, and died after being repatriated to a hospital in Belgium.

The gene, known as the New Delhi metallo-beta-lactamase 1 (NDM-1), is already widespread in India and Pakistan.

So far, there have been no reported cases here, said a Ministry of Health (MOH) spokesman.

The Lancet Infectious Diseases journal published on Aug 11 said that NDM-1 bacteria have infected more than 140 people in India and Pakistan.

Superbugs are bacteria that cannot be killed by most antibiotics



PICTURE: AFP

BUG MAN: **Microbiologist Denis Pierard holding a dish of bacteria culture. He is based at the hospital where the first fatal victim of the superbug was treated.**

selected patients who are at risk.

Superbugs might affect people who strain

the hospital and the doctor is happy to dis-charge you, don't stay on when there is no

Antibiotics use in Singapore stable: MOH

ANTIBIOTIC usage in Singapore has been relatively stable and public hospitals have mechanisms to track it, said a spokesman for the Ministry of Health (MOH).

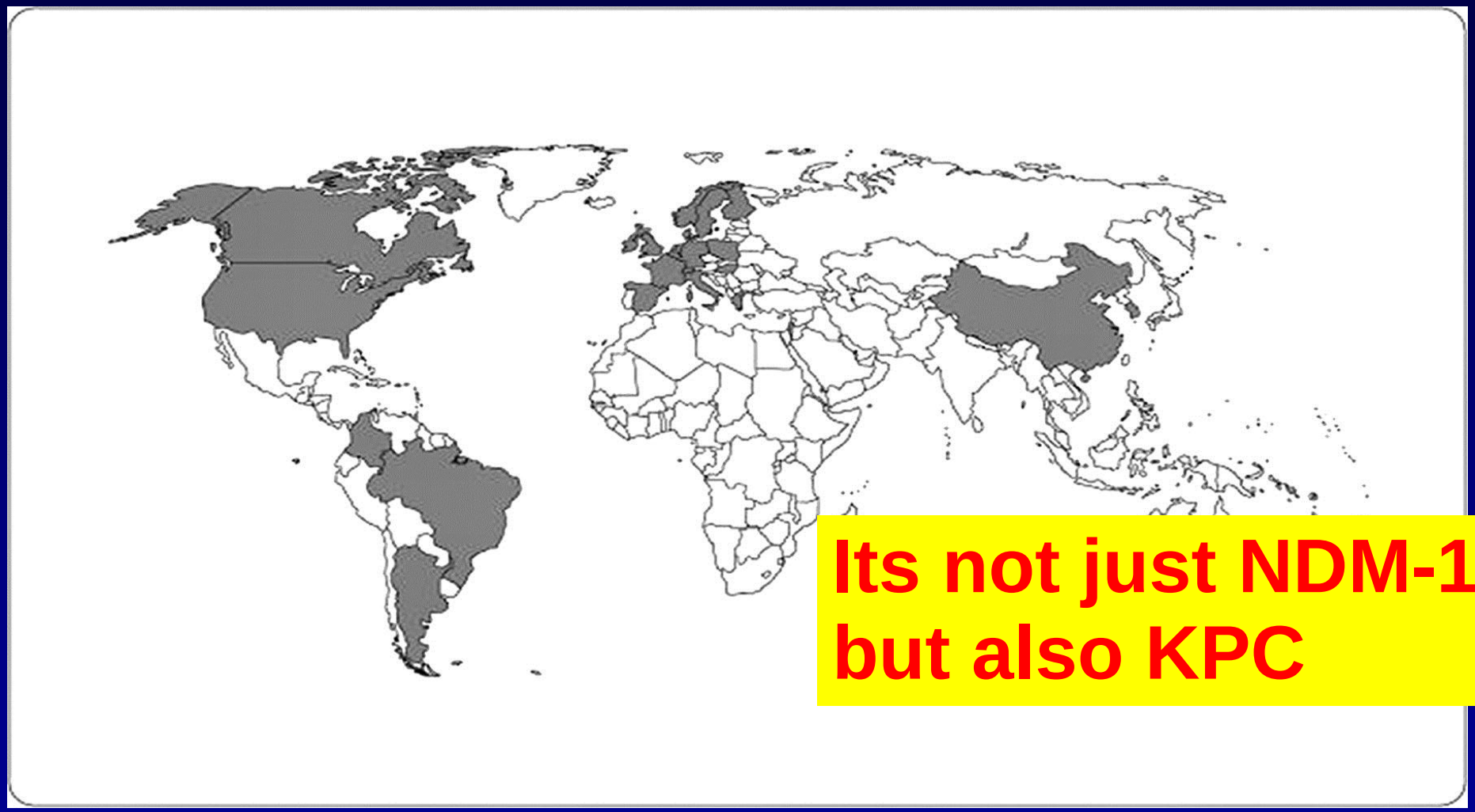
She said doctors have to be aware of the resistance patterns of certain bacteria and prescribe the appropriate drug to treat certain diseases.

"Our focus is on the prudent use of antibiotics...rather than just the amount of antibiotics being used," she added.

MOH has over the years, together with local healthcare professionals and institutions, taken measures to reduce antibiotic resistance in Singapore.

These included clinical practice

International dissemination of Klebsiella pneumoniae carbapenemase (KPC)–producing Enterobacteriaceae.



Its not just NDM-1 but also KPC

Gupta N et al. Clin Infect Dis. 2011;53:60-67

Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2011.

Clinical Infectious Diseases

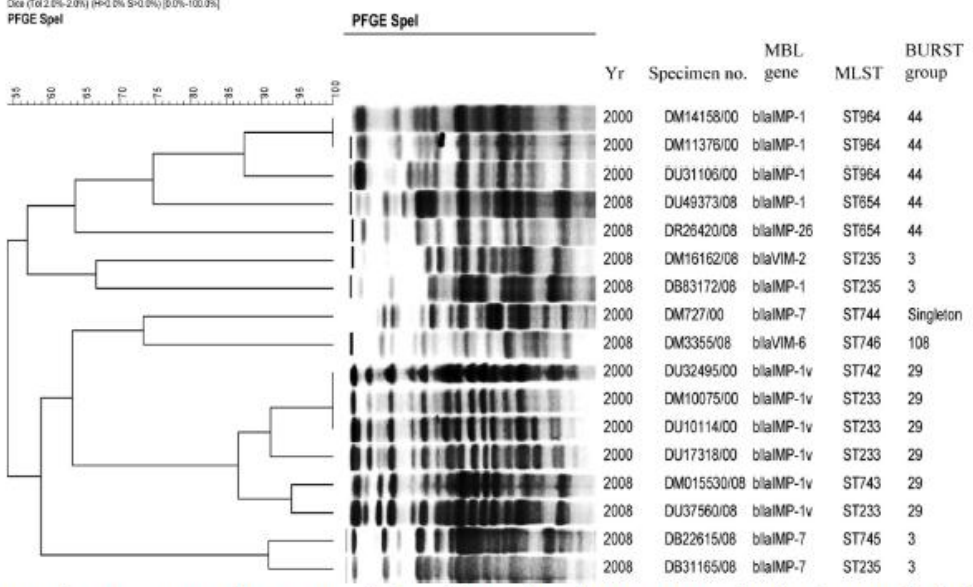


FIG. 1. Dendrogram of PFGE patterns of *P. aeruginosa* isolates with metallo-β-lactamase genes, showing the year of isolation, MLST sequen
ype, and BURST group.

JOURNAL OF CLINICAL MICROBIOLOGY, July 2010, p. 2563–2564
0095-1137/10/$12.00 doi:10.1128/JCM.01905-09

Multilocus Sequence Types *Pseudomonas aeruginosa* Metallo-β-Lactamase Genes, Including the Novel bla_{IMP-26} Gene▽

Tse Hsien Koh,*[1] Cheng Teng Khoo,[1] Thuan Tong Tan,[2] Mohamed Amir Bin Mohamed Arshad,[3] Li Ping Ang,[3] Lee Jin Lau,[3] Li-Yang Hsu,[4] and Eng Eong Ooi[5]

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Received 26 September 2009/Returned for modification 13 October 2009/Accepted 26 April 2010

**Nine imipenem-resistant *Pseudomonas aeruginosa* isolates were fou
lactamase genes, including bla_{IMP-1}, bla_{IMP-7}, bla_{VIM-2}, bla_{VIM-6}, and th
typing showed a diversity of sequence types. Comparison with isolates
epidemic clones from 2000 have not become established.**

Even in SG

Carbapenem-resistant *Pseudomonas aeruginosa* is an increasing problem worldwide. While many underlying mechanisms may account for carbapenem resistance in this species,

PFGE and MLST. MLST profiles were submitted to eBURST V3 (http://eburst.mlst.net/) on 10 March 2010. Isolates sharing six out of seven alleles were assigned to the same BURST

Know Your Local Bugs

Antibiotics	*E. coli*					*Klebsiella spp*					*Proteus spp*					*Acinetobacter spp*					*P. aeruginosa*				
	Urine			Non-Urine		Urine			Non-Urine		Urine			Non-Urine		Urine			Non-Urine		Urine			Non-Urine	
	Gen Ward (353)	ICU (33)	Blood Culture (210)	Gen Ward (113)	ICU (22)	Gen Ward (224)	ICU (47)	Blood Culture (148)	Gen Ward (222)	ICU (55)	Gen Ward (55)	ICU (6)	Blood Culture (28)	Gen Ward (15)	ICU (8)	Gen Ward (72)	ICU (11)	Blood Culture (82)	Gen Ward (225)	ICU (93)	Gen Ward (128)	ICU (16)	Blood Culture (49)	Gen Ward (50)	ICU (91)
Ampicillin	30	26	34	31	23	0	0	1	0	0	33	83	18	40	25	0	0	0	0	0					
Amp/sulbactam	39	39	51	38	35	23	11	48	54	36	48	100	31	50	57	24	9	37	19	9					
Amoxi/clavulanate	39	39	51	38	23	23	11	48	60	46	48	100	31	46	43		0		0	2					
Gentamicin	78	71	85	67	62	38	26	65	63	46	44	80	29	50	29	13	9	32	26	18	39	63	59	69	62
Amikacin	93	97	97	90	89	91	89	93	95	92	80	100	56	86	86	51	36	51	59	56	42	69	62	74	70
Cephradin	68	60				22	11				44	100				0	0								
Cefuroxime	62	60		62	50	20	11		47	24	46	100		50	25	0	0	0	0	0					
Ceftriaxone	74	71	82	65	59	28	11	54	61	46	87	100	63	71	75	0	0	0	0	0					
Cefotaxime																									
Ceftazidime	71	68	80	59	52	25	11	50	58	53	49	100	38	43	38	7	9	21	21	19	42	56	55	69	5
Imipenem	100	100	100	100	100	100	100	100	100	100	40	100	33	31	43	7	9	24	25	18	61	85	64	78	6
Meropenem	100	100	100	100	100	99	100	100	100	100	100	100	100	100	100	8	9	24	24	18	56	92	68	79	65
Ciprofloxacin	54	53	69	65	67	24	15	57	62	48	36	80	28	50	57	7	9	35	25	16	38	62	55	69	65
Co-trimoxazole	53	43	54	43	27	32	18	58	61	48	38	80	29	40	29	25	9	28	40	20					
Nitrofurantoin	90	89				20	23				0	0				0	0								
Aztreonam	89	69	79	60	62	22	7	36	59	57	92	67	84	50	63	1	0	1	16	14	29	38	42	56	3

Original Article

The Excess Financial Burden of Multidrug Resistance in Severe Gram-negative Infections in Singaporean Hospitals

Esther Ng,[1] MRCP, Arul Earnest,[2,3] PhD, David C Lye,[1,4] FRACP, Moi Lin Ling,[5] FRCPath, Ying Ding,[1] PhD, Li Yang Hsu,[1] MPH

Table 3. Significant Covariates on Multivariable Analysis with Total Hospitalisation Cost as the Outcome

Characteristic	Hospitalisation cost		
	Coefficient*	95% CI	*P* value
MDR† bacteremia	0.61	0.42 to 0.81	<0.001
Higher APACHE II score	0.04	0.02 to 0.05	<0.001
Higher Charlson comorbidity index	– 0.05	– 0.07 to – 0.02	<0.001
Intensive care unit stay	0.94	0.50 to 1.38	<0.001
Other sites of infection			
• Skin and soft tissue infection	0.31	0.04 to 0.58	0.024
• Urinary tract infection	– 0.41	– 0.59 to – 0.22	<0.001
Appropriate definitive therapy	0.83	0.31 to 1.36	0.002

MDR GNR infx
Independent risk fx
For increased cost

Journal of Hospital Infection 78 (2011) 36–40

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Economic and clinical impact of nosocomial meticillin-resistant *Staphylococcus aureus* infections in Singapore: a matched case–control study

S.K. Pada [a], Y. Ding [a], M.L. Ling [b], L.-Y. Hsu [a,*], A. Earnest [c], T.-E. Lee [a], H.-C. Yong [a], R. Jureen [d], D. Fisher [a]

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[c] *Clinical Research Unit, Tan Tock Seng Hospital, Singap*
[d] *Department of Laboratory Medicine, National Univers*

MRSA as well

Table IV
Univariate analysis of the impact of subject characteristics on post-discharge healthcare financial costs and health-related quality of life (as measured by EQ-5D summary index)

Characteristic	Post-discharge healthcare financial costs			Health-related quality of life		
	R^2	95% CI	*P*-value	R^2	95% CI	*P*-value
MRSA infection	0.50	0.18–0.82	0.003	−0.22	−0.26 to −0.17	<0.001
Age	−0.00	−0.02 to 0.01	0.277	0.00	−0.00 to 0.00	0.773
Male gender	−0.31	−0.70 to 0.07	0.112	−0.02	−0.07 to 0.04	0.504
Ethnicity						
Chinese (reference)	0.00	–	–	0.00	–	–
Malay	0.03	−0.61 to 0.67	0.925	−0.03	−0.11 to 0.05	0.431
Indian	0.34	−0.11 to 0.78	0.138	0.02	−0.05 to 0.10	0.504
Surgical discipline	−0.76	−1.15 to −0.37	<0.001	0.01	−0.05 to 0.06	0.826
Charlson score	0.04	−0.01 to 0.09	0.132	−0.01	−0.02 to 0.00	0.077
APACHE II score	0.07	0.04–0.11	<0.001	−0.01	−0.01 to −0.00	0.031
Infection type						
Skin/soft tissue infection	0.51	0.15–0.87	0.006	−0.22	−0.27 to −0.18	<0.001
Bacteraemia	0.55	−0.11 to 1.21	0.103	−0.17	−0.26 to −0.09	<0.001
Bone/joint infection	0.89	0.24–1.54	0.008	−0.17	−0.31 to −0.03	0.018
Pneumonia	1.34	0.39–2.30	0.006	−0.20	−0.35 to −0.05	0.008
Post-procedure infection	−0.04	−0.43 to 0.35	0.849	−0.15	−0.22 to −0.08	<0.001

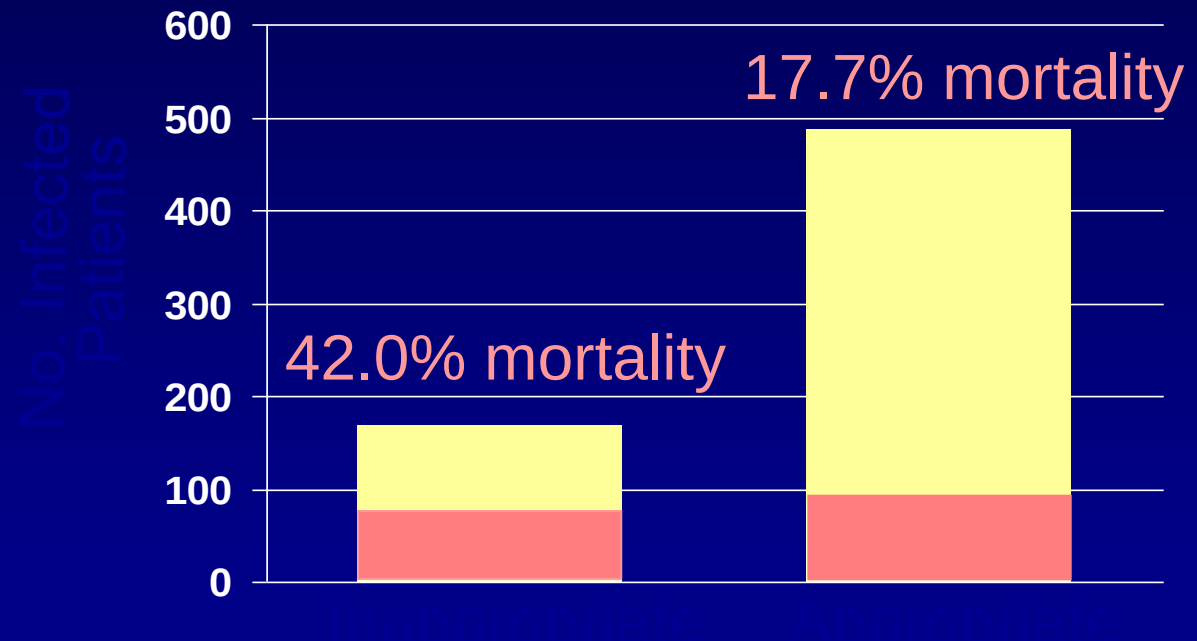
CI, confidence interval; MRSA, meticillin-resistant *Staphylococcus*; APACHE II, Acute Physiological Assessment and Chronic Health Evaluation II.

ECDC definitions

- MDR
  - – not susceptible to three classes of antibiotics that the organism is usually susceptible to
- XDR
  - only susceptible to 1 or 2 classes of antibiotics
- PDR
  - resistant to all classes of antibiotics

Targeted therapy
not empiric therapy

Inappropriate Antimicrobial Therapy: Impact on Mortality



Relative Risk = 2.37
(95% C.I. 1.83-3.08; p < .001)

Source: Kollef M,et al: Chest 1999;115:462-74

Table 4—*Microorganisms Associated With Infections**

Pneumonia	Bloodstream	Urinary Tract	Other
I. Inadequate antimicrobial treatment			
A. Community-acquired infections			
P aeruginosa, 9	Candida spp, 9	Enterobacter spp, 5	*E coli*, 8
ORSA, 5	ORSA, 4	VRE, 2	Candida spp, 7
OSSA, 5	Enterococcus spp, 4	Enterococcus spp, 2	ORSA, 5
Aspergillus spp, 5	VRE, 4	Candida spp, 1	*K pneumoniae*, 3
Cytomegalovirus, 5	Acinetobacter spp, 3	Citrobacter spp, 1	*P mirabilis*, 3
Haemophilus influenzae, 3	Enterobacter spp, 3	*K species*, 1	OSSA, 2
Streptococcus pneumoniae, 2	*K pneumoniae*, 3	*P mirabilis*, 1	*P aeruginosa*, 2
Citrobacter freundii, 2	OSSA, 2		
Pneumocystis carinii, 2	*P aeruginosa*, 2		
Xanthomonas maltophilia, 1	CNS, 1		
Alcaligenes xylosoxidans, 1	*Providencia rettgeri*, 1		
Acinetobacter spp, 1	Cytomegalovirus, 1		
Klebsiella pneumoniae, 1	*Proteus mirabilis*, 1		
Adenovirus, 1	*S pneumoniae*, 1		
Mycobacterium kansasii, 1			
Mycobacterium avium-intracellulare, 1			
B. Nosocomial infections			
P aeruginosa, 33	Candida spp, 10	Candi	
ORSA, 18	ORSA, 8	VRE,	
Enterobacter spp, 14	Enterococcus spp, 6	Enter	
X maltophilia, 13	Enterobacter spp, 5	*X malt*	
K pneumoniae, 5	VRE, 3	*P aeruginosa*, 1	*P aeruginosa*, 3
OSSA, 3	*P aeruginosa*, 3	*P mirabilis*, 1	Citrobacter spp, 2
Cytomegalovirus, 3	Corynebacterium spp, 2	ORSA, 1	VRE, 1
Serratia marcescens, 3	CNS, 1	*K pneumoniae*, 1	OSSA, 1
Herpes simplex virus, 2	*Streptococcus viridans*, 1		*K pneumoniae*, 1
P carinii, 2	Peptostreptococcus spp, 1		Enterobacter spp, 1
P mirabilis, 1	*K pneumoniae*, 1		*Cryptococcus neoformans*, 1
E coli, 1	*X maltophilia*, 1		
Citrobacter spp, 1			
Rhinovirus, 1			

Inappropriate? Viruses and fungi covered routinely??

Kollef et al Chest 1999;115:462-474

A Systematic Review of the Methods Used to Assess the Association between Appropriate Antibiotic Therapy and Mortality in Bacteremic Patients

Jessina C. McGregor,[1] Shayna E. Rich,[2] Anthony D. Harris,[2,4] Eli N. Perencevich,[2,4] Regina Thomas P. Lodise, Jr.,[5] Ram R. Miller,[2] and Jon P. Furuno[2]

[1]Oregon State University College of Pharmacy, Portland; Departments of [2]Epidemiology and Preventive Medicine University of Maryland School of Medicine, and [4]Veterans Affairs Maryland Health Care System, Baltimore; and of Pharmacy, Albany, New York

There are methodological issues

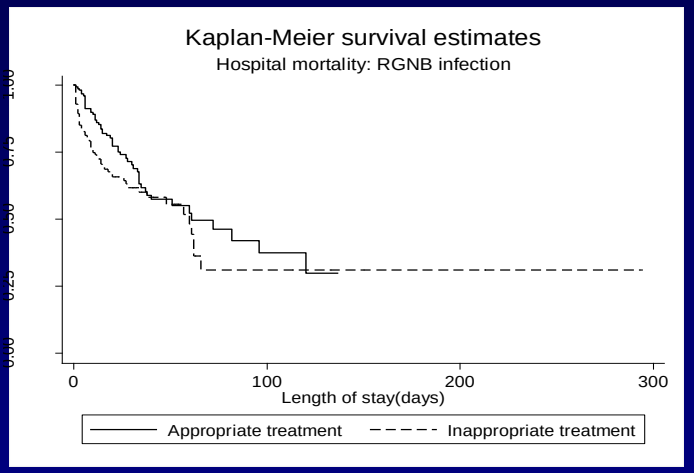
Clin Infect Dis 2007;45:329-37

Table 4. Key recommendations for future studies of the association between appropriate antibiotic therapy and mortality among bacteremic patients.

Recommendations
Appropriate antibiotic therapy should be assessed separately for empiric and definitive therapy.
Empiric antibiotic therapy is that which is administered until the point at which culture and antibiotic susceptibility test results are known.
finitive antibiotic therapy refers to the therapy administered ubsequent to the receipt of antibiotic susceptibility test esults.
efinition for appropriate antibiotic therapy should take into sideration the in vitro antibiotic susceptibility test results , when available, current clinical practice guidelines regarding dosing, route, and pattern of administration.
lity should be measured in a manner that best represents underlying construct within the biologically plausible window effect. Statistical analyses should be used to account for loss to follow-up (e.g., because of hospital discharge).
Analyses should control for the effects of confounding factors but typically should not control for intermediate factors in the causal pathway. Patient severity of illness is an important confounder of the association between appropriate antibiotic therapy and patient mortality. Severity of illness should be measured before the onset of bacteremia and should be controlled for in final statistical analyses.
All studies should provide a comprehensive description of their study population, study design, the definition of all variables collected, and methods of data analysis.

Impact -Clinical Impact

Impact of inappropriate treatment RGNB Infection



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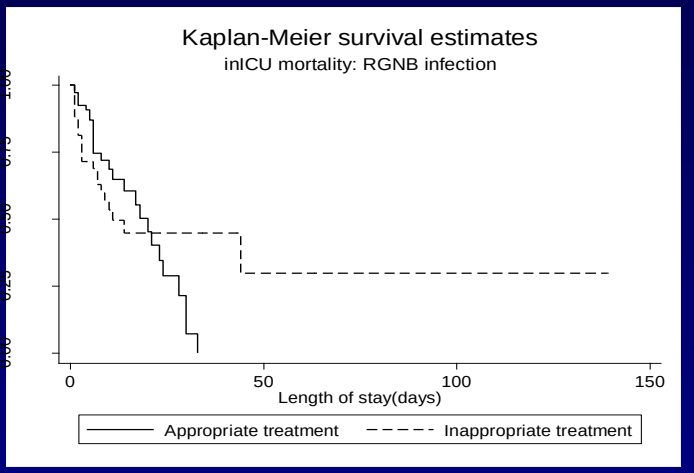

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De-escalation is risky

Carbapenems and subsequent multiresistant bloodstream infectio… treatment duration matter?

Annabelle D. Donaldson[a,b], Lubna Razak[b], Li Jia Liang[c], Dale A. Fisher[a,b], Paul A. Tambyah[a,b,*]

[a] Yong Loo Lin School of Medicine, National University of Singapore, 5 Lower Kent Ridge Road, Singapore 119074, Sing
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ABSTRACT

It has been proposed that initial empirical broad-sp… outcomes and that shorter courses will reduce the …

Table 2
Results of Cox proportional hazards model for multidrug-resistant bloodstream infection.

Variable	Hazard ratio	95% CI	*P*-value
Days of carbapenem	0.935	0.869–1.005	0.070
Male	0.980	0.472–2.032	0.960
Age	0.979	0.958–1.000	0.065
Any co-morbidity	1.664	0.695–3.979	0.250
Ventilation >96 h	2.703	1.195–6.106	0.017
Length of stay	0.991	0.977–1.004	0.230
Malignancy	2.157	0.999–4.647	0.050

CI, confidence interval.

…). In this cohort of critically ill patients, a shorter duration …ct against subsequent development of MDR BSI. Strategies …trum antibiotic duration may be inadequate in preventing …

Table 3
Results of Cox proportional hazards model for Gram-negative multidrug-resistant bloodstream infection.

Variable	Hazard ratio	95% CI	*P*-value
Days of carbapenem	0.944	0.868–1.027	0.180
Male	0.799	0.352–1.813	0.590
Age	0.967	0.943–0.992	0.011
Any co-morbidity	1.812	0.667–4.911	0.240
Ventilation >96 h	3.954	1.456–10.72	0.007
Length of stay	0.979	0.957–0.999	0.046
Malignancy	2.360	0.987–5.631	0.053

CI, confidence interval.

Yanagihara *et al. Critical Care* 2010, **14**:R159
http://ccforum.com/content/14/4/R159

CRITICAL CARE

RESEARCH Open Access

Evaluation of pathogen detection from clinical samples by real-time polymerase chain reaction using a sepsis pathogen DNA detection kit

Katsunori Yanagihara[1*], Yuko Kitagawa[2], Masao Tomonaga[3], Kunihiro Tsukasaki[3], Shigeru Kohno[4], Masafumi Seki[4], Hisashi Sugimoto[5], Takeshi Shimazu[5], Osamu Tasaki[5], Asako Matsushima[5], Yasuo Ikeda[6], Shinichiro Okamoto[6], Naoki Aikawa[7], Shingo Hori[7], Hideaki Obara[2], Akitoshi Ishizaka[6], Naoki Hasegawa[6], Junzo Takeda[8], Shimeru Kamihira[1], Kazuyuki Sugahara[1], Seishi Asari[9], Mitsuru Murata[10], Yoshio Kobayashi[10], Hiroyuki Ginba[11], Yoshinobu Sumiyama[12], Masaki Kitajima[2]

Abstract

Introduction: Sepsis is a serious medical condition that requires rapidly administered, appropriate antibiotic treatment. Conventional methods take three or more days for final pathogen identification and antimicrobial susceptibility testing. We organized a prospective observational multicenter study in three study sites to evaluate the diagnostic accuracy and potential clinical utility of the Septi*Fast* system, a multiplex pathogen detection system used in the clinical setting to support early diagnosis of bloodstream infections.

Methods: A total of 212 patients, suspected of having systemic inflammatory response syndrome (SIRS) caused by bacterial or fungal infection, were enrolled in the study. From these patients, 407 blood samples were taken and blood culture analysis was performed to identify pathogens. Whole blood was also collected for DNA Detection Kit analysis immediately after its collection for blood culture. The results of the DNA Detection Kit, blood culture and other culture tests were compared. The chosen antimicrobial treatment in patients whose samples tested positive in the DNA Detection Kit and/or blood culture analysis was examined to evaluate the effect of concomitant antibiotic exposure on the results of these analyses.

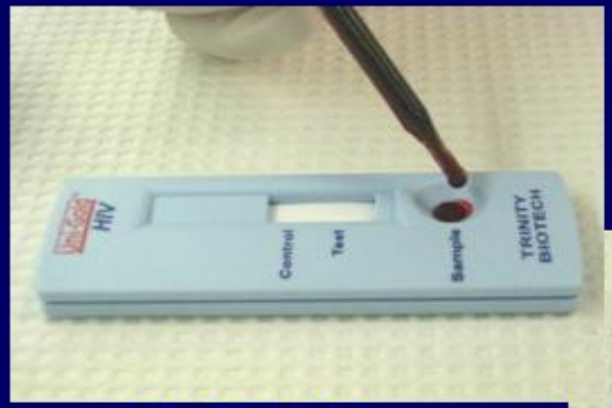
Results: Septi*Fast* analysis gave a positive result for 55 samples, while 43 samples were positive in blood culture analysis. The DNA Detection Kit identified a pathogen in 11.3% (45/400) of the samples, compared to 8.0% (32/400) by blood culture analysis. Twenty-three pathogens were detected by Septi*Fast* only; conversely, this system missed five episodes of clinically significant bacteremia (Methicillin-resistant *Staphylococcus aureus* (MRSA), 2; *Pseudomonas aeruginosa*, 1; *Klebsiella spp*, 1; *Enterococcus faecium*, 1). The number of samples that tested positive was significantly increased by combining the result of the blood culture analysis with those of the DNA Detection Kit analysis (P = 0.01). Among antibiotic pre-treated patients (prevalence, 72%), Septi*Fast* analysis detected more bacteria/fungi, and was less influenced by antibiotic exposure, compared with blood culture analysis (P = 0.02).

Conclusions: This rapid multiplex pathogen detection system complemented traditional culture-based methods and offered some added diagnostic value for the timely detection of causative pathogens, particularly in antibiotic pre-treated patients. Adequately designed intervention studies are needed to prove its clinical effectiveness in improving appropriate antibiotic selection and patient outcomes.

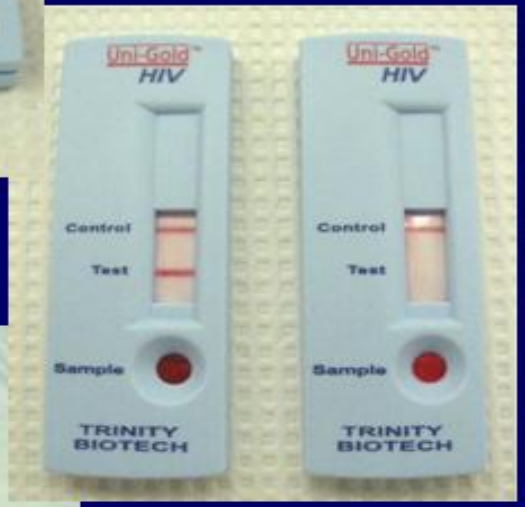
New technologies are critical

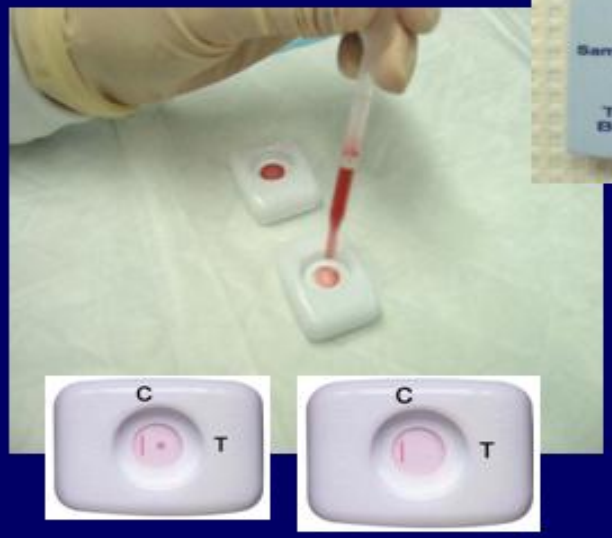
Table … culture analyses

Pathogen	Strain detected		
	Only by BC	Only by Septi*Fast*	Both methods
S.aureus (MSSA)	0	3	3
S.aureus (MRSA)	2	0	4
S.pneumoniae	0	1	0
Streptococcus spp.	0	2	1
Enterococcus faecalis	0	1	0
Enterococcus faecium	2	0	0
Enterobacter aerogenes/ cloacae	0	3	1
Escherichia coli	0	3	9
Klebsiella pneumoniae/ oxytoca	1	5	1
Pseudomonas aeruginosa	1	4	1
Candida albicans	0	1	0
Candida tropicalis	0	1	1
Sub-total	6	24	21
Not detectable by SeptiFast	5	0	0
Total	11	24	21



Uni-Gold
Recombigen





Reveal
G2

Multispot
HIV-1/HIV-2

OraQuick
Advance

Back to my patient

Lab Result - Microsoft Internet Explorer

eLab Trending

Year 2004 Period 1 Month

Refresh

Lab Results from 09/09/2004 To 09/10/2004

Laboratory Type

General Lab Microbiology

Date & Time	Test	Loc	Status
05/10/2004 14:39	TISSUE/BIOPSY AEROBIC AND ANAEROBIC C/S		F
05/10/2004 10:46	GRAM STAIN SMEAR		F
	FLUID O2 & ANO2 C/S		F
05/10/2004 01:19	AEROBIC C/S		F
02/10/2004 13:08	BLOOD O2 & ANO2 C/S	WD47	P
01/10/2004			

3+ - Gram negative rods

*** Culture Results ***

Pseudomonas aeruginosa - (Moderate)

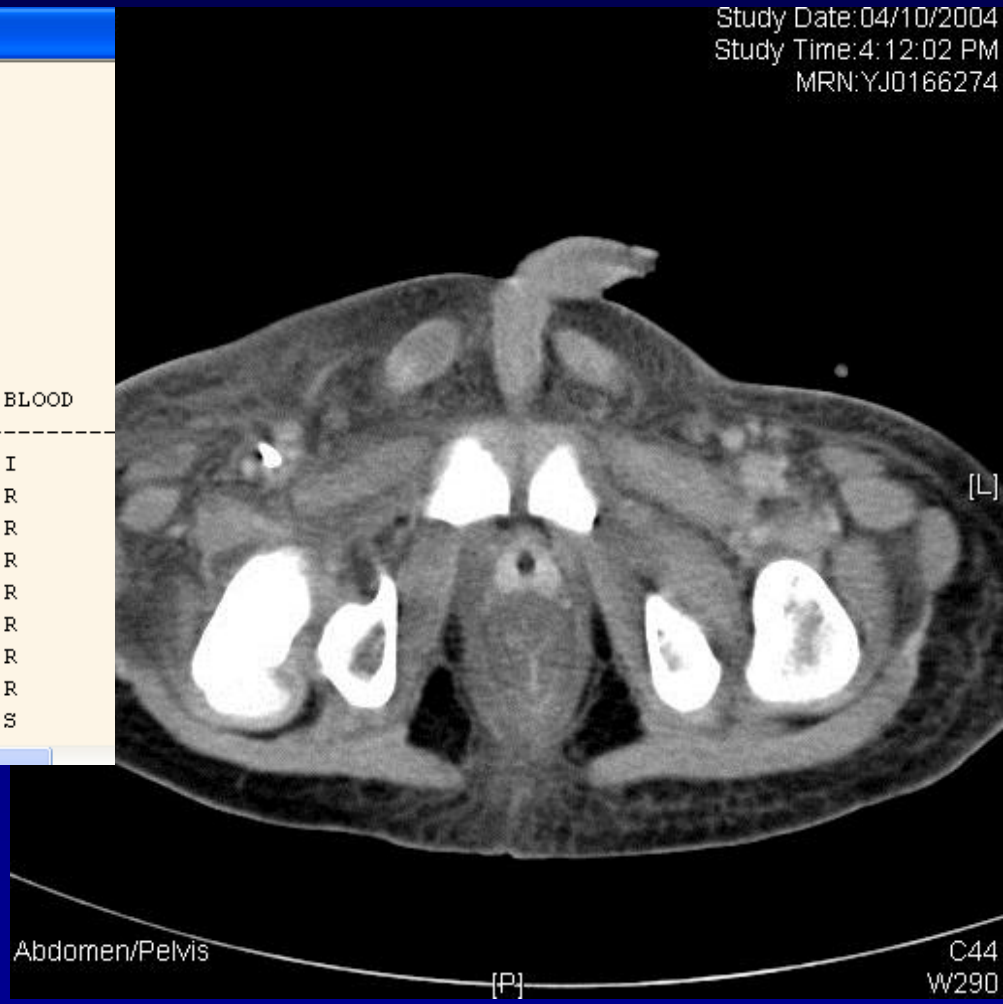
*** Reportable Comments ***

No anaerobic bacterial growth

*** Sensitivity Results ***

ast-gn09 (VITEK2) - Pseudo aeruginosa

ANTIMICROBIAL	MIC		BLOOD
Amikacin	32	NC	I
Aztreonam	>=64	NC	R
Ceftazidime	>=64	NC	R
Ciprofloxacin	>=4	NC	R
Gentamicin	>=16	NC	R
Imipenem	>=16	NC	R
Meropenem	>=16	NC	R
Piperacillin	>=128	NC	R
Polymycin B	-	NC	S



INVITED ARTICLE REVIEWS OF ANTI-INFECTIVE AGENTS

Louis D. Saravolatz, Section Editor

Colistin: The Revival of Polymyxins for the Management of Multidrug-Resistant Gram-Negative Bacterial Infections

Matthew E. Falagas[1,2,3] and Sofia K. Kasiakou[1]

[1]Alfa Institute of Biomedical Sciences (AIBS) and [2]Department of Medicine, "Henry Dunant" Hospital, Athens, Greece; and [3]Tufts University School of Medicine, Boston, Massachusetts

The emergence of multidrug-resistant gram-negative bacteria and the lack of new antibiotics to combat them have led the revival of polymyxins, an old class of cationic, cyclic polypeptide antibiotics. Polymyxin B and polymyxin E (colistin) are the 2 polymyxins used in clinical practice. Most of the reintroduction of polymyxins during the last few years is related to colistin. The polymyxins are active against selected gram-negative bacteria, including *Acinetobacter* species, *Pseudomonas aeruginosa*, *Klebsiella* species, and *Enterobacter* species. These drugs have been used extensively worldwide for decades for local use. However, parenteral use of these drugs was abandoned ~20 years ago in most countries, except for treatment of patients with cystic fibrosis, because of reports of common and serious nephrotoxicity and neurotoxicity. Recent studies of patients who received intravenous polymyxins for the treatment of serious *P. aeruginosa* and *Acinetobacter baumannii* infections of various types, including pneumonia, bacteremia, and urinary tract infections, have led to the conclusion that these antibiotics have acceptable effectiveness and considerably less toxicity than was reported in old studies.

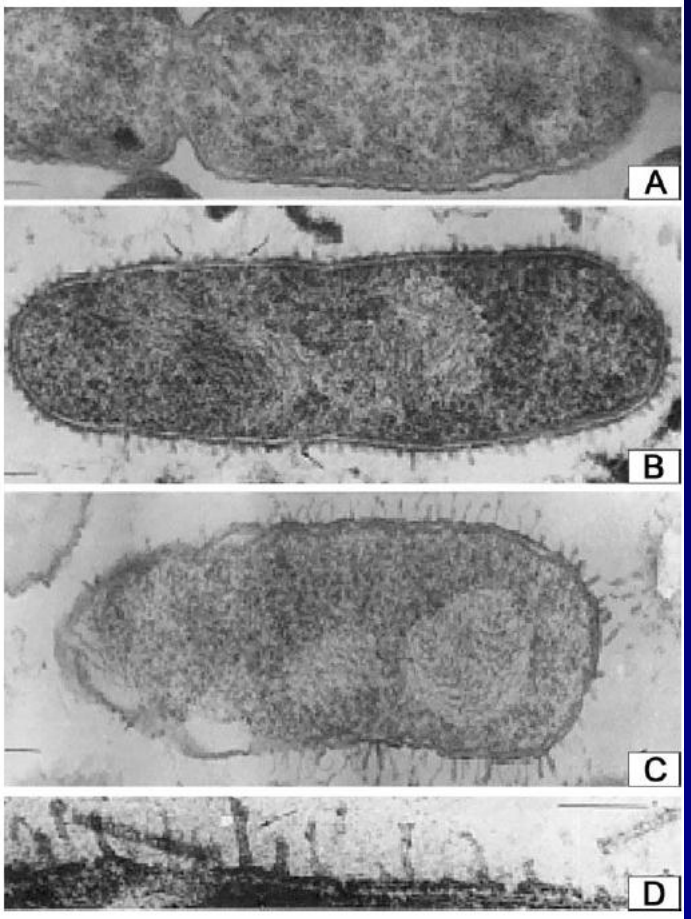


Figure 2. Sections of a *Pseudomonas aeruginosa* strain showing the alterations in the cell following the administration of polymyxin B (25 μg/mL for 30 min) and colistin methanesulfate (250 μg/mL for 30 min). (Provided with permission from the American Society for Microbiology). *A*, untreated cell; *B*, cell treated with polymyxin B; *C*, cell treated with colistin methanesulfate; *D*, cell treated with polymyxin B (from panel *B*) at higher magnification. Bar = 0.1 μm.

Treatment recommendations of hospital-acquired pneumonia in Asian countries: first consensus report by the Asian HAP Working Group

Jae-Hoon Song, MD, PhD, and the Asian HAP Working Group
Seoul, Korea

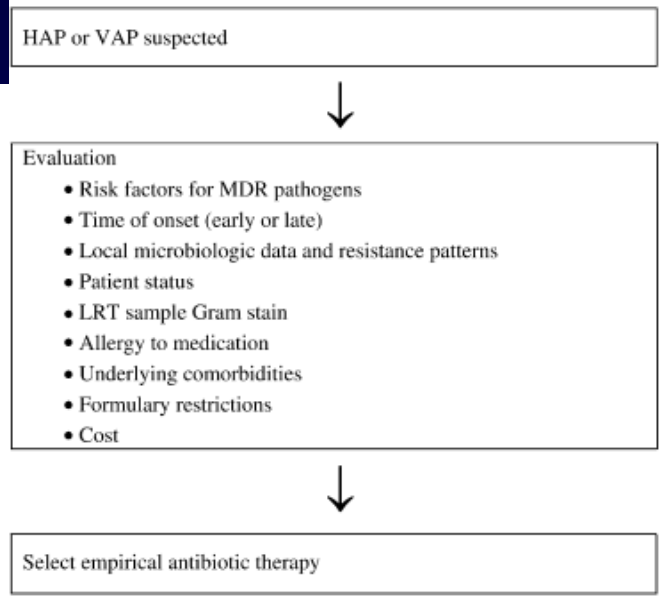


Figure 1. Initial approach to empirical antibiotic therapy in Asian countries.

...ed pneumonia (HAP) and ventilator-associated pneumonia (VAP), ...guidelines for the diagnosis and treatment of HAP and VAP have ... guidelines may not be app... ...cal practice may vary amor... ...ative cost. In addition, and ... ...eatment choices compared ... ...nfectious Diseases, togethe... ...roup to discuss current clin... ...sensus treatment recomme... ...s from 10 Asian countries. (Am J Infect Control 2008;36:S83-92.)

Table 5. Antibiotic regimens against specific antibiotic-resistant pathogens

Pathogen	Rank	Antibiotic regimen
MRSA	1	Vancomycin or teicoplanin
	2	Linezolid or tigecycline
MDR *Pseudomonas aeruginosa*	1	Piperacillin/tazobactam or carbapenems plus/minus aminoglycosides or fluoroquinolones (cipro)
	2	Polymyxin B or colistin plus/minus ciprofloxacin
MDR *Acinetobacter*	1	Cefoperazone/sulbactam and/or tigecycline
	2	Polymyxin B or colistin
ESBL$^+$ *Klebsiella pneumoniae*	1	Carbapenems or tigecycline
	2	Piperacillin/tazobactam
ESBL$^+$ *Escherichia coli*	1	Carbapenems or tigecycline
	2	Piperacillin/tazobactam

Polymyxins now Recommended???

Experience with polymyxins growing

Review Article

Polymyxins: A Review of the Current Status Including Recent Developments

Andrea L Kwa,[1] *PharmD*, Vincent H Tam,[2] *PharmD*, Matthew E Falagas,[3,4] *MD, MSc, DSc*

Abstract

Introduction: Polymyxins have become the drug of choice for treatment of multidrug-resistant gram-negative bacilli infections in Singapore, simply because these pathogens are only susceptible to either aminoglycosides and polymyxins, or polymyxins only. Furthermore, there is no new antibiotic in the pipeline that targets these difficult-to-treat infections. Materials and Methods:

Kwa et al Ann Acad Med Sing 2008;37:870-3

Polymyxin Problems

- Nephrotoxicity, neurotoxicity, dermatotoxicity
- Hetero-resistance has emerged as well as complete resistance
- Efficacy might not be as high

Outcome among patients with CRAb BSI according to PB treatment

	Treated with PB	Not treated		p value
Outcome				
Documented microbiological clearance	6/ 7 (85.7%)	10/12 (83.3%)		0.70
All-cause mortality	8/16 (50.0%)	5/10 (50.0%)		0.66

PB: polymyxin B

Chai et al ICAAC 2004

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study

Karthikeyan K Kumarasamy, Mark A Toleman, Timothy R Walsh, Jay Bagaria, Fafhana Butt, Ravikumar Balakrishnan, Uma Chaudhary, Michel Doumith, Christian G Giske, Seema Irfan, Padma Krishnan, Anil V Kumar, Sunil Maharjan, Shazad Mushtaq, Tabassum Noorie, David L Paterson, Andrew Pearson, Claire Perry, Rachel Pike, Bhargavi Rao, Ujjwayini Ray, Jayanta B Sarma, Madhu Sharma, Elizabeth Sheridan, nore, Neil Woodford

	UK (n=37)		Chennai (n=44)		Haryana (n=26)	
	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*
Imipenem	32; 128	0%	64; 128	0%	32; 128	0%
Meropenem	32; 32	3%	32; >32	3%	>32; >32	3%
Piperacillin-tazobactam	>64; >64	0%	>64; >64	0%	>64; >64	0%
Cefotaxime	>256; >256	0%	>256; >256	0%	>256; >256	0%
Ceftazidime	>256; >256	0%	>256; >256	0%	>256; >256	0%
Cefpirome	>64; >64	0%	>64; >64	0%	>64; >64	0%
Aztreonam	>64; >64	11%	>64; >64	0%	>64; >64	8%
Ciprofloxacin	>8; >8	8%	>8; >8	8%	>8; >8	8%
Gentamicin	>32; >32	3%	>32; >32	3%	>32; >32	3%
Tobramycin	>32; >32	0%	>32; >32	0%	>32; >32	0%
Amikacin	>64; >64	0%	>64; >64	0%	>64; >64	0%
Minocycline	16; >32	0%	32; >32	0%	8; 16	0%
Tigecycline	1; 4	64%	4; 8	56%	1; 2	67%
Colistin	0·5; 8	89%†	1; 32	94%†	1; 2	100%†

MIC=minimum inhibitory concentration. *Susceptibility defined by British Society for Antimicrobial Chemotherapy and European Committee on Antimicrobial Susceptibility Testing breakpoints; doxycycline breakpoints were used for minocycline. †Colistin-resistant UK isolates were one isolate of *Morganella morganii* and one *Providencia* sp (both intrinsically-resistant species), also one *Klebsiella pneumoniae* and one *Enterobacter* sp.

Table: **Antibiotic susceptibilities for NDM-1-positive Enterobacteriaceae isolated in the UK and north (Chennai) and south India (Haryana)**

red by New Delhi metallo-β-
the prevalence of NDM-1, in

lia—Chennai (south India),
ry. Antibiotic susceptibilities
lished by PCR. Isolates were
vere analysed by S1 nuclease
avel and recent admission to

and 73 in other sites in India
oniae (111), which were highly
om Haryana were clonal but
the NDM-1 gene on plasmids:
not conjugative. Many of the
ad links with these countries.

nd co-ordinated international

Lancet Infect Dis 2010; 10: 597–602

Published Online August 11, 2010 DOI:10.1016/S1473-3099(10)70143-2

See Reflection and Reaction page 578

Department of Microbiology, Dr ALM PG IBMS, University of Madras, Chennai, India (K K Kumarasamy MPhil, P Krishnan PhD); **Department of Infection, Immunity and Biochemistry, School of Medicine, Cardiff University, Cardiff, UK** (M A Toleman PhD, Prof T R Walsh PhD); **Health Protection Agency Centre for Infections, London, UK** (J Bagaria MD, R Balakrishnan MD, M Doumith PhD, S Maharjan MD, S Mushtaq MD, T Noorie MD, A Pearson PhD, C Perry PhD, R Pike PhD, B Rao MD, E Sheridan PhD, J Turton PhD, M Warner PhD, W Welfare PhD

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DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE
www.elsevier.com/locate/diagmicrobio

Pharmacology

Use of a clinically derived exposure–response relationship to evaluate potential tigecycline-Enterobacteriaceae susceptibility breakpoints

Paul G. Ambrose[a,*], Alison K. Meagher[b,1], Julie A. Passarell[b], Scott A. Van Wart[a], Brenda B. Cirincione[b], Chris M. Rubino[a], Joan M. Korth-Bradley[c], Timothy Babinchak[c], Evelyn Ellis-Grosse[c,2]

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Received 23 January 2008; accepted 22 September 2008

Abstract

Potential tigecycline-Enterobacteriaceae susceptibility breakpoints were evaluated using 2 ap probabilities assessed by MIC value. Using a previously derived tigecycline population pharma a probability density function of steady-state area under the concentration–time curve for 24 h generated. $AUC_{SS(0-24)}$ values were divided by clinically relevant fixed MIC values to derive calculate the clinical response expectation by MIC value based upon a logistic regression mo approach, the probability of pharmacokinetic–pharmacodynamic (PK-PD) target attainment was $AUC_{SS(0-24)}$/MIC ratios greater than the threshold value of 6.96, the PK-PD target associated w clinical response and PK-PD target attainment were poorly correlated at MIC values >0.25 m clinical success was 0.76, whereas the probability of PK-PD target attainment was 0.27 at a probability of PK-PD target attainment metrics underestimates the clinical performance of tig

Keywords: Tigecycline; Enterobacteriaceae; Susceptibility breakpoints; Pharmacokinetic–pharmacodynam

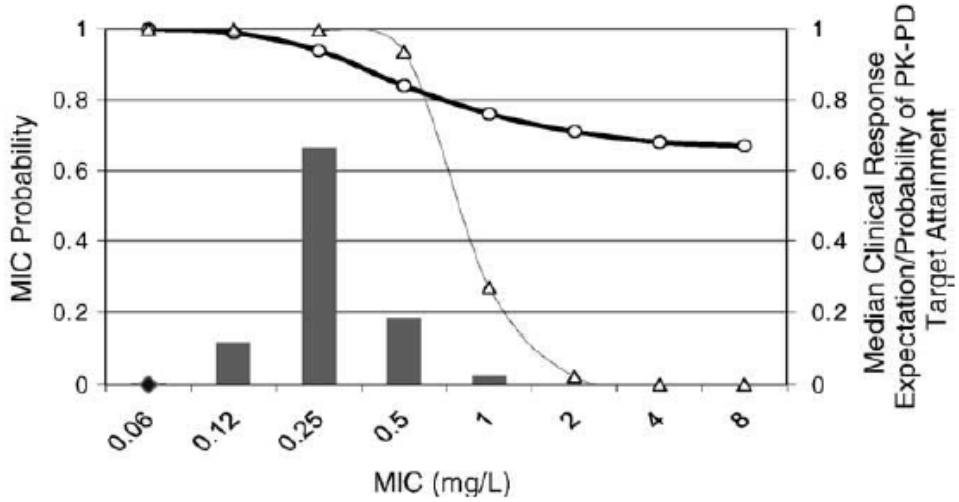
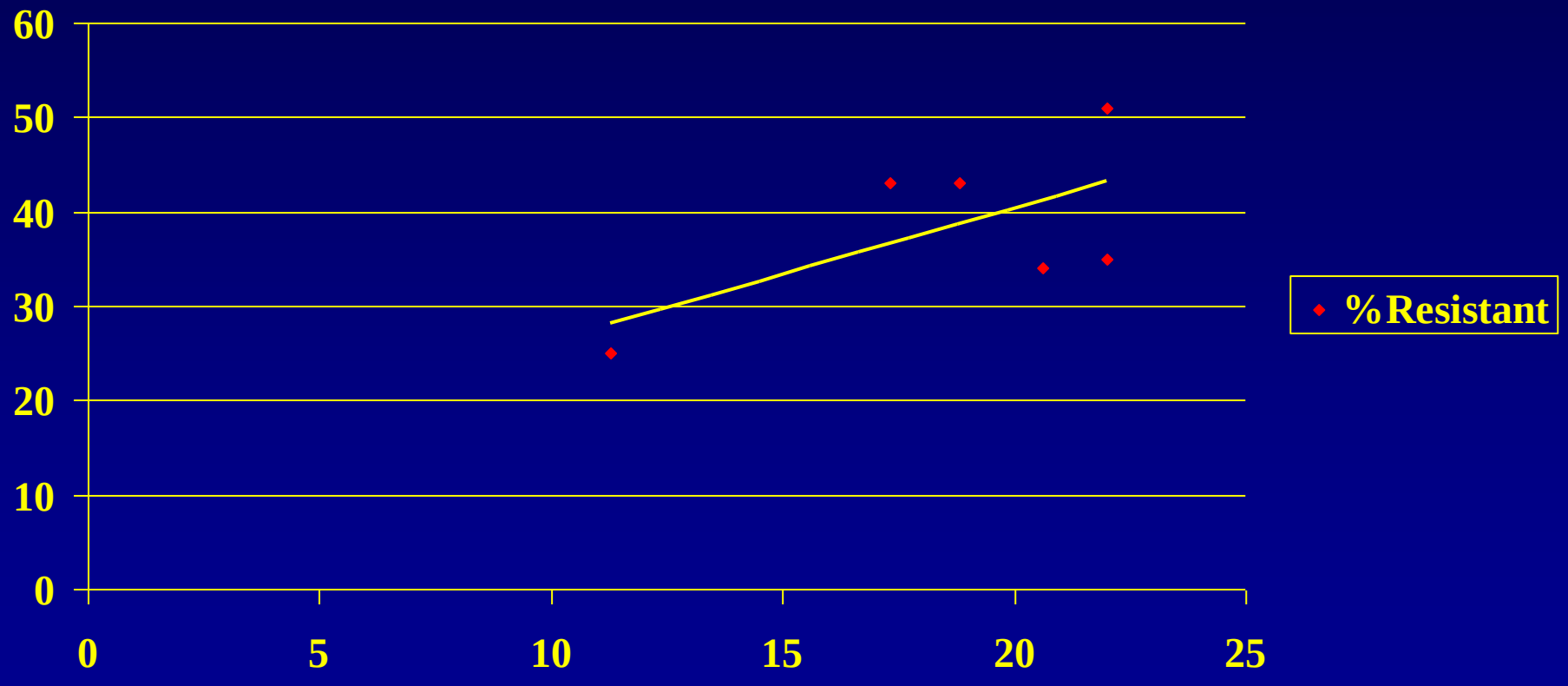


Fig. 1. Median clinical response expectation (circle symbols) and probability of PK-PD target ($AUC_{SS(0-24)}$/MIC ratio of 6.96) attainment (triangle symbols) overlaid on the MIC distribution (gray bars) of tigecycline against *E. coli* ($n = 440$).

Carbapenems

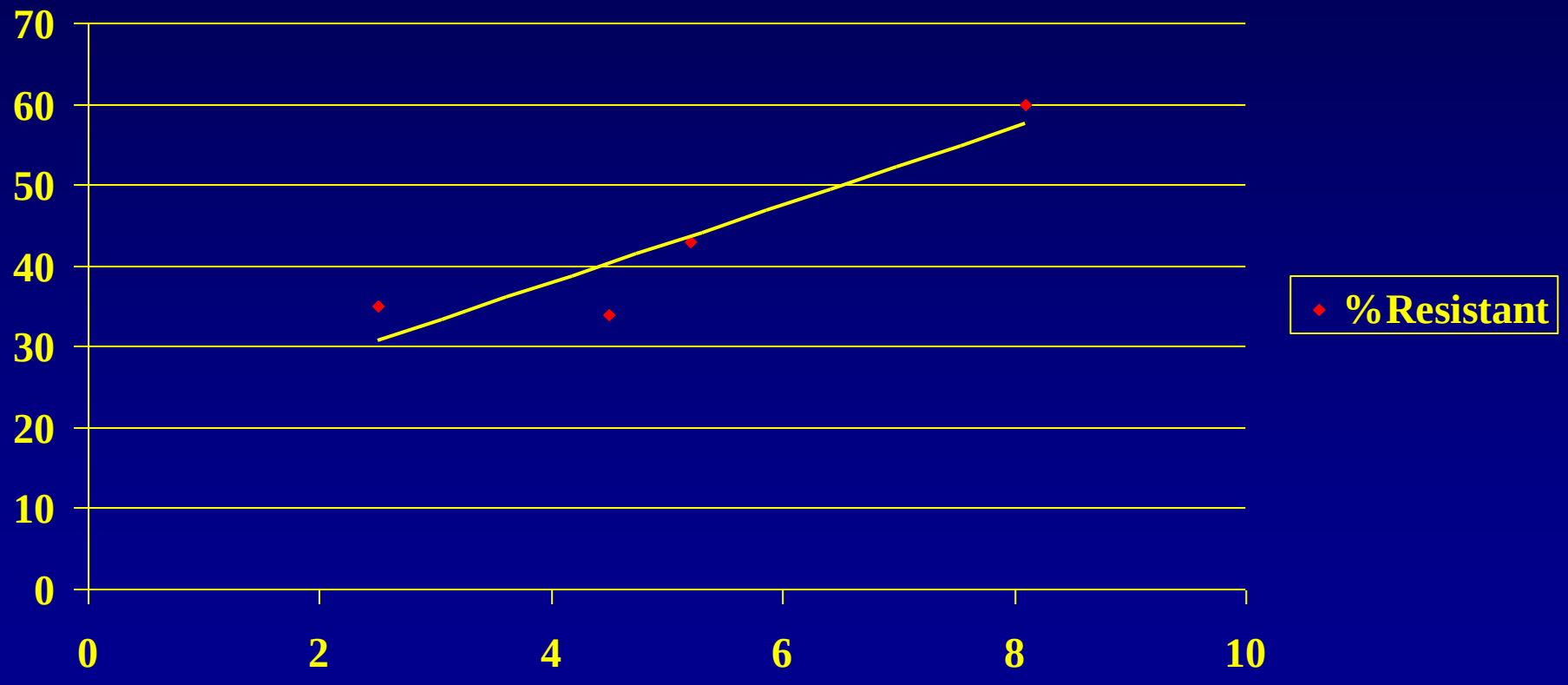
- MIC varies: EUCAST vs CLSI
- For sensitive species with low MIC values
- Prolonged infusion time ?

Ceftazidime Use and Resistance in Acinetobacter spp



Tambyah et al SHEA 2000

Ciprofloxacin Use and Resistance in Acinetobacter spp



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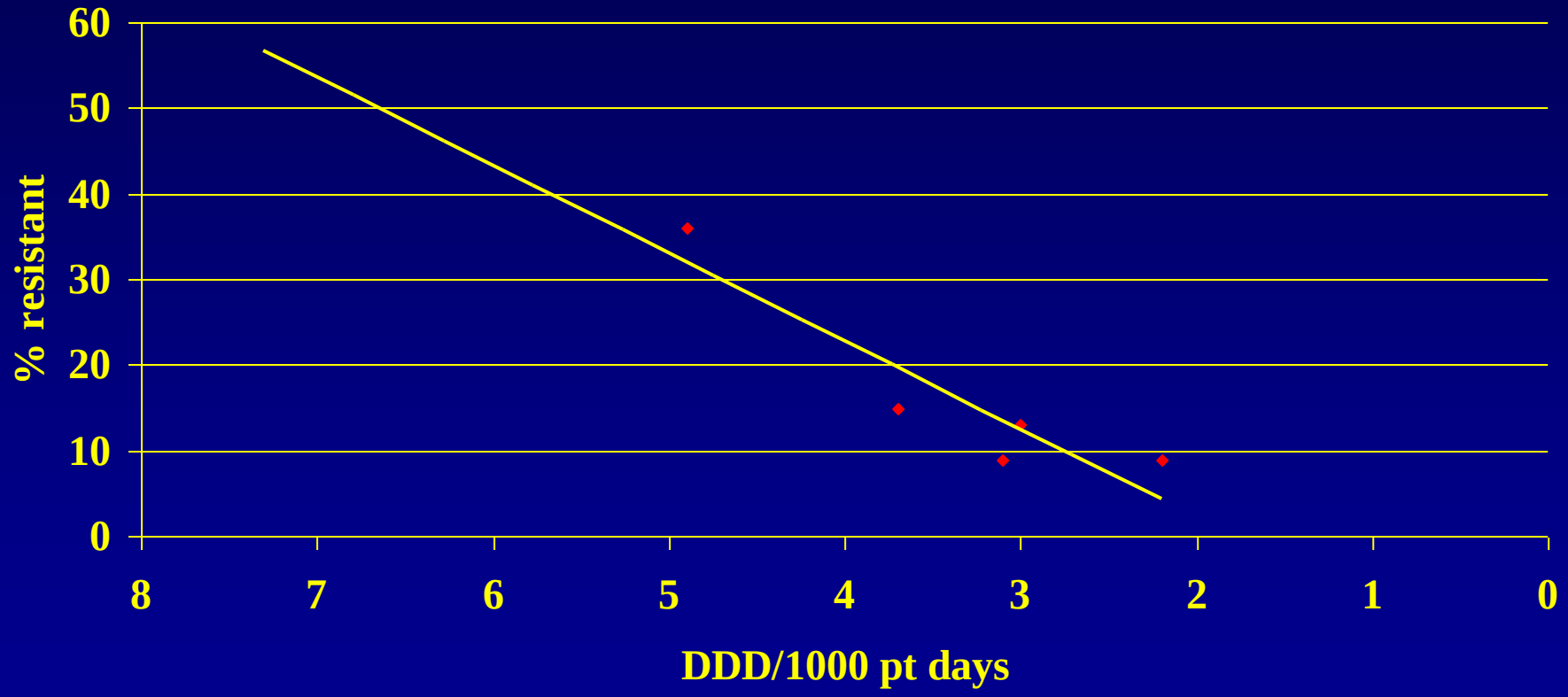
Amikacin Use and Resistance in Acinetobacter spp



Tambyah et al SHEA 2000

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0066-4804/10/$12.00 doi:10.1128/AAC.01235-09

In Vitro Activity of Fosfomycin against *bla*$_{KPC}$-Containing *Klebsiella pneumoniae* Isolates, Including Those Nonsusceptible to Tigecycline and/or Colistin▽

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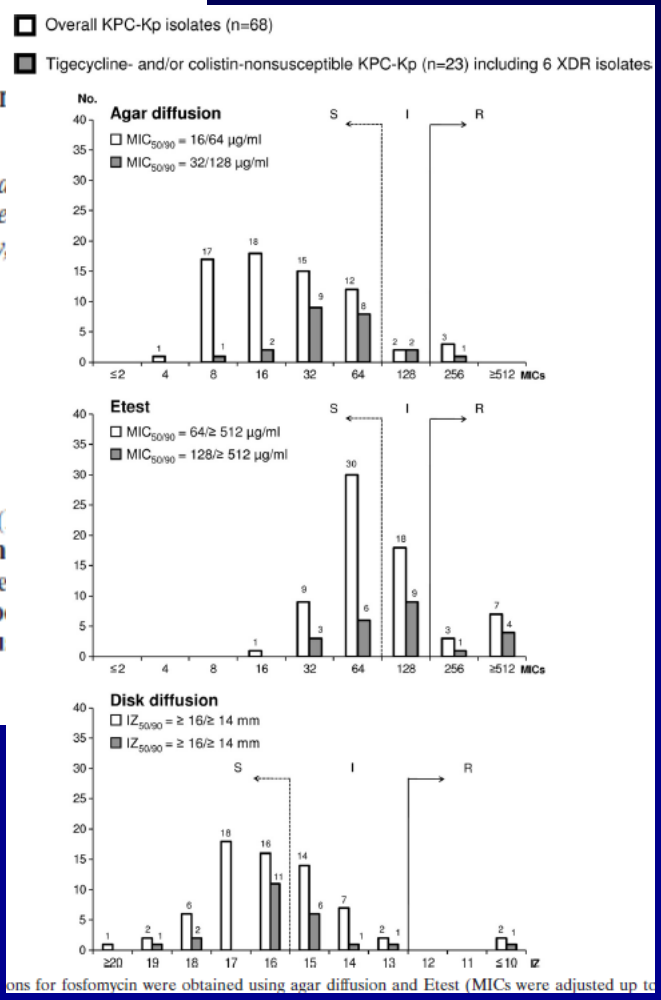
In vitro **activity of fosfomycin was evaluated against 68 *bla*$_{KPC}$-possessing *Klebsiella pneumoniae* (isolates, including 23 tigecycline- and/or colistin-nonsusceptible strains. By agar dilution, 93% of th KpKPC were susceptible (MIC$_{50/90}$ of 16/64 μg/ml, respectively). The subgroup of 23 tigecycline colistin-nonsusceptible strains showed susceptibility rates of 87% (MIC$_{50/90}$ of 32/128 μg/ml, resp Notably, 5 out of 6 extremely drug-resistant (tigecycline and colistin nonsusceptible) KpKPC were su to fosfomycin. Compared to agar dilution, disk diffusion was more accurate than Etest.**

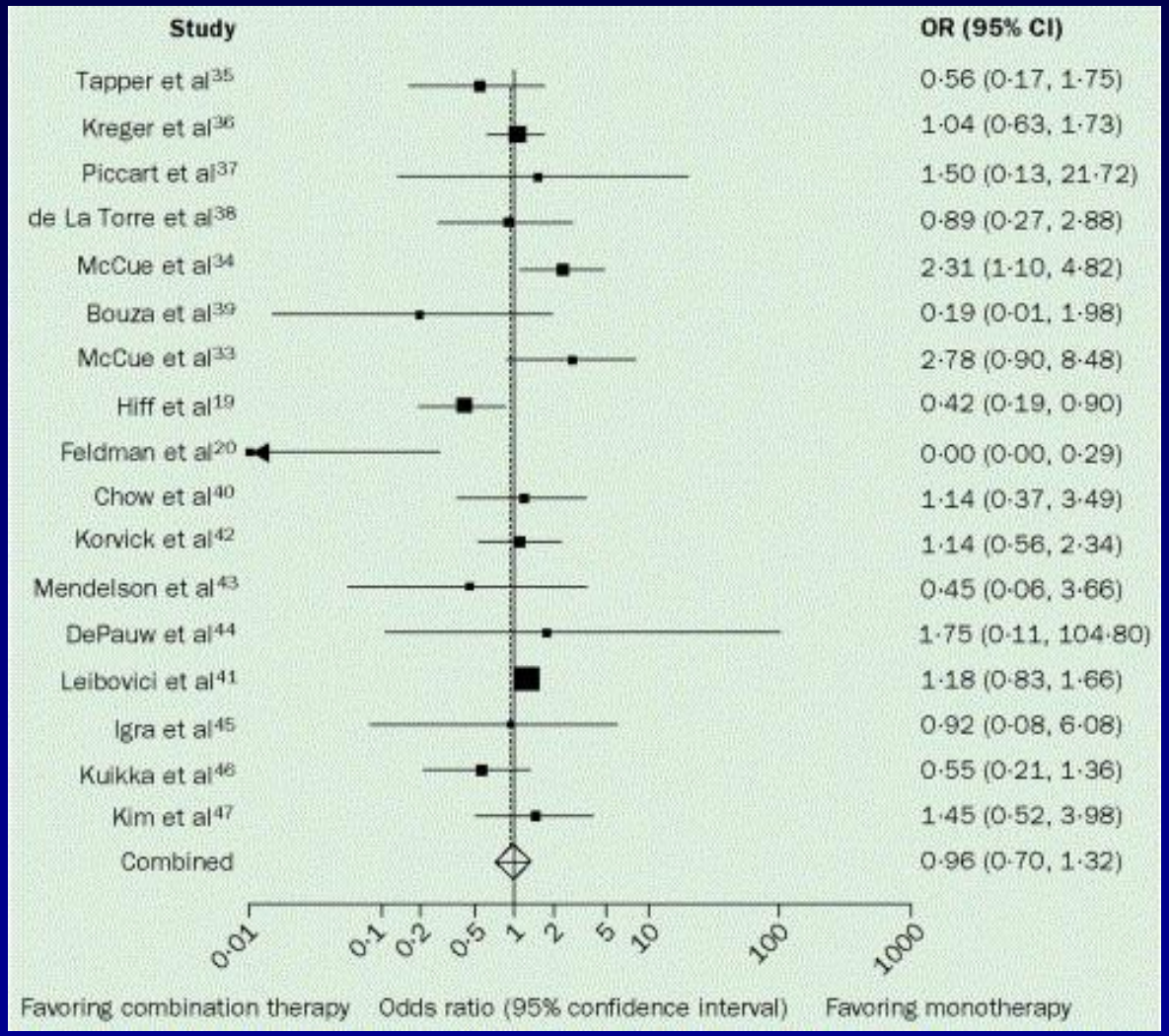


ons for fosfomycin were obtained using agar diffusion and Etest (MICs were adjusted up to

Combination therapy

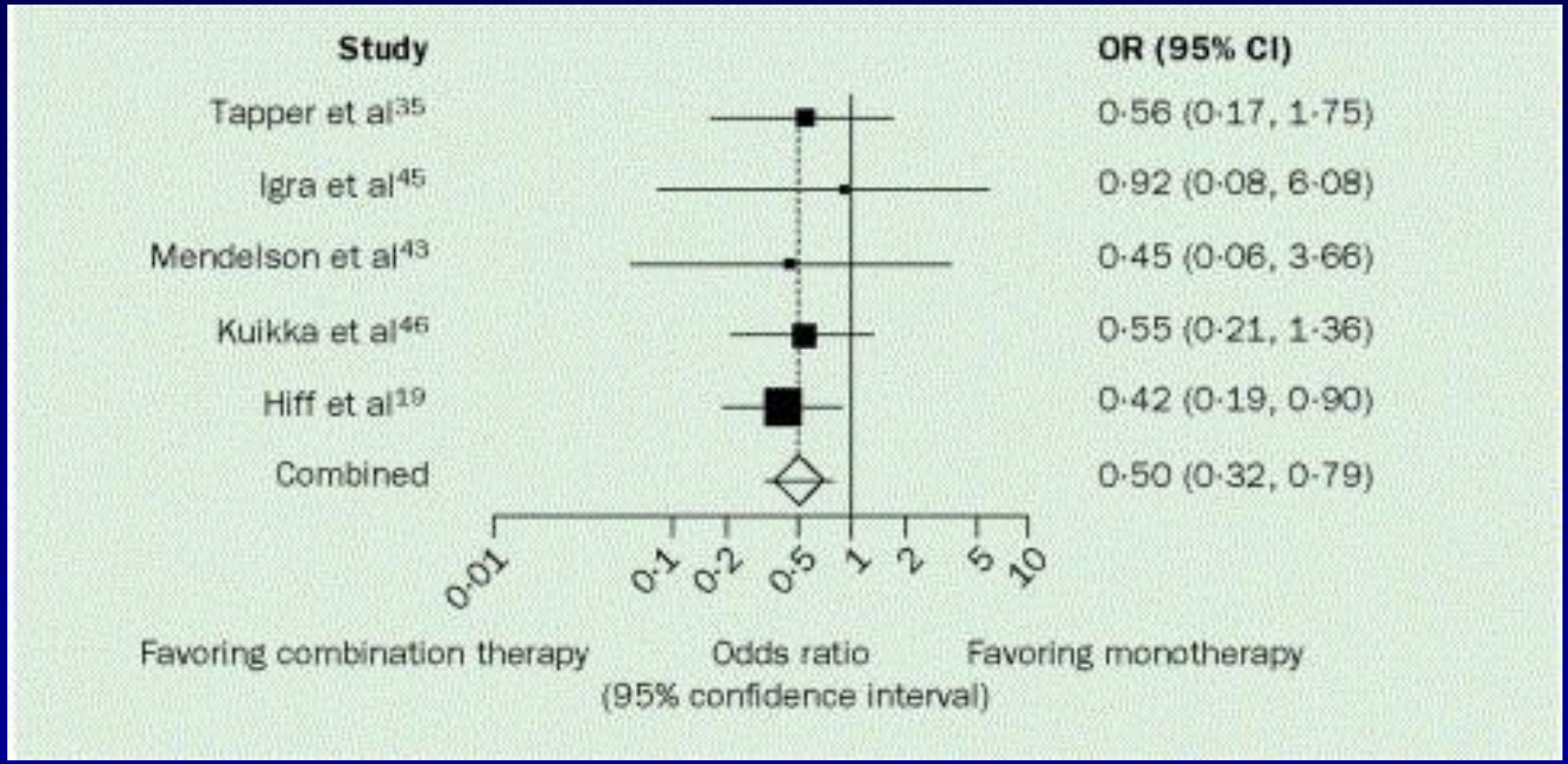
- Works well for HIV, TB
- Never been adequately studied in GNR infections in RCTs
- Concerns re: increased toxicity and greater change in microbial ecology leading to a paradoxical increase in resistance

Does combination therapy work?



Safdar N, Handelsman J, Maki DG. Lancet Infect Dis. 2004;4:519-27.

Does combination therapy work?



Safdar N, Handelsman J, Maki DG. Lancet Infect Dis. 2004;4:519-27.

Predictors of Mortality in Bloodstream Infections Caused by *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*: Importance of Combination Therapy

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Background. The spread of *Klebsiella pneumoniae* (Kp) strains that produce *K. pneumoniae* ca (KPCs) has become a significant problem, and treatment of infections caused by these pathogens is lenge for clinicians.

Methods. In this multicenter retrospective cohort study, conducted in 3 large Italian teaching examined 125 patients with bloodstream infections (BSIs) caused by KPC-producing Kp isolates (K nosed between 1 January 2010 and 30 June 2011. The outcome measured was death within 30 da positive blood culture. Survivor and nonsurvivor subgroups were compared to identify predictors of

Results. The overall 30-day mortality rate was 41.6%. A significantly higher rate was observed a treated with monotherapy (54.3% vs 34.1% in those who received combined drug therapy; $P = .0$ regression analysis, 30-day mortality was independently associated with septic shock at BSI onse [OR]: 7.17; 95% confidence interval [CI]: 1.65–31.03; $P = .008$); inadequate initial antimicrobial thera 95% CI: 1.61–10.76; $P = .003$); and high APACHE III scores (OR: 1.04; 95% CI: 1.02–1.07; $P < .001$) gram therapy with a combination of tigecycline, colistin, and meropenem was associated with lo (OR: 0.11; 95% CI: .02–.69; $P = .01$).

Conclusions. KPC-Kp BSIs are associated with high mortality. To improve survival, combined treatment with 2 or more drugs with in vitro activity against the isolate, especially those also including a carbapenem, may be more effective than active monotherapy.

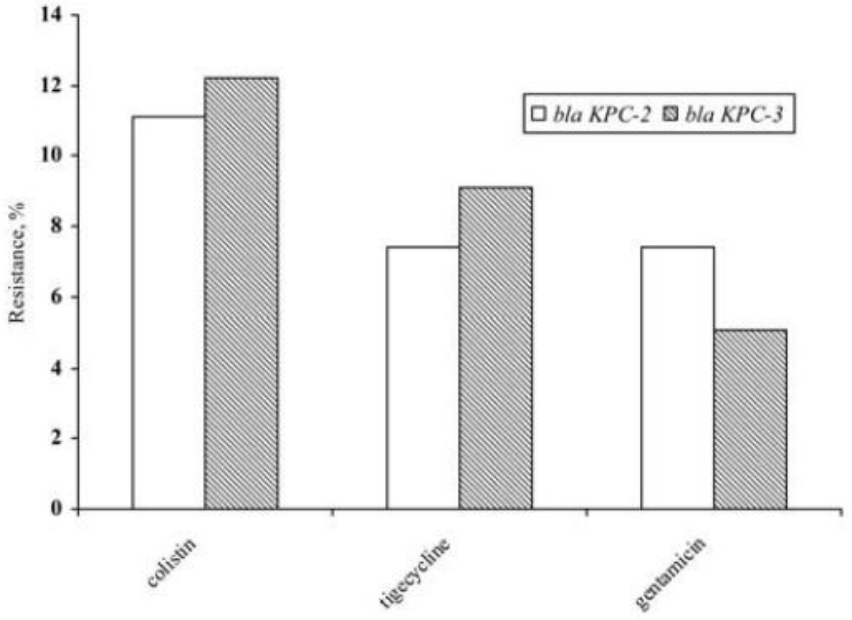

Figure 1. Colistin, tigecycline, and gentamicin resistance rates among *Klebsiella pneumoniae* isolates harboring the bla_{KPC-2} and bla_{KPC-3} genes. Abbreviation: KPC, *Klebsiella pneumoniae* carbapenemase.

Table 1. Univariate Analysis of Factors Associated With Death Among Patients With Bloodstream Infections Due to *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*

Variable	No. (%) of Patients		*P* Value	OR (95% CI)
	Nonsurvivors (n = 52)	Survivors (n = 73)		
Univariate analysis				
Demographic variables				
Male sex	32 (61.5)	41 (56.2)	.54	1.13 (.74–1.75)
Age, years, mean ± SD	61.5 ± 14.3	62.9 ± 16.5	.61	…
Ward				
Medicine	18 (34.6)	26 (35.6)	.90	0.97 (.62–1.50)
Surgery	12 (23.1)	16 (21.9)	.87	1.03 (.63–1.69)
Intensive care unit	22 (42.3)	31 (42.5)	.98	0.99 (.65–1.51)
LOS, days, median (IQR)	57 (29–63)	78 (36–90)	.02	…
Previous hospitalization[a]	38 (73.1)	29 (39.7)	<.001	2.34 (1.42–3.88)
Previous bacterial infections[b]	25 (48.1)	33 (45.2)	.75	1.06 (.70–1.62)
Invasive procedures[c]	28 (53.8)	46 (63.1)	.30	0.80 (.52–1.21)
Indwelling central venous catheter	40 (76.9)	48 (65.7)	.17	1.40 (.83–2.35)
Indwelling urinary catheter	36 (69.2)	46 (63.1)	.47	1.17 (.74–1.86)
Nasogastric tube[c]	18 (34.6)	17 (23.3)	.16	1.36 (.89–2.06)
Surgical drainage[c]	11 (21.1)	17 (23.3)	.77	0.92 (.55–1.55)
Previous surgery[d]	18 (34.6)	25 (34.2)	.96	1.01 (.65–1.56)
Immunosuppressive therapy[d]	10 (19.2)	6 (8.2)	.06	1.62 (1.03–2.53)
Previous antibiotic therapy[d]	47 (90.4)	58 (79.4)	.10	1.79 (.81–3.93)
Comorbidities				
Diabetes mellitus	9 (17.3)	20 (27.4)	.18	0.69 (.38–1.24)
Heart failure	12 (23.1)	12 (16.4)	.35	1.26 (.79–2.01)
Chronic renal failure	6 (11.5)	6 (8.2)	.53	1.22 (.66–2.25)
Solid tumor	10 (19.2)	15 (20.5)	.85	0.95 (.55–1.62)
Hematological malignancy	7 (13.4)	6 (8.2)	.34	1.34 (.77–2.32)
Charlson Comorbidity Index, median (IQR)	2 (0–4)	2 (0.5–2.5)	.82	…
Postantibiogram antimicrobial regimens				
Monotherapy	25 (48.1)	21 (28.7)	.02	1.59 (1.06–2.38)
Tigecycline	10 (19.2)	9 (12.3)	.28	1.32 (.81–2.16)
Colistin	11 (21.5)	11 (15.1)	.37	1.25 (.77–2.03)
Gentamicin	4 (7.6)	1 (1.3)	.09	1.98 (1.21–3.23)
Combination therapy	27 (51.9)	52 (71.2)	.02	0.62 (.41–.94)
2-drug combinations	23 (44.2)	33 (45.2)	.91	0.97 (.64–1.48)
Tigecycline + colistin	7 (13.4)	16 (21.9)	.22	0.68 (.35–1.32)
Tigecycline + gentamicin	6 (11.5)	6 (8.2)	.53	1.22 (.66–2.25)
Other 2-drug combinations[e]	10 (19.2)	11 (15.1)	.54	1.17 (.71–1.95)
3-drug combinations	4 (7.7)	19 (26.1)	.009	0.36 (.15–.92)
Tigecycline + colistin + meropenem	2 (3.8)	14 (19.2)	.009	0.27 (.07–1.01)
Other 3-drug combinations[f]	2 (3.8)	5 (6.8)	.47	0.67 (.21–2.21)
Inadequate initial antimicrobial treatment	39 (75)	36 (49.3)	.003	2.00 (1.19–3.34)
Presentation with septic shock	13 (25)	4 (5.5)	.002	2.11 (1.47–3.04)
APACHE III score (mean ± SD)	40 ± 22	24 ± 15	<.001	…

Read the fine print

Our multivariate analysis demonstrated that a triple-drug regimen that included tigecycline, colistin, and meropenem was significantly linked to a reduced risk of death. Indeed, this appeared to be the most effective approach to the treatment of KPC-Kp BSIs, even when compared with other drug combinations. In their review, Hirsch and Tam analyzed 11 KPC-Kp infections (none of which were BSIs) treated with drug combinations that included a polymyxin. The overall clinical success rate was 73% (66% in the 6 patients treated with colistin plus tigecycline) [10]. The percentages of our patients receiving colistin plus tigecycline in the survivor and nonsurvivor groups

This finding is unexpected because carbapenems are hydrolyzed by KPCs. However, in a recent review of the literature (mostly case reports) on carbapenem treatment of infections caused by carbapenemase-producing strains of Kp, Daikos et al found that if the isolate had a carbapenem MIC of ≤4 mg/L, combined therapy with a carbapenem plus 1 other active drug (an aminoglycoside or colistin or tigecycline) was associated with significantly lower mortality than combinations of noncarbapenem drugs with in vitro activity, and these findings were also in line with human pharmacokinetic/pharmacodynamic data reviewed by the authors [11]. In our study,

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Treatment Outcome of Bacteremia Due to KPC-Producing *Klebsiella pneumoniae*: Superiority of Combination Antimicrobial Regimens

**Zubair A. Qureshi,[a] David L. Paterson,[a,b] Brian A. Potoski,[a,c] Mary C. Kilayko,[d] Gabriel
Jennifer M. Adams-Haduch,[a] and Yohei Doi[a]**

Division of Infectious Diseases,[a] Department of Pharmacy,[c] University of Pittsburgh Medical Center, Pittsbur
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TABLE 3 Definitive antimicrobial therapy and mortality in 17 patients who received combination therapy and 19 patients who received monotherapy

Definitive treatment	*n* (%)	Mortality *n* (%)
Combination therapy	15 (44)	2 (13.3)
Colistin-polymyxin B combined with:		
Carbapenem	5 (33)	1 (20)
Tigecycline	1 (7)	0
Fluoroquinolone	1 (7)	0
Tigecycline combined with:		
Carbapenem	3 (20)	0
Aminoglycoside	2 (12)	0
Carbapenem-fluoroquinolone	1 (7)	1 (100)
Aztreonam-fluoroquinolone	1 (7)	0
Cefepime-gentamicin	1 (7)	0
Monotherapy	19 (46)	11 (57.8)
Colistin-polymyxin B	7 (36.8)	4 (57.1)
Tigecycline	5 (26.3)	4 (80)
Carbapenem	4 (21)	2 (50)
Gentamicin	1 5.2)	0
Ampicillin-sulbactam	1 (5.2)	0
Piperacillin-tazobactam	1 (5.2)	1 (100)
Total	34 (83)	13 (38.2)

TABLE 1 Predictors of mortality in 41 patients with bacteremia due to KPC-producing *K. pneumoniae*

			Univariate analysis		Multivariate analysis[b]	
Variable	Survived ($n = 25$)[a]	Died ($n = 16$)[a]	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Demographics						
Caucasian	14 (56)	6 (37.5)	0.4 (0.10–2.02)	0.34		
Age ≥65	9 (36)	8 (50)	1.5 (0.35–6.44)	0.74		
Male	10 (40)	7 (43)	1.1 (0.27–5.02)	1.00		
APACHE II ≥20	12 (48)	9 (56)	0.7 (0.13–4.24)	0.72		
In ICU at enrollment	13 (52)	9 (56)	1.5 (0.35–6.45)	0.75		
Therapy						
Inappropriate empirical therapy	21 (65.6)	11 (34.3)	0.2 (0.07–2.33)	0.27		
Combination definitive therapy	13 (60)	2 (12.5)	0.13 (0.01–0.82)	0.01	0.07 (0.009–0.71)	0.02
Appropriate therapy at any time	18 (78.2)	10 (62.5)	0.46 (0.08–2.35)	0.30		
Source of bacteremia						
Pneumonia	3 (12)	7 (43.7)	5.7 (0.98–3.68)	0.03		
Line related	9 (36)	4 (25)	0.5 (0.12–2.88)	0.51		
Urinary tract	5 (20)	2 (12.5)	0.5 (0.12–2.88)	0.51		
Primary bacteremia	5 (20)	1 (6.2)	0.2 (0.01–2.87)	0.38		
Underlying diseases						
Diabetes mellitus	5 (20)	5 (31.2)	1.8 (0.35–9.67)	0.48		
Chronic renal failure	5 (20)	4 (25)	1.3 (0.24–7.47)	0.72		
COPD[c]	2 (8)	0 (0)	0.0 (0.00–6.72)	0.51		
Cardiovascular	0	5 (31.2)	∞ (1.59–∞)	0.01		
Cerebrovascular	2 (8)	0	0.0 (0.00–6.72)	0.51		
Chronic liver disease	0	3 (18.7)	∞ (0.72–∞)	0.05		
Malignancy	5 (20)	3 (18.7)	0.9 (0.14–5.67)	1.00		
Solid organ malignancy	5 (20)	2 (12.5)	0.5 (0.06–4.16)	0.68		
Transplant	7 (28)	2 (12.5)	0.3 (0.04–2.46)	0.44		
HIV	2 (8)	1 (6.2)	0.7 (0.02–2.47)	1.00		
Immunocompromised state	16 (64)	10 (66.6)	0.9 (0.21–4.18)	1.00		
Renal dialysis	5 (20)	6 (37.5)	2.4 (0.48–12.39)	0.28		
Events in prior 30 days						
Prior use of antimicrobials	18 (72)	13(81.2)	1.6 (0.30–10.27)	0.71		
Surgery	9 (36)	6 (37.5)	1.0 (0.24–4.73)	1.00		
Events in prior year						
Hospitalization	24 (96)	16 (100)	∞ (0.03–∞)	1.00		
Surgery	17 (68)	8 (50)	0.5 (0.10–2.05)	0.33		
Admitted to ICU	18 (72)	10 (62.5)	0.6 (0.14–3.00)	0.73		
Indwelling devices						
Urinary catheter	9 (36)	9 (56)	2.2 (0.53–0.12)	0.33		
Tracheostomy tube	12 (48)	5 (31.2)	0.4 (0.11–2.19)	0.34		
Vascular catheter	18 (72)	13 (81.2)	1.7 (0.30–10.27)	0.71		
Gastrostomy tube	9 (36)	7 (43.7)	1.4 (0.32–6.04)	0.75		

[a] Data are presented as *n* (%).
[b] Combination definitive therapy, pneumonia as the source of bacteremia, chronic liver disease, and coronary artery disease were included in the multivariate analysis.
[c] COPD, chronic obstructive pulmonary disease.

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Treatment Outcome of Bacteremia Due to KPC-Producing *Klebsiella pneumoniae*: Superiority of Combination Antimicrobial Regimens

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***Klebsiella pneumoniae* producing *Klebsiella pneumoniae* carbapenemase (KPC) has been associated with serious infections and high mortality. The optimal antimicrobial therapy for infection due to KPC-producing *K. pneumoniae* is not well established. We con**
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TABLE 2 Analysis of clinical variables in 34 patients that received definitive therapy

Variable	Combination therapy ($n = 15$)[a]	Monotherapy ($n = 19$)[a]	*P* value	OR (95% CI)
Demographics				
Age ≥65	6 (40)	11 (57.8)	0.49	0.4 (0.09–2.35)
Male	8 (53.3)	7 (36.8)	0.50	1.7 (0.36–8.31)
Severity of illness				
In ICU at enrollment	10 (66.6)	10 (52.6)	0.49	1.8 (0.36–9.28)
APACHE II	17.4 ± 6.65	21.3 ± 8.69	0.15	
LOS[b]	35 ± 28	34.9 ± 72	0.99	
Underlying diseases				
Immunocompromised state	11 (73.3)	9 (47.3)	0.17	3.0 (0.58–17.14)
Chronic renal failure	3 (20)	3 (15.8)	1.00	1.3 (0.17–10.54)
Malignancy	3 (20)	5 (15.8)	1.00	0.7 (0.02–4.51)
Transplant	8 (53.3)	0	≤0.001	∞ (3.01–∞)

[a] Data are presented as *n* (%) or mean ± standard deviation (SD).
[b] LOS, length of stay before bacteremia.

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What remains against carbapenem-resistant Enterobacteriaceae chloramphenicol, ciprofloxacin, colistin, fosfomycin, minocycline temocillin and tigecycline

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ABSTRACT

Carbapenem-resistant Enterobacteriaceae present an increasing and div of multiple species with metallo-β-lactamases (IMP, NDM or VIM) and enzymes as well as those combining an extended-spectrum β-lactamas porin loss. Most strains, except those with OXA-48 alone, are broadly r multiple aminoglycoside-modifying enzymes; those with NDM-1 carbap rRNA methylases, conferring complete aminoglycoside resistance. In thi phenicol, ciprofloxacin, colistin, fosfomycin, minocycline, nitrofurantoin evaluated against 81 carbapenem-resistant Enterobacteriaceae isolates formed by the Clinical and Laboratory Standards Institute (CLSI) agar dilu ciprofloxacin and nitrofurantoin inhibited <25% of the isolates at the br active against 75/81 isolates (92.6%), the exceptions being four *Klebsiel cloacae* isolates along with members of inherently resistant genera. Fosfo isolates (60.5%), including 7/7 *Escherichia coli*, 16/20 *Enterobacter* and *Citro siella* spp. Tigecycline was active against 38/81 isolates (46.9%) and was i (33.3%), with resistance scattered amongst *K. pneumoniae* and *Enteroba* fosfomycin and tigecycline was unrelated to the isolates' carbapenem res was fully active [minimum inhibitory concentration (MIC) ≤8 mg/L] ag but inhibited a further 22 isolates (27.2%) at the British Society for Antir urinary breakpoint (32 mg/L), predominantly comprising those isolates ability and an ESBL or AmpC enzyme, along with 6/11 isolates producin with transconjugants and transformants confirmed the small effect of K whereas OXA-48 and NDM-1 conferred clear resistance.

Table 1
Minimum inhibitory concentrations (MICs) of antibiotics in relation to carbapenemase type[a].

Antibiotic/carbapenemase	No. isolates with indicated MIC (mg/L):												
	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	≥256
Chloramphenicol													
IMP								3	2		4		4
NDM							2	1	3	1	1	1	8
VIM							1			1		3	
KPC								1	1	2	4		3
SME-1											1		
OXA-48							5	3				4	7
Impermeability + ESBL							2	1		2	1		3
Impermeability + AmpC								2	3	1			
Ciprofloxacin													
IMP	2		1	1	1	1	3			3	1		
NDM	1[b]							2	1	1	4	4	4
VIM					2				1	1			1
KPC										2	3	5	1
SME-1	1[b]												
OXA-48	2[b]	1		1		7	1			1	1	2	3
Impermeability + ESBL						1	1	1		3	3		
Impermeability + AmpC	4[b]						1		1				
Colistin													
IMP				10[b]	3								
NDM				13[b]	2			1			1[c]		
VIM				4[b]	1								
KPC				9[b]	1					1			
SME-1											1[c]		
OXA-48				11[b]	7					1			
Impermeability + ESBL				7[b]	1					1			
Impermeability + AmpC				5[b]	1								
Fosfomycin													
IMP						1[b]	3	4	1	1			3
NDM						6[b]	1	3	1	2	2	1	1
VIM								1	1	1	1		1
KPC								1	4	1	4		1
SME-1									1				
OXA-48						2[b]	1	2	1	5	3	5	
Impermeability + ESBL										2	1	1	5
Impermeability + AmpC						1			1	1	2	1	
Nitrofurantoin													
IMP							1[b]		2	1	1	5	3
NDM									3		3	4	7
VIM											1	1	3
KPC													11
SME-1													1
OXA-48												3	16
Impermeability + ESBL													9
Impermeability + AmpC											1	2	3
Temocillin													
IMP										1	6	5	1
NDM								1	1		4	1	10
VIM												1	4
KPC									2	4	4	1	
SME-1								1					
OXA-48								1					18
Impermeability + ESBL								1	1	7			
Impermeability + AmpC									5	1			
Minocycline													
IMP							2	6	3	1	1[c]		
NDM					1	3	1	5	3	2	2[c]		
VIM							1	3	1				
KPC								6	1	1	3[c]		
SME-1								1					
OXA-48						2	3	8	2	3	1[c]		
Impermeability + ESBL							4	2	2	1			
Impermeability + AmpC							4		1		1[c]		
Tigecycline													
IMP				1	4	4	4						
NDM			1[b]	5	4	3	3	1					
VIM					3	1	1						
KPC					2	6	2	1					
SME-1							1						
OXA-48				3	6	9	1						
Impermeability + ESBL				1	3	3	2						
Impermeability + AmpC					5	1							

ESBL, extended-spectrum β-lactamase.
[a] Unshaded indicates susceptible, dark shading indicates resistant and light shading indicates intermediate (tigecycline) or susceptible at British Society for Antimicrobial Chemotherapy (BSAC) urinary breakpoint (temocillin).
[b] MIC ≤ indicated value.
[c] MIC ≥ indicated value.

Table 2
Minimum inhibitory concentrations (MICs) of antibiotics in relation to bacterial species[a,b].

Antibiotic/species	No. isolates with indicated MIC (mg/L):												
	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	≥256
Chloramphenicol													
Klebsiella spp.[c]							9	7	1	4	8	7	16
Enterobacter spp./*Citrobacter freundii*[d]							1	3	6	3	2	5[g]	
Escherichia coli[e]								1	1			1	4
Ciprofloxacin													
Klebsiella spp.	5[f]	1		2	2	8	5	1	1	6	7	7	7
Enterobacter spp./*C. freundii*	4[f]		1		1	1	1	1	2	5	1	2	1
E. coli								1			4	1	1
Colistin													
Klebsiella spp.				36[f]	13				1	2			
Enterobacter spp./*C. freundii*				16[f]	3			1					
E. coli				6[f]	1								
Fosfomycin													
Klebsiella spp.						2[f]	2	7	5	9	10	7	10
Enterobacter spp./*C. freundii*						2[f]	3	3	4	4	3	1	
E. coli						5[f]	1	1					
Nitrofurantoin													
Klebsiella spp.							1[f]		2	1		9	39[g]
Enterobacter spp./*C. freundii*									1		4	4	11[g]
E. coli									2		1	2	2[g]
Minocycline													
Klebsiella spp.						3	10	22	10	6	1[g]		
Enterobacter spp./*C. freundii*						1	5	5	3	1	5[g]		
E. coli					1	1		3		1	1[g]		
Tigecycline													
Klebsiella spp.				6	15	22	9						
Enterobacter spp./*C. freundii*				1	9	5	3	2					
E. coli			1	3	3								

[a] Excludes single isolates of (i) *Morganella morganii* with NDM-1 enzyme: MICs, chloramphenicol 16 mg/L, ciprofloxacin 128 mg/L, colistin >32 mg/L, fosfomycin 512 mg/L, nitrofurantoin 64 mg/L, temocillin 8 mg/L, minocycline >32 mg/L and tigecycline 4 mg/L; and (ii) *Serratia marcescens* with SME-1 enzyme: MICs, chloramphenicol 64 mg/L, ciprofloxacin <0.03 mg/L, colistin >32 mg/L, fosfomycin 16 mg/L, nitrofurantoin 256 m g/L, temocillin 8 mg/L, minocycline 8 mg/L and tigecycline 4 mg/L.

[b] Unshaded indicates susceptible, dark shading indicates resistant and light shading indicates intermediate.

MICs are important

TABLE 4 Antimicrobial susceptibility of 41 KPC-producing *K. pneumoniae* bacteremic isolates

	CLSI 2009 breakpoints			CLSI 2011 breakpoints			MIC (μg/ml)	
Antimicrobial agent	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant	50%	90%
Ertapenem	3[a]	8	30	0	0	41	>4	>4
Imipenem	23	7	11	2	8	31	4	>8
Meropenem	21	5	15	1	11	29	4	>8
Doripenem				8	11	22	>2	>2
Ceftazidime	0	1	40	0	0	41	>16	>16
Cefepime	22	7	12				8	>16
Ticarcillin-clavulanate	0	0	41				>128/2	>128/2
Piperacillin-tazobactam	0	1	40				>64/4	>64/4
Amikacin	24	15	2				16	32
Gentamicin	6	16	19				8	>16
Tobramycin	0	0	41				>8	>8
Ciprofloxacin	2	1	38				>2	>2
Levofloxacin	3	0	38				>8	>8
Doxycycline	33	5	3				4	8
Minocycline	28	9	4				4	16
Tigecycline	40	0	1				0.5	1
Colistin	37	0	4				≤0.25	>4
Polymyxin B	37	0	4				0.5	>4

[a] These isolates initially tested as intermediate in the clinical laboratories based on the CLSI 2009 breakpoints and were positive for the KPC gene by PCR and sequencing but tested as susceptible using the manual broth microdilution method in the research laboratory.

Singapore Med J 2008; 49 (10) : 746

Reducing antimicrobial resistance: a bold call to action

Tambyah P A, Tan B H

In this edition of the Singapore Medical Journal, Hsu et al have issued a bold call to action on the problem of antimicrobial resistance
the form of a position pa
infectious diseases and clin
To our knowledge, this is t
of professional societies h
independent of the Ministry
and is a refreshing evidenc
civil society in Singapore.
Annals of the Academy of M
et al, suggested roles for hur
(HIV)-infected healthcare v
second document is a timely
of antimicrobial resistance.
measures: for enhanced dat
scale and impact of the pr
misuse; for the MOH to tak
antibiotic use; for hospitals to support antimicrobial
stewardship programmes; and finally for an update of the
code of conduct regulating the relationship between the

accurate information using internationally standardised definitions for the rates of antibiotic resistance in a range

prescription" as some doctors derive a large proportion of their revenue from the sale of medications, including antibiotics. In Taiwan, inappropriate prescribing of

1.More data dissemination
2.Support for Stewardship/Novel technologies
3.Infection Control
4.One health approach

DISPATCHES

Antimicrobial Drug Resistance in Singapore Hospitals

Li-Yang Hsu,[*1] Thean-Yen Tan,[†1] Roland Jureen,[‡] Tse-Hsien Koh,[§] Prabha Krishnan,[¶] Raymond Tzer-Pin Lin,[*] Nancy Wen-Sin Tee,[#] and Paul Ananth Tambyah[*]

A new national antimicrobial resistance surveillance program in Singapore public hospitals that uses WHONET detected high levels of methicillin resistance among *Staphylococcus aureus* (35.3%), carbapenem resistance among *Acinetobacter* spp. (49.6%), and third-generation cephalosporin resistance among *Klebsiella pneumoniae* (35.9%) hospital isolates in 2006. Antimicrobial drug resistance is a major problem in Singapore.

National Surveillance in SG

Hsu LY et al, Emerg Infect Dis 2007;13:1944-7

Table. Drug-resistant clinical bacterial isolates cultured at public sector hospitals, Singapore, 2006*

Isolates	All resistant isolates		Resistant blood isolates			Resistant ICU isolates		
	No. (%) of all isolates†	% Range for single hospitals‡	No. (%) of all blood isolates†	% Range for single hospitals‡	p value§	No. (%) of all ICU isolates†	% Range for single hospitals†	p value¶
Methicillin-resistant *S. aureus*	3,517 (35.3)	18.0–44.3	497 (39.8)	23.8–44.4	<0.01	261 (46.7)	26.8–70.5	<0.01
Vancomycin-resistant enterococci (*E. faecium* or *E. faecalis*)	31 (0.8)	0–1.3	5 (1.3)	0–2.4	0.25	3 (1.2)	0–3.2	0.46
3rd-generation cephalosporin-resistant *E. coli*	2,257 (17.5)	6.1–22.8	284 (17.9)	7.4–19.0	0.66	123 (33.4)	12.7–41.4	<0.01
Quinolone-resistant *E. coli*	4,227 (34.4)	15.2–40.1	453 (28.6)	15.4–40.5	<0.01	150 (41.6)	12.0–54.6	<0.01
Cephalosporin and quinolone-resistant *E. coli*	1,080 (8.4)	0.8–19.9	181 (11.4)	5.7–15.3	<0.01	79 (21.4)	2.9–40.5	<0.01
3rd-generation cephalosporin-resistant *K. pneumoniae*	2,651 (35.9)	9.6–49.7	294 (30.6)	13.8–34.5	<0.01	187 (37.2)	8.8–46.6	0.54
Quinolone-resistant *K. pneumoniae*	3,074 (42.5)	11.5–58.3	321 (33.6)	11.1–39.6	<0.01	183 (36.7)	6.2–47.6	<0.01
Cephalosporin- and quinolone-resistant *K. pneumoniae*	1,839 (24.9)	2.0–46.1	214 (22.3)	6.9–35.2	0.05	135 (26.2)	0.0–41.2	0.47
Carbapenem-resistant *P. aeruginosa*	477 (9.6)	2.4–12.2	45 (16.5)	9.1–23.1	<0.01	74 (18.3)	3.3–27.2	<0.01
Carbapenem-resistant *Acinetobacter* spp.	929 (49.6)	16.9–65.5	86 (48.1)	18.2–66.7	0.66	164 (59.7)	31.6–68.8	<0.01
Multidrug-resistant *Acinetobacter* spp.*	354 (18.2)	3.6–26.1	34 (17.8)	0.0–29.8	0.88	64 (23.4)	0.0–30.2	0.02

Hsu LY et al, Emerg Infect Dis 2007;13:1944-7

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2010, p. 1173–1178 Vol. 54, No. 3
0066-4804/10/$12.00 doi:10.1128/AAC.01076-09

Surveillance and Correlation of Antibiotic Prescription and Resistance of Gram-Negative Bacteria in Singaporean Hospitals▽†

Li-Yang Hsu,[1]* Thean-Yen Tan,[2] Vincent H. Tam,[1,3] Andrea Kwa,[4] Dale Andrew Fisher,[1] Tse-Hsien Koh,[5] and the Network for Antimicrobial Resistance Surveillance (Singapore)

Department of Med
Laboratory Mec
University of I

Correlation not so clear cut

TABLE 3. Trends in antimicrobial resistance in Singapore hospitals, 2006 to 2008

Organism(s), drug resistance, and isolate type	Gradient (incidence density/1,000 inpatient-days per quarter)	R^2	*P* value	95% CI[a]	Trend
Escherichia coli					
Ceftriaxone					
All isolates[b]	0.032	0.609	<0.01	0.014–0.050	Increasing
Blood isolates[b]	0.007	0.572	<0.01	0.003–0.011	Increasing
	0.031	0.424	0.02	0.005–0.056	Increasing
	0.007	0.518	<0.01	0.002–0.011	Increasing
	−0.074	0.838	<0.01	−0.096–−0.051	Decreasing
	−0.005	0.412	0.02	−0.009–−0.007	Decreasing
	−0.091	0.902	<0.01	−0.112–−0.070	Decreasing
	−0.004	0.264	0.08	−0.009–0.001	Stable
Acinetobacter spp., imipenem					
All isolates	−0.009	0.135	0.24	−0.263–0.007	Stable
Blood isolates[b]	0.003	0.394	0.03	0.003–0.005	Increasing
Pseudomonas aeruginosa, imipenem					
All isolates	0.0004	0.081	0.37	−0.006–0.014	Stable
Blood isolates	0.002	0.257	0.09	−0.004–0.005	Stable

[a] 95% CI, 95% confidence interval.
[b] Results where R^2 was >0.3 and *P* was <0.05.

ELSEVIER

International Journal of Antimicrobial Agents 18 (2001) 391–393

INTERNATIONAL JOURNAL OF Antimicrobial Agents

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Short communication

Widespread resistance to new antimicrobials in a university hospital before clinical use

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[b] *Department of Medicine, National University Hospital*

Received 26 March 2

We have to go outside the hospital

Abstract

The activity of cefpirome, cefepime and piperacillin/tazobactam previously unused in the hospital was evaluated in parallel with five broad-spectrum antibiotics (ceftazidime, ceftriaxone, imipenem, ciprofloxacin and amikacin) currently being used to treat serious infections in the National University Hospital, Singapore. Two hundred and two clinically significant, organisms consecutively isolated during 1998 were included in the study. In vitro efficacy of cefepime, cefpirome and piperacillin/tazobactam was not superior to imipenem, ciprofloxacin and amikacin which are currently used. More than 40% of Enterobacteriaceae were

Singapore Med J 2008; 49 (10) : 749

Reducing antimicrobial resistance through appropriate antibiotic usage in Singapore

Hsu L Y, Kwa A L, Lye D C, Chlebicki M P, Tan T Y, Ling M L, Wong S Y, Goh L G

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ABSTRACT

Two alarming trends threaten the future utility of antimicrobial agents: rise of antimicrobial resistance and decline in development of new antibiotics. The continuing emergence and spread of antimicrobial-resistant microbes—a global publi… pauci… publi… the h… world… past t… surve… probl… it is difficult to assess the scale of antimicrobial resistance in the community in view of the lack of recent research, although indirect evidence suggests that this is also a source of concern. A panel comprising representatives from multiple professional healthcare societies was convened to address the issue of antimicrobial resistance in Singapore, focusing on the conservation of antibiotics against resistance. From a review of the medical literature, potentially successful strategies involve facilitating prudent and appropriate use of antimicrobial agents in tandem with other interventions in infection control. Presently, there is a lack of data on the appropriate use of antibiotics in Singapore. The recommendations of the panel are: The professions should look into ways and means to support systematic data

Keywords: antibiotic usage, antibiotic surveillance, antimicrobial drug resistance, antimicrobial stewardship, clinical education, pharmaceutical industry

Singapore Med J 2008;49(10):749-755

as ancillary treatment for the further development of surgical and cancer therapies. However, its impact has diminished dramatically with the advent of two alarming trends: the rise of antimicrobial resistance and the drying-up of the pharmaceutical antimicrobial development pipeline.[2] In view of these interlinked trends, one obvious strategy is to promote the prudent and appropriate use of antimicrobials in the clinical setting to retard the development of resistance and extend the viability of existing drugs. While this paper focuses mainly on the issue of uncontrolled and inappropriate antibiotic prescription in the local setting, it is important to appreciate that a concerted response—including strategies to spur the development of new antimicrobial agents—is key to resolving the current problems posed by antimicrobial resistance.

There are problems locally

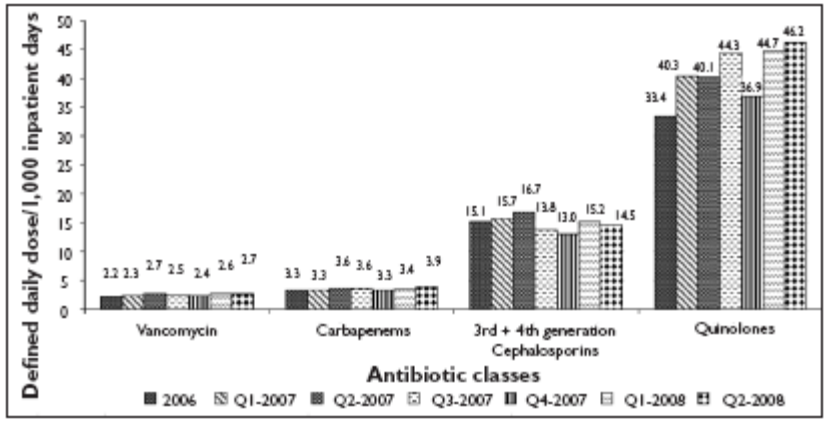

Fig. 1 Bar chart shows combined usage data of key antibiotic classes in local public hospitals according to defined daily dose per 1,000 patient-days.

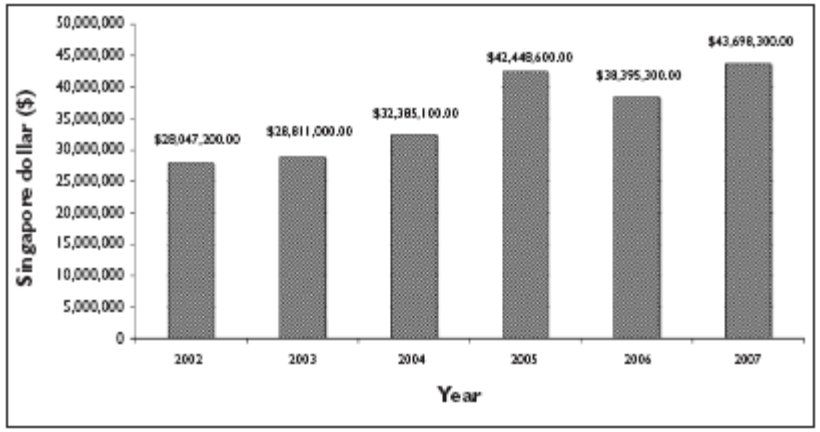

Fig. 2 Bar chart shows approximate overall sales of systemic antibiotics by pharmaceutical companies in Singapore to both private and public healthcare sectors. It does not include antifungal agents and topical antimicrobial agents (data from IMS Health reports).

control programmes. ASPs may be part of, or separate from, existing infection control programmes.

(b) Award funding to the public sector hospitals for ASPs in proportion to the savings made from public healthcare subsidies.

(c) Facilitate the sharing of laboratory and prescription data from private and public laboratories and pharmacies for surveillance purposes.

(d) Re-examine the current situation, where general practitioners and private specialists may have a financial incentive to prescribe more and expensive antibiotics.

(e) Support research or quality improvement projects on finding effective mechanisms of control at the healthcare facilities.

(f) Coordinate collaborative work among public and private hospitals in improving antimicrobial stewardship (similar to the successful IHI collaborative work on various improvement programmes in the US).

(g) Track prescribing practices in the country, e.g.

Singapore Med J 2008; 49 (10) : 749

Reducing antimicrobial resistance ugh appropriate antibiotic usage in apore

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Main issues are economic

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Antimicrobial Stewardship was safe in SG

Impact of an antimicrobial stewardship programme on patient safety Singapore General Hospital

Yi Xin Liew[a,*], Winnie Lee[a], Joan Chain Zhu Loh[b], Yiying Cai[a], Sarah Si Lin Tang[a], Che
Jocelyn Teo[a], Rachel Wen Qin Ong[a], Andrea Lay-Hoon Kwa[a,*], Maciej Piotr Chlebicki[b]

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Table 2
Types of intervention recommended by the antimicrobial stewardship programme that may have an impact on morbidity and mortality ($N = 743$).

Intervention	Accepted [n (%)][a]		Rejected [n (%)][a]		P-value
	Total	Patients who died	Total	Patients who died	
De-escalation based on culture results	97 (16.8)	13 (2.2)	27 (16.4)	5 (3.0)	0.555
Discontinue antibiotic	270 (46.7)	32 (5.5)	86 (52.1)	11 (6.7)	0.851
Narrowing of empirical coverage	49 (8.5)	6 (1.0)	38 (23.0)	1 (0.6)	0.239
Intravenous-to-oral switch	162 (28.0)	4 (0.6)	14 (8.5)	1 (0.6)	0.346
Total	578/743 (77.8)	55 (9.5)	165/743 (22.2)	18 (10.9)	0.557

[a] Percentages are out of the total accepted or rejected, respectively; except where indicated.

tions. In conclusion, interventions recommended by the ASP in SGH were safe and were associated with a reduction in the duration of hospital stay, 14-day re-infection rate and infection-related re-admissions.

Eur J Clin Microbiol Infect Dis (2012) 31:947–955
DOI 10.1007/s10096-011-1391-y

ARTICLE

The effect of a whole-system approach in an antimicrobial stewardship programme at the Singapore General Hospital

J. Teo • A. L. H. Kwa • J. Loh • M. P. Chlebicki

Received: 4 March 2011 / Accepted: 18 August 2011 / Pub

Abstract Inappropriate antibiotic use contribute
microbial resistance. Multi-faceted antimicrobial
ship programmes (ASPs) are recommended for su
changes in prescribing practices. A multi-discipli

It is a bit complex

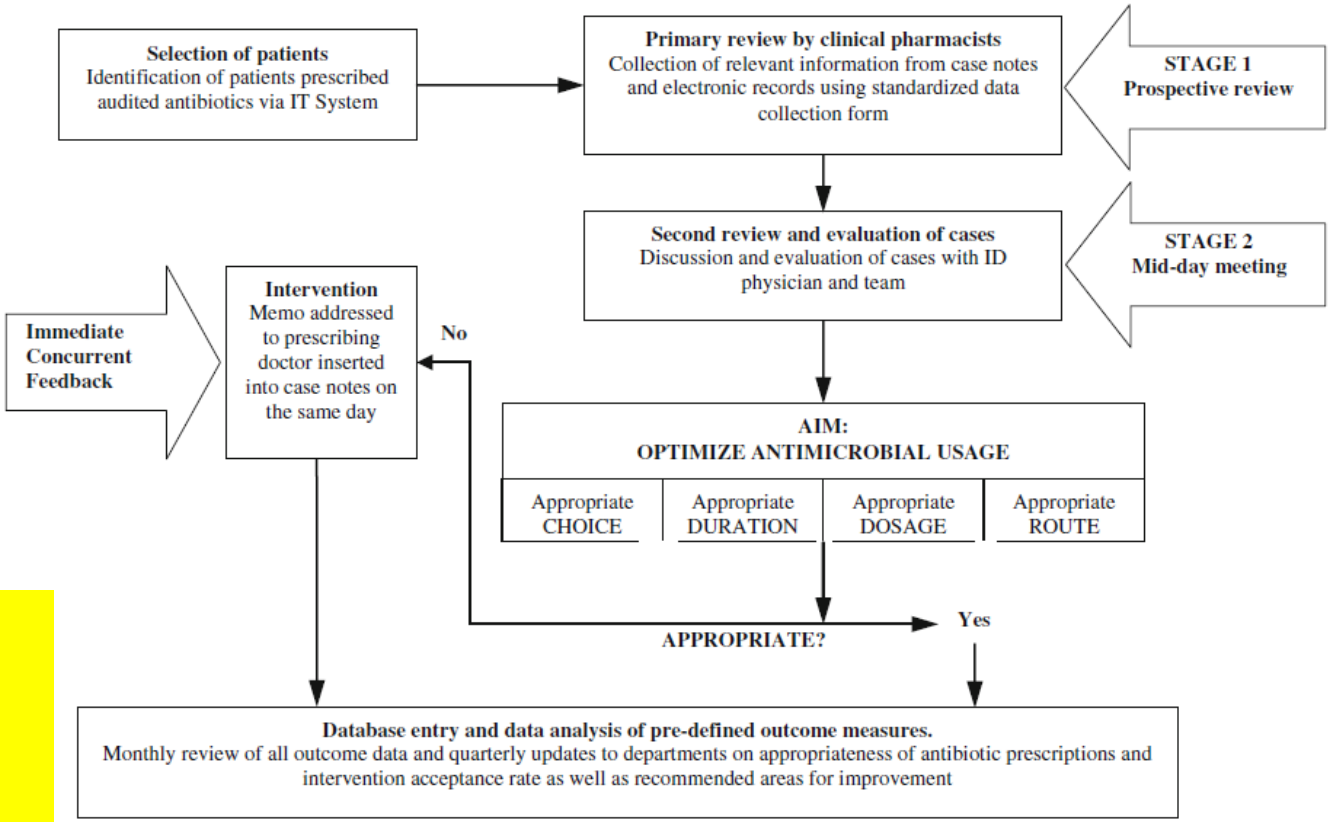

Fig. 2 Schematic diagram of the antimicrobial stewardship programme (ASP) prospective audit with immediate concurrent feedback (ICF) workflow

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ARTICLE

The effect of a whole-system approach in an antimicrobial stewardship programme at the Singapore General Hospital

J. Teo · A. L. H. Kwa · J. Loh · M. P. Chlebicki · W. Lee

It does work

Received: 4

Abstract
microbial
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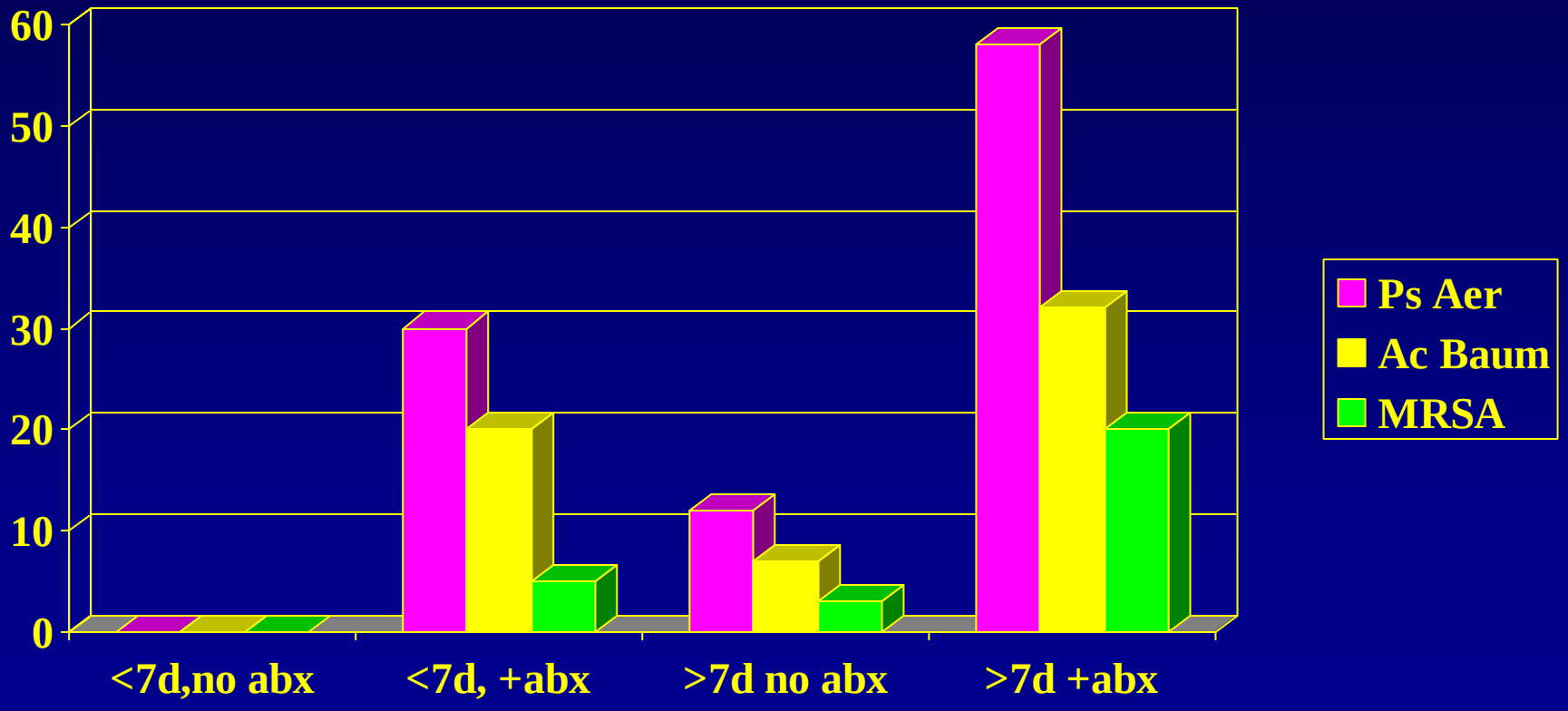
changes ir

Table 2 Change in the levels and slopes of antibiotics consumption and change in the levels of expenditures between the pre-ASP and post-ASP periods

Antibiotic	Change in 12-month consumption levels (DDDs/100 patient-days) (% change)	*p*-value	Change in consumption slopes	*p*-value	Change in 12-month expenditures levels ($) (% change)	*p*-value
Total antibiotics (including non-audited)	−1.7 (4.5)	0.248	+0.992	0.004	−141,554.26 (7.1)	0.151
Total audited antibiotics	−1.3 (10.0)	0.032	+0.301	0.065	−198,575.51 (13.2)	0.011
Individual audited antibiotics						
Cefepime	+0.3 (19.8)	0.122	−0.114	0.043	+19,531.20 (19.3)	0.115
Ciprofloxacin	−1.0 (37.0)	<0.001	−0.107	0.016	−116,150.92 (37.3)	<0.001
Piperacillin–tazobactam	−0.7 (14.0)	0.039	+0.151	0.033	−88,878.96 (14.4)	0.034
Ertapenem	+0.6 (49.0)	0.037	+0.298	<0.001	+51,208.74 (48.4)	0.042
Imipenem-cilastatin	−0.4 (51.2)	0.016	+0.150	<0.001	−53,543.73 (51.4)	0.016
Meropenem	−0.1 (3.6)	0.739	−0.077	0.229	−10,741.84 (4.0)	0.778

Ecological impact of antibiotics



Trouillet JL et al. Am J Resp Crit Care Med 1998;157:531-9

Effect of Hand Hygiene on Resistant Organisms

Year	Author	Setting	Impact on organisms
1982	Maki	adult ICU	decreased
1984	Massanari	adult ICU	decreased
1990	Simmons	adult ICU	no effect
1992	Doebbeling	adult ICU	decreased with one versus another hand hygiene product
1994	WebsterNICU	MRSA eliminated	
1999	Pittet	hospital	MRSA decreased

ICU = intensive care unit; NICU = neonatal ICU

MRSA = methicillin-resistant *Staphylococcus aureus*

Source: Pittet D: Emerg Infect Dis 2001;7:234-240

➢ *Link to: Improving hand hygiene*

Emergence and Dissemination of Extended-Spectrum β-Lactamase–Producing *Escherichia coli* in the Community: Lessons from the Study of a Remote and Controlled Population

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Background. Intestinal carriage is a key factor in ex but is difficult to study in open communities. To o Amerindians for whom we reported an ESBL carriag

Methods. In 2006, ESBL carriage was assessed amo and their molecular resistance mechanisms were char epidemiological characteristics of the population were

Results. In 2006, the ESBL carriage prevalence, consisted of CTX-M–type ESBL. The strains and pla producing strain was found in 4.3% of the subjects overall antibiotic use had almost doubled since 2001.

Conclusions. In this population, the frequency of M ESBL, mimicking what occurs in the developed w of new strains and plasmids and from interindivid substantially increased.

Antibiotic resistance is a major public health concer worldwide. Many studies have underlined the increas

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ure 1. Phylogenetic tree of a panel of 248 *Escherichia coli* strains representing the diversity of the species studied (72 ECOR strains [24], 161 eremic strains [22], 15 completely sequenced genomes [25], and the 9 extended-spectrum β-lactamase [ESBL]–producing *E. coli* strains). The tree reconstructed from multilocus sequence typing concatenated sequences, using the PHYML procedure. *Escherichia fergusonii* was used as an roup. Bootstrap values are shown for values >70%. The main phylogenetic groups (A, B1, B2, and D) as well as the 3 additional phylogenetic ups C, E, and F) are shown [22]. The 9 ESBL-producing strains isolated in Trois-Sauts are boxed.

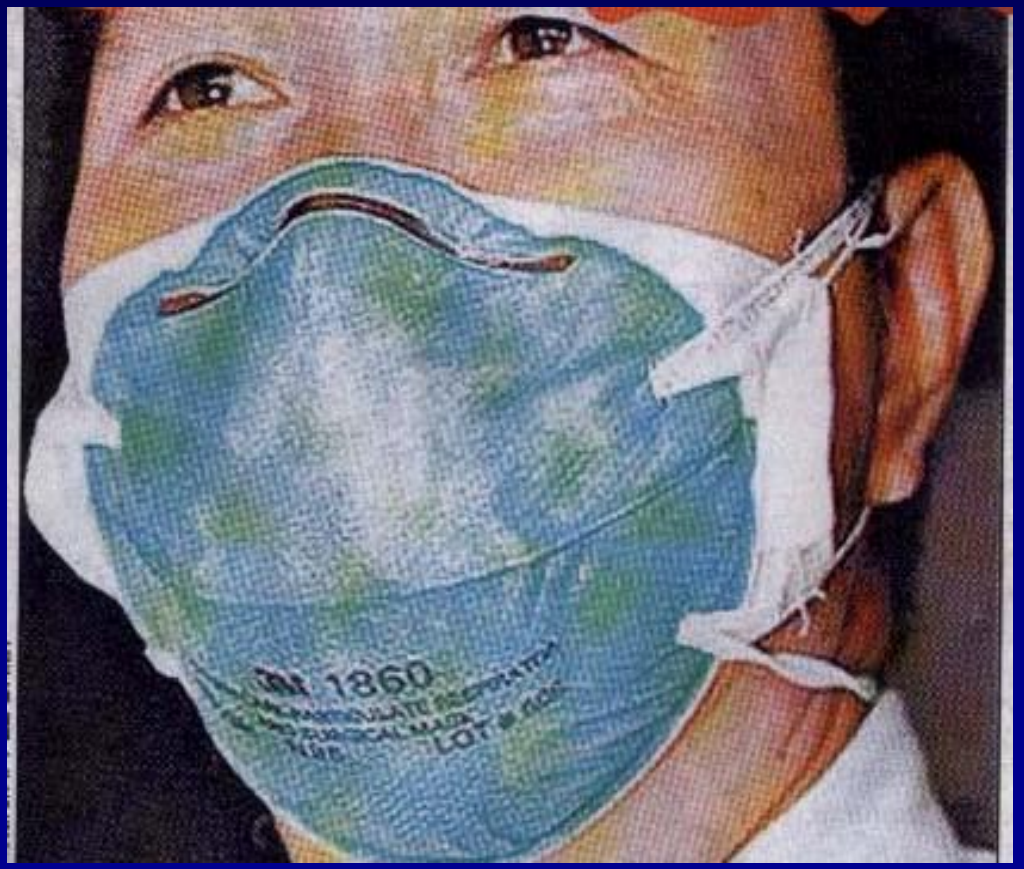
Infection Control in a nutshell

Everything I needed to know about infection control,
I learned in kindergarten

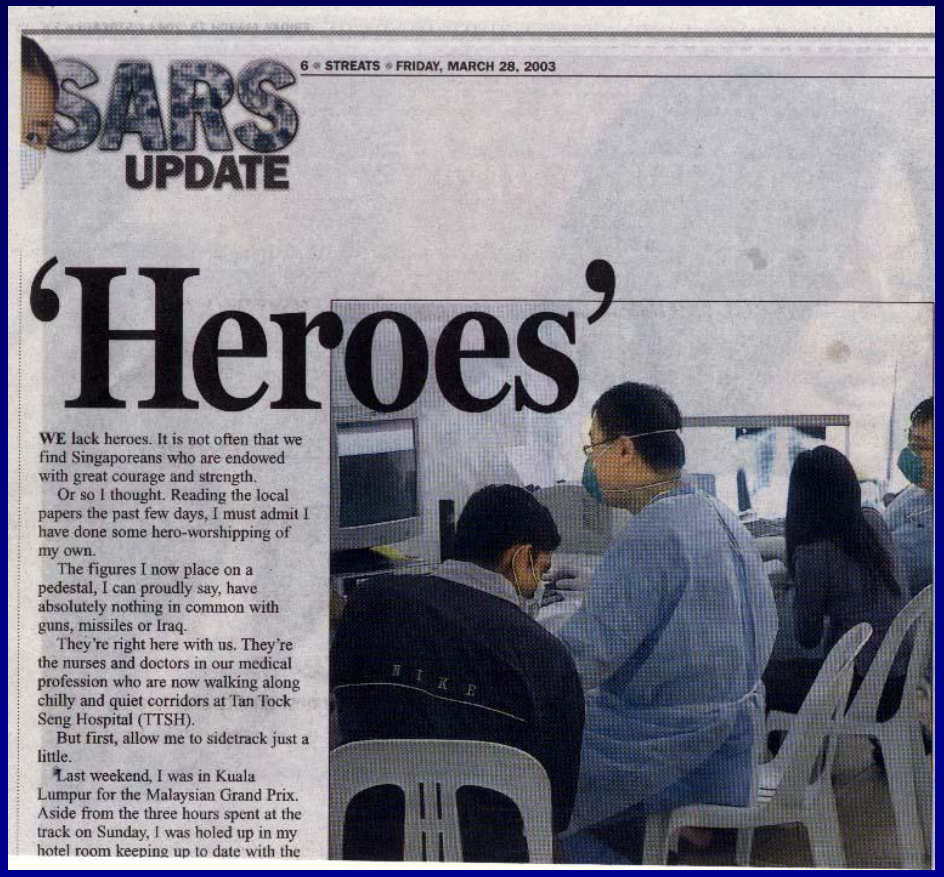
– Julie Gerberding, former Director US CDC

Always clean your hands

Cover your mouth when you cough



Don’t go to work when you are sick



6 ● STREATS ● FRIDAY, MARCH 28, 2003

SARS UPDATE

‘Heroes’

WE lack heroes. It is not often that we find Singaporeans who are endowed with great courage and strength.

Or so I thought. Reading the local papers the past few days, I must admit I have done some hero-worshipping of my own.

The figures I now place on a pedestal, I can proudly say, have absolutely nothing in common with guns, missiles or Iraq.

They’re right here with us. They’re the nurses and doctors in our medical profession who are now walking along chilly and quiet corridors at Tan Tock Seng Hospital (TTSH).

But first, allow me to sidetrack just a little.

Last weekend, I was in Kuala Lumpur for the Malaysian Grand Prix. Aside from the three hours spent at the track on Sunday, I was holed up in my hotel room keeping up to date with the

3rd International Congress of The Infection Control Association (Singapore)

27Feb – 01Mar 2013

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CALL FOR ABSTRACTS

Submission Date: **30th November 2012**
Please refer to event website **www.icas.org.sg** for details

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