**COMITÉ DE INFECTOLOGÍA CRÍTICA, SATI**

# GUÍAS PARA EL CONTROL DE INFECCIONES POR ENTEROBACTERIAS RESISTENTES A CARBAPENEMES O PRODUCTORAS DE CARBAPENEMASAS

**Adaptadas de las Guías del Centre for Disease Control and Prevention (CDC) y del Healthcare Infection Control Practices Advisory Committee (HICPAC)**

**http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5810a4.htm**

Las infecciones por ***Enterobacteriaceae*** **resistentes a carbapenemes o productoras de carbapenemasas (EPC)** han emergido como un importante desafío en los centros de salud. Actualmente, la ***Klebsiella pneumoniae*** **resistente a carbapenemes o productora de carbapenemasas (KPC)** es la especie de EPC más frecuentemente encontrada. La KPC es resistente a casi todos los antibióticos (ATB) disponibles, y la infección con KPC ha sido asociada con altas tasas de morbilidad y mortalidad, especialmente en los pacientes con internación prolongada, y en pacientes críticos multiinvadidos (ventilación mecánica, catáteres, etc.) Desde el 2001 se describe la aparición de KPC en varios lugares del mundo con un comportamiento endémico y epidémico. Su importancia radica en la capacidad que posee de trasmitir resistencia a todos los antibióticos *B* lactamicos limitando las opciones terapéuticas. Las medidas de control para limitar los casos son fundamentales. En Argentina, el primer caso se describe en el 2006 y hasta el momento se ha detectado en 24 de distintas provincias según red Whonet.

**El CDC y el HICPAC han recomendado:**

1.- estrategias estrictas de control de infecciones y precauciones de contacto.

2.- cultivos de prevalencia vigilancia a todos los pacientes internados en el área donde se diagnosticó el caso índice.

3.- cultivos de vigilancia de todos los pacientes ingresados provenientes de áreas con alta prevalencia. Cultivos de vigilancia en todas las áreas consideradas de alto riesgo: cuidados intensivos, salas con alto uso de ATB de amplio espectro, etc. Las muestras de materia fecal, hisopado rectal o perirectal pueden ser superiores al testeo de otras partes de cuerpo (narinas, piel, etc.)

4.- los cultivos de vigilancia deben hacerse hasta que no se identifiquen nuevos casos; la perioricidad de los mismos (1-2 veces/semana, cada 15 días, etc.) dependerá de las posibilidades logísticas de cada institución. Se aconseja como mínimo 1 vez/semana.

5.- en las áreas donde las EPC y especialmente las KPC son endémicas, implementar medidas agresivas para disminuir drásticamente su incidencia y diseminación.

6.- implementación de las guías de Clinical and Laboratory Standards Institute (CLSI) para la detección de la producción de carbapenemasas.

7.- en las áreas donde las EPC y las KPC no son endémicas, si es posible revisar los registros microbiólogicos de los 6-12 meses precedentes para determinar si las mismas han sido recuperadas en las instituciones.

8.- minimizar el uso de carbapenemes a los casos estrictamente necesarios.

9.- implementar cualquier otra estrategia específica de cada institución para disminuir la diseminación y la aparición de nuevos casos. Como ejemplo: reuniones periódicas para evaluar la situación: frecuencia de aparición de nuevos casos, por qué aparacen los nuevos casos, complacencia con las medidas de control de infecciones, necesidad de reforzar las mismas con mayor perioricidad, incrementar la educación, etc.

10- EN **TODOS LOS PACIENTES COLONIZADOS O INFECTADOS CON EPC O KPC SE DEBEN IMPLEMENTAR LAS MEDIDAS DE PRECAUCIONES DE CONTACTO.**

Específicamente, para las KPC, debido al gen productor de carbapenemasa, la diseminación de la misma es muy rápida. En 2007, el CDC reportó que el 8% de todos los aislados de *Klebsiella* fueron KPC, comparado con menos del 1% en 2000.

La KPC posee un desafío terapéutico importante y ha sido asociada a mayor mortalidad y estadía hospitalaria, e incremento de los costos.

Una de las dificultades en la detección de las EPC es que pueden tener una concentración inhibitoria mínima (CIM) elevada pero aún dentro del rango de sensibilidad a los carbapenemes. Como estas cepas son sensibles a los carbapenemes no son identificadas como potenciales riesgos de infección clínica o para la implementación de medidas de control de infecciones usando las guías actuales de testeo de sensibilidad. Por esto, en 2009, el CLSI publicó unas recomendaciones de *Enterobacteriaceae* sensibles a carbapenemes con una CIM elevada o con una zona disminuidad de difusión en disco para detectar la presencia de carbapenemasas usando el test modificado Hodge (MHT). El MHT es un test fenotípico usado para detectar carbapenemasas en aislados que demuestran una CIM elevada pero dentro del rango de sensible a carbapenemes, y ha demostrado una sensibilidad y una especificidad mayor al 90% en identificar *Enterobacteriaceae* productoras de carbapenemasas. Si el MHT revela la presencia de carbapenemasa, el CLSI recomienda que un comentario sea agregado al reporte microbiológico para informar al médico e implementar las

medidas de control de infecciones. Las cepas de *Enterobacteriaceae* con sensibilidad intermedia o resistente a carbapenemes serán reportadas como tales y no necesitan sujetarse al informe de MHT.

Otros reportes recientes han demostrado que la vigilancia microbiológica para las KPC puede ser realizada usando técnicas de cultivos basadas en agar cromogénico y PCR.

Los pacientes con una colonización con KPC no reconocida serán resorvorios para la transmisión y brotes de la misma. Por lo tanto, además de las prácticas de control de infecciones, cultivos de vigilancia deben realizarse a todos los pacientes internados en la misma unidad donde se confirmó la KPC. Todos los pacientes (+) deben ser colocados en precauciones de contacto. El control de los brotes puede ser difícil si no hay una estricta adherencia a las prácticas de control de infecciones.

**MEDIDAS DE CONTROL DE INFECCIONES:**

1.- **lavado de manos antes y después de tocar al paciente y su entorno**. **Cumplir con los 5 momentos siempre**

2.- el personal de salud que atiende al paciente debe vestir camisolín y guantes, los mismos deben ser desechados cuando no se requieran más. **No colgar el camisolín usado dentro de la habitación del paciente para ser usado nuevamente; el camisolín usado debe ser desechado, no se vuelve a usar nuevamente con el mismo paciente ni con otro paciente.**

3.- **no salir de la habitación del paciente colonizado o infectado con los guantes y el camisolín con que se está atendiendo al paciente**. Si el personal necesita salir, debe desechar el camisolín y los guantes, y colocarse unos nuevos al volver a entrar.

4.- **no trasladar elementos, insumos o cualquier otro dispositivo de la habitación del paciente colonizado o infectado a otra habitación de un paciente no afectado.** Todo lo que el paciente necesita, debe estar en cantidad suficiente dentro de la habitación y reponer lo que se usa todas las veces que fuere necesario para evitar salir de la habitación a buscar el insumo.

5.- **una vez que el paciente colonizado o infectado es dado de alta o fallece, todo los insumos descartables que quedaron dentro de la habitación y no fueron usados, aunque no se hayan abierto, deben ser desechados.** Los reusables, deben ser adecuadamente decontaminados, esterilizados, y toda la habitación: paredes, pisos, cama, puertas, monitores, respirador, bombas de infusión, ventanas, etc. deben ser profundamente limpiados y decontaminados. **Limpieza terminal**

6.- **los pacientes pueden ser "cohortizados",** es decir, colocar en una misma habitación (si la habitación es para 2 ó más pacientes) 2 ó más pacientes colonizados/infectados con EPC o KPC.

7- Si el paciente se deriva a otra sala y/o institución avisar a médicos y enfermeras que el paciente se encuentra colonizado/infectado por EPC y cohortizarlo en habitaciones individuales o con pacientes con el mismo germen.

8- Limitar el traslado de estos pacientes. Si fuera inevitable, el personal que lo traslada deberá colocarse el equipo de protección personal (camisolín y guantes).

9- Informar a la familia de las medidas adoptadas para los pacientes colonizados.

La duración del aislamiento se desconoce aún. Algunos lo continúan durante toda la internación del paciente y otros le retiran el aislamiento con 3 hisopados negativos consecutivos separados por 1 semana como mínimo. La elección dependerá de las características y políticas de cada institucion.

**TRATAMIENTO:**

Los ATBs que parecen ser efectivos contra las EPC y las KPC son: Tigeciclina, Colistin, Amikacina y Fosfomicina. De todos modos, estos ATB deben ser testeados en el laboratorio de microbiología. También es posible buscar sinergia entre los mismos para incrementar la eficacia terapéutica.

Las dosis de estos ATBs son las habitualmente usadas para infecciones producidas por otros BGN no productores de carbapenemasas.

**ABSTRACTS DE BIBLIOGRAFÍA RECOMENDADA:**

Infect Control Hosp Epidemiol. 2010 Dec;31(12):1250-6. Epub 2010 Oct 25.

**Bloodstream infections caused by metallo-β-lactamase/Klebsiella pneumoniae Carbapenemase-producing K. pneumoniae among intensive care unit patients in Greece: risk factors for infection and impact of type of resistance on outcomes.**

Mouloudi E, Protonotariou E, Zagorianou A, Iosifidis E, Karapanagiotou A, Giasnetsova T, Tsioka A, Roilides E, Sofianou D,Gritsi-Gerogianni N.

Intensive Care Unit, Hippokration General Hospital, Thessaloniki, Greece.

**Abstract**

**OBJECTIVE:** To determine risk factors for bloodstream infections (BSIs) caused by Klebsiella pneumoniae producing metallo-β-lactamases (MBLs) or K. pneumoniae carbapenemases (KPCs), as well as risk factors for mortality

associated with carbapenem-resistant K. pneumoniae, among intensive care unit (ICU) patients.

**METHODS:** Two case-control studies were conducted in a patient cohort with K. pneumoniae BSIs in an 8-bed ICU in a Greek hospital from January 1, 2007, through December 31, 2008. In study 1, patients with K. pneumoniae BSIs were allocated among 3 groups according to isolate susceptibility profile: (1) carbapenem-susceptible insolates (control group), (2) MBL-producing isolates, or (3) KPC-producing isolates. The MBL and KPC groups were compared with the control group to identify risk factors for development of K. pneumoniae BSI. In study 2, patients with K. pneumoniae BSIs who died were compared with survivors to identify risk factors for mortality.

**RESULTS:** Fifty-nine patients had K. pneumoniae BSIs (22 with carbapenem-susceptible isolates, 18 with MBL-producing isolates, and 19 with KPC-producing isolates). All KPC-producing isolates carried the bla(KPC-2) gene, and 17 of 18 MBL-producing isolates carried bla(VIM-1). Acute Physiology and Chronic Health Evaluation II score (odds ratio, 1.13 [95% confidence interval, 1.03-1.25]; [Formula: see text]) was independently associated with KPC-producing K. pneumoniae BSIs. Nine (41%) of 22 control patients, 8 (44%) of 18 MBL group patients, and 13 (68%) of 19 KPC group patients died in the ICU. Nine (41%) of 22 control patients, 10 (56%) of 18 MBL group patients, and 15 (79%) of 19 KPC group patients died in the hospital. Isolation of KPC-producing K. pneumoniae was an independent predictor of ICU death ([Formula: see text]) and in-hospital death ([Formula: see text]) but not infection-attributable death.

**CONCLUSIONS:** BSIs due to KPC-producing K. pneumoniae resulted in significantly increased mortality. The accurate and rapid detection of these pathogens is necessary for therapeutic considerations and for the implementation of infection control measures to contain them.

Emerg Infect Dis. 2010 Sep;16(9):1349-56.

**Worldwide diversity of Klebsiella pneumoniae that produce beta-lactamase blaKPC-2 gene.**

Cuzon G, Naas T, Truong H, Villegas MV, Wisell KT, Carmeli Y, Gales AC, Venezia SN, Quinn JP, Nordmann P.

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**Abstract**

Klebsiella pneumoniaeisolates that produce carbapenemases (KPCs) are rapidly disseminating worldwide. To determine their genetic background, we investigated 16 blaKPC-2-harboring K. pneumoniae isolates from 5 countries. The isolates were multidrug resistant, possessed the blaKPC-2 gene, and differed by additional Beta-lactamase content. They harbored a naturally chromosome-encoded bla gene (blaSHV-1 [12.5%], blaSHV-11 [68.7%], or blaOKP-AVB [18.8%]) and several acquired and plasmid-encoded genes (blaTEM-1 [81.3%], blaCTX-M-2 [31.3%],

blaCTX-M-12 [12.5%], blaCTX-M-15 [18.7%], and blaOXA-9 [37.5%]). The blaKPC-2 gene was always associated with 1 of the Tn4401 isoforms (a, b, or c). Tn4401 was inserted on different-sized plasmids that belonged to different incompatibility groups. Several blaKPC-containing K. pneumoniae clones were found: 9 different pulsotypes with 1 major (sequence type 258) and 7 minor distinct allelic profiles. Different clones harboring different plasmids but having identical genetic structure, Tn4401, could be at the origin of the worldwide spread of this emerging resistance gene.

J Antimicrob Chemother. 2010 Jun;65(6):1119-25. Epub 2010 Apr 8.

**Detection and treatment options for Klebsiella pneumoniae carbapenemases (KPCs): an emerging cause of multidrug-resistant infection.**

Hirsch EB, Tam VH.

University of Houston College of Pharmacy, and St Luke's Episcopal Hospital, Houston, TX, USA.

**Abstract**

Bacteria producing Klebsiella pneumoniae carbapenemases (KPCs) are rapidly emerging as a cause of multidrug-resistant infections worldwide. Bacterial isolates harbouring these enzymes are capable of hydrolysing a broad spectrum of beta-lactams including the penicillins, cephalosporins, carbapenems and monobactam. Detection of isolates harbouring carbapenemases can be inconsistent using automated systems, often requiring subsequent confirmatory tests. Phenotypic methods utilizing boronic acid disc tests have demonstrated promising results and appear practical for use in clinical microbiology laboratories. Treatment of infection caused by KPC bacteria is particularly worrisome as the carbapenems are often agents of the last resort for resistant Gram-negative infections. The optimal treatment of infections caused by KPC bacteria is not well established and clinical outcome data remain sparse. We reviewed the current literature regarding clinical outcomes following KPC infections, with a specific effort to summarize the clinical data available for specific antimicrobial agents. A total of 15 papers involving 55 unique patient cases were reviewed. While the total number of patients is relatively small, some useful insights could still be gathered to guide clinicians in the management of KPC infections. Tigecycline and the aminoglycosides were associated with positive outcomes in the majority of cases. Clinical success rates were low when the polymyxins were used as monotherapy, but were much higher when they were used in combination. Studies examining combination therapy and

well-controlled clinical trials are needed to ascertain the optimal treatment of infections caused by KPC bacteria.

Clin Infect Dis. 2010 Feb 1;50(3):364-73.

**An outbreak of infection due to beta-Lactamase Klebsiella pneumoniae Carbapenemase 2-producing K. pneumoniae in a Greek University Hospital: molecular characterization, epidemiology, and outcomes.**

Souli M, Galani I, Antoniadou A, Papadomichelakis E, Poulakou G, Panagea T, Vourli S, Zerva L, Armaganidis A,Kanellakopoulou K, Giamarellou H.

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**Abstract**

**BACKGROUND:** We describe the emergence and spread of Klebsiella pneumoniae carbapenemase 2 (KPC-2)-producing K. pneumoniae at a Greek University hospital.

**METHODS:** Isolates with a carbapenem minimum inhibitory concentration >1 microg/mL and a negative EDTA-imipenem disk synergy test result were submitted to boronic acid disk test and to polymerase chain reaction (PCR) for KPC gene and sequencing. Records from patients who had KPC-2-producing K. pneumoniae isolated were retrospectively reviewed. Clinical isolates were submitted to molecular typing using pulsed-field gel electrophoresis, and the beta-lactamase content was studied using isoelectric focusing and PCR.

**RESULTS:** From January 2007 through December 2008, 50 patients (34 in the intensive care unit [ICU]) were colonized (n = 32) or infected (n = 18) by KPC-2-producing K. pneumoniae. Increasing prevalence of KPC-2-producing K. pneumoniae coincided with decreasing prevalence of metallo-beta lactamase-producing isolates in our ICU. Multidrug resistance characterized the studied isolates, with colistin, gentamicin, and fosfomycin being the most active agents. Besides KPC-2, clinical isolates encoded TEM-1-like, SHV-11, SHV-12, CTX-M-15, and LEN-19 enzymes. Four different clonal types were detected; the predominant one comprised 41 single patient isolates (82%). Sporadic multiclonal cases of KPC-2-producing K. pneumoniae infection were identified from September 2007 through May 2008. The outbreak strain was introduced in February 2008 and disseminated rapidly by cross-transmission; 38 patients (76%) were identified after August 2008. Fourteen cases of bacteremia, 2 surgical site infections, 2 lower respiratory tract infections (1 bacteremic), and 1 urinary tract infection were

identified. Most patients received a colistin-containing combination treatment. Crude mortality was 58.8% among ICU patients and 37.5% among non-ICU patients, but attributable mortality was 22.2% and 33.3%, respectively.

**CONCLUSIONS:** The emergence of KPC-2-producing K. pneumoniae in Greek hospitals creates an important challenge for clinicians and hospital epidemiologists, because it is added to the already high burden of antimicrobial resistance.

J Hosp Infect. 2010 Sep;76(1):70-3. Epub 2010 Jun 17.

**Hospital outbreak caused by Klebsiella pneumoniae producing KPC-2 beta-lactamase resistant to colistin.**

Kontopoulou K, Protonotariou E, Vasilakos K, Kriti M, Koteli A, Antoniadou E, Sofianou D.

Department of Clinical Microbiology, G. Gennimatas General Hospital, Thessaloniki, Greece.

**Abstract**

We describe a hospital outbreak caused by colistin-resistant Klebsiella pneumoniae producing KPC-2 beta-lactamase in two distinct medical centres. Seven clinical isolates of K. pneumoniae exhibiting resistance to carbapenems were collected from patients with hospital-acquired infection. All isolates were phenotypically positive for carbapenemase activity but negative for metallo-beta-lactamase production. PCR analysis using specific primers for bla(KPC), bla(SHV), bla(TEM) and bla(CTX-M) demonstrated that all clinical strains of K. pneumoniae from hospital A and one isolate from hospital B were genetically related and carried bla(KPC-2) in addition to bla(SHV-12). In contrast, the remaining isolate carried bla(S)(HV-5) with bla(K)(PC-2) and yielded a different profile. These results indicate the clonal spread of KPC producers between hospitals as well as the acquisition of KPC genes by different K. pneumoniae strains. All isolates were resistant to carbapenems, beta-lactams, ciprofloxacin, aminoglycosides and colistin, but intermediately susceptible to tigecycline and susceptible to gentamicin. The infection was fatal in five cases. The emergence of colistin-resistant K. pneumoniae possessing bla(KPC)(-2) underscores the implementation of strict control measures to prevent their dissemination of these organisms in hospitals.

J Clin Microbiol. 2010 Oct;48(10):3558-62. Epub 2010 Aug 4.

**In vitro evaluation of antibiotic synergy for polymyxin B-resistant carbapenemase-producing Klebsiella pneumoniae.**

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**Abstract**

Since carbapenemase-producing Klebsiella pneumoniae strains were first reported in North Carolina, these highly resistant organisms have been isolated with increasing frequency, especially in the New York City area. Polymyxin B is one of the few antimicrobials that retain reliable activity against these organisms. However, polymyxin B MICs are elevated against K. pneumoniae isolates with increasing frequency, leaving clinicians with few therapeutic options. We investigated several antimicrobial agents for potential synergy with polymyxin B against 12 clinical strains of carbapenemase-producing K. pneumoniae. A broth microdilution assay using a 96-well plate was developed in which graded dilutions of polymyxin B and the study drug were incubated with resistant isolates in a checkerboard pattern. Polymyxin B was studied in combination with cefazolin, ceftriaxone, cefepime, imipenem, gentamicin, tigecycline, doxycycline, and rifampin. All K. pneumoniae strains tested positive for K. pneumoniae carbapenemase (KPC) genes by real-time PCR and had elevated polymyxin B MIC values ranging from 16 to 128 μg/ml. Synergy was observed with the combination of polymyxin B and rifampin as well as with polymyxin B and doxycycline, resulting in at least a 4-fold decrease in the polymyxin B MIC. For both combinations, this effect occurred at physiologically achievable concentrations. Less pronounced synergy was noted with tigecycline and polymyxin B. No synergy was observed at physiologic concentrations with the other antimicrobials studied. These results suggest that rifampin, doxycycline, and tigecycline may be useful additions to polymyxin B in the treatment of infections caused by highly resistant carbapenemase-producing K. pneumoniae. Further studies are warranted to determine if these in vitro findings translate into clinical efficacy.

J Antimicrob Chemother. 2010 Jun;65(6):1119-25. Epub 2010 Apr 8.

**Detection and treatment options for Klebsiella pneumoniae carbapenemases (KPCs): an emerging cause of multidrug-resistant infection.**

Hirsch EB, Tam VH.

University of Houston College of Pharmacy, and St Luke's Episcopal Hospital, Houston, TX, USA.

**Abstract**

Bacteria producing Klebsiella pneumoniae carbapenemases (KPCs) are rapidly emerging as a cause of multidrug-resistant infections worldwide. Bacterial isolates harbouring these enzymes are capable of hydrolysing a broad spectrum of beta-lactams including the penicillins, cephalosporins, carbapenems and monobactam. Detection of isolates harbouring carbapenemases can be inconsistent using automated systems, often requiring subsequent confirmatory tests. Phenotypic methods utilizing boronic acid disc tests have demonstrated promising results and appear practical for use in clinical microbiology laboratories. Treatment of infection caused by KPC bacteria is particularly worrisome as the carbapenems are often agents of the last resort for resistant Gram-negative infections. The optimal treatment of infections caused by KPC bacteria is not well established and clinical outcome data remain sparse. We reviewed the current literature regarding clinical outcomes following KPC infections, with a specific effort to summarize the clinical data available for specific antimicrobial agents. A total of 15 papers involving 55 unique patient cases were reviewed. While the total number of patients is relatively small, some useful insights could still be gathered to guide clinicians in the management of KPC infections. Tigecycline and the aminoglycosides were associated with positive outcomes in the majority of cases. Clinical success rates were low when the polymyxins were used as monotherapy, but were much higher when they were used in combination. Studies examining combination therapy and well-controlled clinical trials are needed to ascertain the optimal treatment of infections caused by KPC bacteria.

Clin Microbiol Infect. 2010 Mar 6. [Epub ahead of print]

**Intercontinental spread from Israel to Colombia of a KPC-3-producing Klebsiella pneumoniae strain.**

Lopez JA, Correa A, Navon-Venezia S, Correa AL, Torres JA, Briceño DF, Montealegre MC, Quinn JP, Carmeli Y, Villegas MV.

Hospital Pablo Tobón Uribe, Medellín, Colombia.

**Abstract**

Clin Microbiol Infect Abstract In 2008, an increase in the prevalence of carbapenem-resistant Klebsiella pneumoniae was noted in a 286-bed tertiary case hospital in Colombia, where 84 patients (32 infected and 52 colonized) had positive cultures. The identified index patient came from Israel for a liver transplantation. High level carbapenem resistance was observed. Polymyxin B and tigecycline were the only two antibiotics that remained active. PCR-restriction fragment length

polymorphism analysis and sequencing revealed bla(KPC-3) in the major clone, which was indistinguishable from the K. pneumoniae carbapenemase-3-producing clone described previously in Israel. This exemplifies the threat posed by the global spread of K. pneumoniae carbapenemase-producing pathogens.

Microb Drug Resist. 2010 Mar;16(1):61-5.

**Antimicrobial susceptibility patterns of KPC-producing or CTX-M-producing Enterobacteriaceae.**

Castanheira M, Sader HS, Jones RN.

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**Abstract**

Enterobacteriaceae clinical isolates harboring KPC-(178 strains) or CTX-M-encoding (67 strains) genes were collected during surveillance programs in the 2000-2007 period; and susceptibility was tested by broth microdilution methods. Organisms were dominantly collected in U.S. hospitals (93%). CTX-M-15 and -14 were the most prevalent CTX-M types (97%), all collected from the United States. KPC producers were isolated in the United States (160/178), Israel, China, and Argentina. bla(CTX-M)-carrying isolates were 95.5 and 98.5%, susceptible to Imipenem and meropenem respectively, and were all susceptible to tigecycline, whereas KPC-producing isolates were highly resistant to all antimicrobials tested except polymyxin B and tigecycline (90.6% and 99.4% susceptibility, respectively). The occurrence of KPC-producing and CTX-M-producing isolates has rapidly increased especially in U.S. hospitals, and expanded therapeutic options are needed to treat infections caused by these emerging organisms.

Antimicrob Agents Chemother. 2010 Jan;54(1):526-9. Epub 2009 Nov 9.

**In vitro activity of fosfomycin against blaKPC-containing Klebsiella pneumoniae isolates, including those nonsusceptible to tigecycline and/or colistin.**

Endimiani A, Patel G, Hujer KM, Swaminathan M, Perez F, Rice LB, Jacobs MR, Bonomo RA.

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**Abstract**

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

Ned Tijdschr Geneeskd. 2010;154:A1947.

**Carbapenem resistance in gram-negative bacteria.**

[Article in Dutch]

Bonten MJ, Kluytmans J, Kulberg BJ.

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**Abstract**

Antibiotic resistance poses a serious threat to the successful treatment of hospitalized patients. Micro-organisms that produce carbapenamases, such as Klebsiella pneumoniae carbapenamases (KPCs) represent the next step in the continuously emerging problem of antibiotic resistance. Restrictions on antibiotic use plus optimal adherence to infection control measures will be crucial to limit the spread of KPC in hospitals in the Netherlands in the coming years.

Infect Control Hosp Epidemiol. 2009 Jul;30(7):666-71.

**Carbapenem resistance among Klebsiella pneumoniae isolates: risk factors, molecular characteristics, and susceptibility patterns.**

Hussein K, Sprecher H, Mashiach T, Oren I, Kassis I, Finkelstein R.

Infectious Diseases Unit, Rambam Medical Center, Haifa, Israel.

**Abstract**

**BACKGROUND:** Carbapenem resistance among isolates of Klebsiella pneumoniae has been unusual.

**OBJECTIVES:** To identify risk factors for infection with carbapenem-resistant K. pneumoniae (CRKP) and to characterize microbiological aspects of isolates associated with these infections.

**DESIGN:** Retrospective case-control study.

**SETTING:** A 900-bed tertiary care hospital.

**RESULTS:** From January 2006 through April 2007, K. pneumoniae was isolated from 461 inpatients; 88 had CRKP infection (case patients), whereas 373 had carbapenem-susceptible K. pneumoniae infection (control subjects). The independent risk factors for infection with CRKP were prior fluoroquinolone use (odds ratio [OR], 1.87 [95% confidence interval [CI], 1.07-3.26]; P=.026), previous receipt of a carbapenem drug (OR, 1.83 [95% CI, 1.02-3.27]; P=.042), admission to the intensive care unit (OR, 4.27 [95% CI, 2.49-7.31]; P<.001), and exposure to at least 1 antibiotic drug before isolation of K. pneumoniae (OR, 3.93 [95% CI, 1.15-13.47]; P=.029). All CRKP isolates carried the bla(KPC) gene. Approximately 90% of the tested isolates carried the bla(KPC-2) allele, suggesting patient-to-patient transmission. Almost all CRKP isolates were resistant to all antibiotics, except to colistin (resistance rate, 4.5%), gentamicin (resistance rate, 7%), and tigecycline (resistance rate, 15%).

**CONCLUSIONS:** CRKP should be regarded as an emerging clinical threat. Because these isolates are resistant to virtually all commonly used antibiotics, control of their spread is crucial.

F1000 Med Rep. 2009 Oct 14;1. pii: 79.

**Management of infections due to KPC-producing Klebsiella pneumoniae.**

Deresinski SC, Schirmer P.

**Abstract**

The emergence of the Klebsiella pneumoniae carbapenemases in K. pneumoniae and other Gram-negative bacteria, usually on a background of multidrug resistance, has led to difficult therapeutic choices. Among available antibiotics, tigecycline and the polymyxins are the most frequently active against these organisms in vitro. Optimal therapy of infections due to these bacteria may involve maximization of antibiotic dose as well as their use in combination.

J Clin Microbiol. 2009 Feb;47(2):322-6. Epub 2008 Nov 26.

**Development and evaluation of a real-time PCR assay for detection of Klebsiella pneumoniae carbapenemase genes.**

Cole JM, Schuetz AN, Hill CE, Nolte FS.

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**Abstract**

We developed a novel real-time PCR assay to detect Klebsiella pneumoniae carbapenemases (KPCs) and used this assay to screen clinical isolates of K. pneumoniae and Klebsiella oxytoca for the presence of bla(KPC) genes. The TaqMan real-time PCR assay amplified a 399-bp product from the bla(KPC) gene. The amplicon was designed so that the genes for isoenzymes KPC-1, -2, and -3 could be easily distinguished by subsequent restriction digestion of the amplicon with the enzymes BstNI and RsaI. The assay was validated with reference strains obtained from the Centers for Disease Control and Prevention that contained each of the three described isoenzymes and 69 extended-spectrum beta-lactamase-producing clinical isolates (39 K. pneumoniae and 30 K. oxytoca isolates). Subsequently, the bla(KPC) PCR assay was used to confirm the presence of bla(KPC) genes in any meropenem-resistant Klebsiella spp. The PCR assay detected bla(KPC) in all of the reference strains, in 6 of 7 meropenem-resistant isolates, and in 0 of 62 meropenem-susceptible clinical isolates. The PCR assay was then used to confirm the presence of bla(KPC) in an additional 20 meropenem-resistant isolates from 16 patients. Restriction digestion of the PCR amplicons identified two bla(KPC) gene variants in our patient population: 9 isolates with C and 17 with T at nucleotide 944, consistent with bla(KPC-2) and bla(KPC-3), respectively. The real-time PCR assay is a rapid and accurate method to detect all KPC isoenzymes and was useful in documenting the presence and dissemination of KPC-producing strains in our patient population.

Lancet Infect Dis. 2009 Apr;9(4):228-36.

**The real threat of Klebsiella pneumoniae carbapenemase-producing bacteria.**

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**Abstract**

From early this decade, Enterobacteriaceae that produce Klebsiella pneumoniae carbapenemases (KPC) were reported in the USA and subsequently worldwide. These KPC-producing bacteria are predominantly involved in nosocomial and systemic infections; although they are mostly Enterobacteriaceae, they can also be, rarely, Pseudomonas aeruginosa isolates. KPC beta lactamases (KPC-1 to KPC-7) confer decreased susceptibility or resistance to virtually all beta lactams.

Carbapenems (imipenem, meropenem, and ertapenem) may thus become inefficient for treating enterobacterial infections with KPC-producing bacteria, which are, in addition, resistant to many other non-beta-lactam molecules, leaving few available therapeutic options. Detection of KPC-producing bacteria may be difficult based on routine antibiotic susceptibility testing. It is therefore crucial to implement efficient infection control measures to limit the spread of these pathogens.

J Clin Microbiol. 2009 Mar;47(3):785-6. Epub 2009 Jan 14.

**Specificity of ertapenem susceptibility screening for detection of Klebsiella pneumoniae carbapenemases.**

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**Abstract**

Detection of Klebsiella pneumoniae carbapenemases (KPCs) can be nonspecific, especially when KPCs are uncommon. We determined the positive predictive value and specificity of ertapenem resistance for KPC detection in 2,696 Enterobacteriaceae isolates. The positive predictive value and specificity of ertapenem resistance for KPC detection were 74% and 99.2%, respectively.

Int J Antimicrob Agents. 2007 Dec;30(6):525-9. Epub 2007 Oct 10.

**Outbreak of carbapenem-resistant Klebsiella pneumoniae producing KPC-3 in a tertiary medical centre in Israel.**

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**Abstract**

This report describes an outbreak of carbapenem-resistant KPC-3-producing Klebsiella pneumoniae outside the USA. Ninety patients from different departments of a tertiary medical centre were diagnosed with carbapenem-resistant, extended-spectrum beta-lactamase (ESBL)-negative Klebsiella pneumoniae infection by standard methods over a 10-month period in 2006. Fifteen randomly selected outbreak isolates were subjected to randomly amplified polymorphic DNA (RAPD) polymerase chain reaction (PCR) as well as PCR amplification and sequencing of the KPC genes, and the findings were compared with two carbapenem-susceptible

K. pneumoniae isolates (one ESBL-positive and one ESBL-negative). All the outbreak isolates were resistant to all fluoroquinolones and beta-lactam antibiotics tested, including carbapenems, and were sensitive only to colistin, gentamicin and most of them also to tigecycline. On RAPD-PCR, all 15 outbreak isolates were identical to each other and clearly distinguishable from control strains, indicating clonality. The KPC-3 enzyme was identified by nucleotide sequencing analysis in all outbreak isolates but not in the control strains. These findings should alert government and medical authorities to institute stringent control measures and to initiate research into therapeutic and preventive strategies.

Pharmacotherapy. 2007 Jul;27(7):1052-7.

**Tigecycline for treatment of pneumonia and empyema caused by carbapenemase-producing Klebsiella pneumoniae.**

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**Abstract**

Strains of Klebsiella pneumoniae that produce one of three possible carbapenemases--KPC--have recently been identified with increasing frequency among isolates recovered from patients residing along the East Coast of the United States, particularly within the New York City metropolitan region. These strains have exhibited resistance to multiple antibiotic classes, including carbapenem agents. We report a case of nosocomial pneumonia and empyema caused by a KPC-producing isolate of K. pneumoniae at a large midwestern U.S. tertiary care facility in which the patient was treated with tigecycline. Although the pneumonia was treated successfully, the empyema recurred in association with a treatment-emergent tigecycline minimum inhibitory concentration (MIC) increase from 0.75 to 2 microg/ml. Clinicians should be aware of the potential occurrence of this treatment-emergent MIC increase, especially in the setting of sustained tigecycline therapy. In addition, the emergence of carbapenem-resistant Enterobacteriaceae reinforces the importance of antibiotic stewardship and strict infection control practices.

Clin Infect Dis. 2006 Aug 1;43(3):e26-8. Epub 2006 Jun 19.

**The spread of Klebsiella pneumoniae carbapenemase-producing K. pneumoniae to upstate New York.**

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**Abstract**

Klebsiella pneumoniae carbapenemases (KPCs) have previously been identified in distinct geographic locations. We report the spread of KPC-2 to upstate New York. Our intention is to alert clinicians to problems encountered in identifying KPC-containing isolates. Possible errors as a result of inferring susceptibility of untested carbapenems from the routine antibiogram using agar-based methodology or microdilution testing are discussed.

J Antimicrob Chemother. 2005 Jul;56(1):128-32. Epub 2005 May 25.

**Carbapenemase-producing Klebsiella pneumoniae in Brooklyn, NY: molecular epidemiology and in vitro activity of polymyxin B and other agents.**

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**Abstract**

**OBJECTIVES:** To describe the molecular epidemiology of carbapenem-resistant Klebsiella pneumoniae in Brooklyn, NY and assess the in vitro activity of various antibiotic combinations.

**METHODS:** Clinical isolates with suspected carbapenem resistance were referred to the central research laboratory from August 2003 to June 2004. Isolates underwent MIC testing, ribotyping, and were analysed for the presence of KPC carbapenemases. Time-kill studies using various antibiotic(s) were performed on selected isolates.

**RESULTS:** Ninety-six isolates were referred from 10 Brooklyn hospitals. All isolates were resistant to the carbapenems with most having MICs >32 mg/L. Few were susceptible to fluoroquinolones and cephalosporins; approximately half were susceptible to aminoglycosides, and 90% to polymyxin B. Two-thirds were susceptible to doxycycline, and all were considered susceptible to the investigational glycylcycline antibiotic tigecycline. Virtually all possessed bla(KPC), and over 80% belonged to one ribotype. In time-kill studies involving 16 isolates, tigecycline demonstrated bacteriostatic activity and polymyxin B concentration-dependent bactericidal activity. The combination of polymyxin B at 0.5 x MIC plus

rifampicin had synergic activity against 15/16 isolates, including two polymyxin-resistant strains. The combination of polymyxin B plus imipenem had synergic bactericidal activity against 10/16 isolates, but was antagonistic for three isolates.
**CONCLUSIONS:** Multiresistant K. pneumoniae with bla(KPC) are present in multiple hospitals in New York City. The most consistently active agents in vitro were tigecycline and polymyxin B, particularly when the latter was combined with rifampicin. The clinical efficacy of these agents remains to be determined.