Leveraging antimicrobial stewardship into improving rates of carbapenem-resistant Enterobacteriaceae

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ABSTRACT
Carbapenem-resistant Enterobacteriaceae (CRE) are among the most critical threats facing our healthcare system and account for significant patient mortality. There is considerable interest in the development of new treatment strategies. However, less attention has been paid to reducing CRE infection rates. Antibiotic stewardship programs can be uniquely empowered to reduce widespread pathogen resistance and by extension, optimize patient care and lower healthcare costs.

Defining antibiotic stewardship
Antimicrobial therapy has allowed for rapid advancements in the field of medicine and has had a tremendous impact in patient survival from previously lethal infectious conditions. Prompt initiation of antibiotics has been proven to reduce morbidity and mortality. Despite the significant benefit of antimicrobials, inappropriate and unnecessary use risks adverse drug reactions, Clostridium difficile infection, and selection for more resistant pathogens without a clinical benefit. It is estimated that 20–50% of all antibiotics prescribed in US acute care hospitals are either unnecessary or inappropriate.1,2 As a result, the Centers for Disease Control and Prevention (CDC) estimates greater than 2 million people are infected with antibiotic-resistant organisms, resulting in at least 23,000 deaths each year.1

In reaction to this growing health and public safety crisis of antibiotic-resistant organisms, the President’s Council of Advisors on Science and Technology (PCAST) and the CDC have made improvement of antibiotic use a key priority with Antibiotic Stewardship Programs (ASPs) a core part of this initiative.1,3

Antimicrobial stewardship focuses on optimizing antimicrobial use in regard to selection, dosing, and duration, while minimizing toxicity. CDC guidelines for ASP highlight core principles of leadership commitment, accountability and drug expertise, surveillance and monitoring of antibiotic use and resistance patterns, and providing education.1 These principles are consistent with Infectious Disease Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines which stress the collaboration between antimicrobial stewardship teams, hospital infection control, and pharmacy and therapeutics committees, all in conjunction with support of hospital administration.4

The goal of antimicrobial stewardship is an improvement in patient safety, reduced treatment failures, reduced healthcare expenditures, and a reduction in the selective pressures leading to resistant bacteria. Antimicrobial stewardship programs achieve these objectives by combining a variety of targeted interventions. This includes prospective antibiotic use audit with direct interventions and feedback. ASP should also be involved in determining formulary restriction, implementing educational objectives, and forming clear clinical guidelines and pathways which standardize and streamline antibiotic de-escalation as well as dose optimization.4 Of critical importance, is the consistent finding that under the direction of an ASP, significant reductions in antimicrobial usage occur without a concurrent rise in patient morbidity. As an example, integration of an ASP at an entire tertiary care health system resulted in post-intervention reductions in antimicrobial costs and reductions in rates of key nosocomial infections.5 Another study evaluating the impact of ASP at tertiary hospitals also found a dramatic reduction in antimicrobial use without an increase in patient morbidity.2

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**Carbapenem-resistant Enterobacteriaceae**

Carbapenemase-producing Enterobacteriaceae (CRE) are among the most feared pathogens within health systems and are of considerable interest in development of new treatment strategies. These bacteria are of the highest priority as they are typically resistant to all preferred therapeutic options, and have only less desirable treatment options available, if any. Resistance to carbapenems in CRE is most commonly mediated by the serine *Klebsiella Pneumoniae* Carbapenemase (KPC) or the New Delhi metallo-β-lactamase (NDM). Serine carbapenemases are more common, and remain the predominant mechanism, in the US. In contrast, metallo-β-lactamases predominate in much of Asia. Kitchel et al. from the US Centers for Disease Control performed molecular typing of strains accumulated from 33 US states, as well as Israel and India and found a single strain, ST258, accounted for 70% of isolates.6 Both KPC and NDM resistance is mediated by transmissible plasmids which has allowed for rapid proliferation and endemic spread throughout the United States, as well as throughout Europe, Asia, and Latin America.6-12

The limited treatment options for CRE pathogens have resulted in alarming mortality rates. In multiple studies, infection due to KPC-producing *K. pneumoniae* was independently associated with in-hospital mortality. Case-control studies have consistently shown mortality rates ranging from 32 to 44% for infections caused by carbapenem-resistant versus 9 to 13% for carbapenem-susceptible *K. pneumoniae*.13-15 Critically, mortality was even higher (61%) in patients infected with KPC-expressing *K. pneumoniae* who received initially ineffective therapy.11 New ways to prevent or treat infections caused by these extremely drug resistant (XDR) bacteria are critically needed, especially given the dearth of antibiotics to treat them.16 As such, an emphasis on our collective responsibility to preserve and protect the current limited and exhaustible supply of antimicrobials is necessary. Enhancements in infection prevention, disinfection, decontamination, and the use of rapid diagnostics in collaboration with stewardship activities remain a key mechanism in which to achieve this objective.17

**Antimicrobial exposure as a risk factor for CRE**

A major area of study has been focused upon clarifying the predisposing factors for CRE. Infection caused by KPC-expressing *K. pneumoniae* was independently associated with receipt of mechanical ventilation, longer lengths of hospitalization, and exposure to extended spectrum cephalosporins and carbapenems.13,15,18 Additionally, other case series found a consistent relationship whereas exposure to fluoroquinolones, carbapenems, and anti-pseudomonal penicillins acted as independent risk factors for carbapenem-resistant infections.13,18

Although each antimicrobial exerts a selective pressure for and development of CRE, another critical factor is the duration of antimicrobial exposure. Kritsotakis et al, showed that the risk of extended spectrum β-lactamase (ESBL) and CRE *Klebsiella* increased with longer durations of β-lactam/β-lactamase inhibitor exposure with an odds ratio increase of 1.15 per day.19

Another critical, but incompletely understood determinant in CRE selection is the interaction between concurrent antimicrobial combinations. There is evidence to support an association between development of KPC and prior fluoroquinolone use. Specifically, plasmid encoded qnr genes, which convey low-level fluoroquinolone resistance, are often present in the same conjugative plasmid as KPC genes.13 Consistent with this finding, Kristotakis, showed that increased duration of fluoroquinolones amplified the impact of exposure of carbapenems on ESBL and CRE infection risk.19

Certainly, infection represents the end result, and tip-of-the-iceberg, of nosocomial CRE encounters. A large reservoir of these organisms can be found colonizing patients, for example as part of enteral flora or as bacteriuria; indeed the intestine under selective antimicrobial pressure can become densely colonized with drug-resistant organisms.20 While colonization itself does not directly cause disease, it is a precursor to disease, as injury and loss of mucosal integrity allows for translocation, deep tissue, and bloodstream infection from a colonizing source.20 Consistent with this hypothesis, studies have shown that intestinal colonization precedes bloodstream infection with vancomycin-resistant enterococcus (VRE) and drug-resistant *K. pneumoniae*.20 This suggests the loss of colonization resistance, or the ability of the internal microbiota to resist expansion and persistence of exogenous species, represents an early step in the pathophysiology of infection. An overall reduction in total burden of CRE may concurrently have a subsequent clinical impact.

Clearly, indiscriminate and prolonged carbapenem use is among the most significant factors favoring the development of CRE. However, combatting the proliferation of CRE may be more complicated than simply curtailing carbapenem administration or reducing gross utilization of any single agent. Patel, et al, found that the only factor independently associated with CRE in multivariate analyses was the cumulative number of prior antibiotic exposures.21 The risk of CRE was highlighted by an increasing odds ratio of 1.43, 2.05, and 2.93, for 1, 2 and ≥ 3 antibiotic exposures, respectively.21 Therefore, it stands to reason that the cumulative selective pressure of multiple antimicrobial agents predisposes for CRE. ASP interventions are uniquely positioned to exert an effect on multiple determinants for CRE by broadly
reducing inappropriate antimicrobial use, expediting targeted narrow spectrum therapy, and establishing institutional evidence based guidelines for the appropriate treatment and duration of common infectious syndromes.

Prior attempts to reduce CRE

Antimicrobial stewardship has a direct role in both the reduction of inappropriate antimicrobial use and optimizing targeted therapy. Consequently, judicious antimicrobial use would be expected to reduce the selective pressure favoring these highly resistant pathogens. As a key caveat, many attempts to assess the association between antibiotic consumption and resistance have been attempted but the results have been inconsistent and this association was not uniform among all antibiotic-organism pairs. A potential explanation for this inconsistency is that proliferation of resistant pathogens, such as CRE, is multifactorial due to the combination of antimicrobial administration, patient comorbidities, and infection control practices. Additionally, a large reservoir of CRE is within chronic care and long term care facilities. Thus, it is difficult to tease out the effect of antimicrobial stewardship from the concurrent effects of confounding factors.

The difficulty in systemic controlled studies has resulted in very limited literature on the effect of antimicrobial stewardship specifically on CRE. However, a systemic review found that after 6 months, most stewardship interventions had been associated with decreased resistance rates among key ICU pathogens. In particular with respect to CRE, in one case, in the 10-month intervention period following development of ASP, a broad decline in resistance was observed in multiple organisms, specifically including imipenem resistance among Acinetobacter baumannii and K. pneumoniae. Likewise, in another instance, a computer-assisted decision support system to guide appropriate antimicrobial use and duration was implemented over 7 years and was also associated with improved susceptibility of Pseudomonas and Enterobacteriaceae to carbapenems, aminoglycosides, and fluoroquinolones.

The role of infection control practices must be integrated in concert with ASP initiatives in order to approach the multifactorial problem of CRE. In regard to attempts to curtail rates of CRE, at a tertiary academic hospital, routine rectal surveillance cultures were performed upon admission to the ICU and thereafter weekly to screen for the presence of carbapenem-resistant pathogens in high risk patients. These high risk patients were cohorted within one-end of a unit, placed in contact isolation, and had enhanced environmental decontamination and hand hygiene stressed. Following implementation of this protocol, the mean number of new patients per 1,000 patient-days with cultures yielding carbapenem-resistant K. pneumoniae decreased by over 60% (from 9.7 to 3.7). As CRE outbreaks tend to occur in clusters, this may represent regression to the mean of overall incidence; however, it is promising that ASP in conjunction with infection control has been associated with termination of local outbreaks.

Similarly, a bundled intervention with chlorhexidine gluconate baths, enhanced environmental cleaning, surveillance cultures at admission and thereafter serial surveillance, isolation precautions, and additional infection control training of staff was able to reduce KPC-producing bacteria carriage rates. Active surveillance with rectal cultures and collection of a database to identify patients with prior CRE infection and the early initiation of infection control procedures resulted in a 4.7-fold reduction on CRE-infection in an outbreak setting at an Israeli hospital. These examples highlight the importance of integration of ASP with infection control in addressing the problem of CRE.

Stewardship initiatives for related MDR organisms

Although direct data in regard to impact on CRE rates has not been independently studied, there are comparable data in the setting of related drug-resistant nosocomial pathogens that suggests a high potential benefit. There has been increasing evidence that infections with multi-resistant organisms including methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococcus, Clostridium difficile, extended-spectrum β-lactamase-producing gram-negative bacilli, and Candida all share a commonality of risk factors. Advanced age, severity of illness, inter-facility transfers especially from a nursing home, prolonged hospitalizations, gastrointestinal surgery, transplantation, invasive devices such as central venous catheters, and most pertinent, exposure to antimicrobial drugs, especially cephalosporins, all were risk factors for resistant organisms. Therefore, effective interventions to reduce the incidence of a single resistant organism may have a more far reaching benefit in reducing overall burden of a multitude of resistant organisms. ASP initiatives are uniquely positioned to seize upon this opportunity.

ASP initiatives have been found to have an impact on the incidence of multiple hospital acquired infections. ASP has consistently had a significant reduction in the incidence of Clostridium difficile infection (CDI). Although, CDI remains a tremendous challenge for nosocomial infection, ASP initiatives have been able to reduce antibiotic use in multiple studies with a concurrent reduction of CDI incidence by up to 50%.
Similarly, reductions in another critical nosocomial pathogen, *P. aeruginosa*, have also been achieved with ASP initiatives. In a retrospective, longitudinal, multi-center analysis of academic health centers, a large statistically significant association was found between lower carbapenem use and reduced incidence rates of carbapenem-resistant *P. aeruginosa*. This association was sustained over a 5-year retrospective review period. Ultimately, the effects of ASP have been only examined in limited studies and remain difficult to quantify while lacking an immediacy in regard to their true impact on the spectrum of resistance. However, available studies, all showing a consistent association suggesting a reduction in resistant organisms are indicative that ASP can be leveraged into an overall sustainable reduction in multi-drug resistant (MDR) organisms and by extension incidence of CRE.

**Features of a successful ASP to impact CRE**

There is extensive literature on tactical solutions to antimicrobial stewardship. However, there has been much less emphasis on national/societal efforts to encourage healthcare systems and providers to participate in and comply with stewardship programs. Space limits preclude a thorough discussion of the strategic principles needed to align societal interests in stewardship with payer, regulator, and provider interests. We emphasize that incorporation of stewardship principles into national treatment guidelines, public reporting of antimicrobial usage with linkage to reimbursement penalties or bonuses, novel psychological approaches to combating inappropriate prescribing, incorporation of rapid diagnostics into clinical practice, and regulatory reform so that approved indications for new antimicrobials consider stewardship principles, are all necessary if we are to implement widespread and effective stewardship tactics nationally and internationally.

Implementation of tactical antibiotic stewardship interventions have documented up to 36% reductions in antimicrobial consumption, annual pharmacy cost reductions of up to $900,000, decreases in the rates of *C. difficile* infection, and improvements in the rates of clinical cure and mortality for various infectious disease syndromes. Despite consistent evidence of the dramatic impact of these programs, approximately half of hospitals in the United States and worldwide do not have an implemented and structured ASP. The primary barrier to implementation is consistently cited to be a lack of personnel or funding; only 15% of ASP in a large scale survey reported dedicated funding for ASP initiatives. The absence of widespread implementation of tactics known to reduce unnecessary antibiotic prescriptions underscores the need for a strategic, national policy approach to encouraging tactical implementation.

A critical first aspect in developing an ASP requires a strong commitment from administration with dedicated staff and resources to allow for active antibiotic audit, surveillance, and feedback. The effectiveness of an antibiotic approval program also depends on who is making the recommendations. Program leadership, preferably by an infectious disease specialist, can set clear objectives that can best maximize initial impact. For example, restriction of cefotaxime via a program requiring approval from a chief resident or attending physician had no impact on its use. In contrast, recommendations facilitated by an antimicrobial management team consisting of a pharmacist and infectious diseases physician resulted in an increased appropriateness, clinical cure rate, and a trend toward improved economic outcome.

A study comparing the effects of 3 different ASPs at comparable size and acuity hospitals in Taiwan found that the ASP with a preauthorization requirement as opposed to a post-authorization program, had the greatest effective impact in multiple areas including the reduction of inappropriate antimicrobial use, a reduction in drug-resistant gram negative organisms, and decreased cost. However, it was noted that a pre-authorization model of antimicrobial restriction was the most time and staff intensive, further highlighting the need for sustained administration buy-in and support of ASP resources. Therefore, institutional commitment to a well-designed, dedicated stewardship team is critical to achieve and optimize effective results.

CRE carriage, and subsequent infection is the culmination of unnecessarily broad or prolonged antimicrobial therapy, a failure of infection control practices, and delayed identification. Therefore, an ASP can serve as a key intermediary in the coordination between pharmacists, physician care providers, the microbiology lab, and infection control teams during every phase in the natural progression of CRE within a healthcare environment.

The initial burden of CRE starts prior to the arrival at an inpatient hospital setting. This entails chronic carriage of CRE by patients residing in outpatient chronic care facilities and in those patients with a prior known history of CRE infections. Early identification of known carriers upon arrival to an inpatient facility will allow for early infection control protocols in an attempt to reduce lateral nosocomial transmission.

Targeted screening utilizing rectal or stool surveillance cultures of high risk individuals, such as those on dialysis with end-stage renal disease, can further expedite isolation precautions. Additionally, the identification of these high-risk patients allows for more appropriate empirical therapy, which may offer a direct benefit in patient morbidity.
ASPs are tasked with developing and enforcing institutional guidelines for empiric antimicrobial use. ASP teams can be proactive in forming evidence based institutional guidelines for defining and treating common infections such as pneumonia or pyelonephritis. This will facilitate greater standardization of appropriate empirical therapy and consistency in treatment regimens and duration. Additionally, development of institutional surgical prophylaxis protocols is another avenue to curtail inappropriate antibiotic use. Similarly, ASPs can act to ensure discontinuation of surgical prophylaxis; thereby, reducing associated drug toxicity and drug-resistant organism risk in a tremendously vulnerable post-operative population. An ASP can also maximize its potential impact by determining which antimicrobials to focus restriction policies; essentially maximizing impact of available resources. Key antimicrobials that predispose to CRE, notably the carbapenems, but also broad spectrum cephalosporins and quinolones, can be targeted for focused audit and feedback.

The next critical aspect upon which an ASP can exert an impact is in the utilization of rapid diagnostics and leveraging this technology into focused CRE interventions. New developments in polymerase chain reaction (PCR) with fluorescent probe diagnostics, nucleic acid extraction and PCR amplification, and MALDI (matrix assisted laser desorption/ionization), are rapid diagnostic techniques that have dramatically reduced the time to determine bacterial speciation. They also provide an additional ability to identify key resistance genes. Standard biochemical techniques for identification of organisms require at least 48–72 hours for final results, compared with rapid diagnostic tests which can provide final organism identification within hours of growth. This reduction in identification time must be leveraged into real-time feedback and optimally de-escalation of broad spectrum empiric antimicrobial therapy. As time to appropriate antimicrobial therapy is the single most important predictor of mortality in sepsis, identifying a causative pathogen and its sensitivities sooner is invaluable for optimization of patient care. An ASP can serve as the key intermediary connecting the microbiology results with inpatient care providers, and if necessary facilitating a formal infectious disease consultation.

In the absence of real-time intervention then the maximal benefit, and the tremendous innovative power of this technology is negated. Highlighting this value is a study that found in patients with gram negative sepsis, MALDI when performed directly on positive blood cultures, combined with real-time notification resulted in a 46-hour reduction in the time to antimicrobial optimization compared to conventional methods with an improved time to active treatment by 36.7 hours in patients who had been on inactive therapy. There was also a significantly decreased length of hospitalization from 11.9 to 9.3 days, which notably is an additional underestimated ASP cost benefit.

Stewardship programs also offer the unique opportunity for a targeted intervention within health-care facilities. One key finding by Papadimitriou-Oliveros et al, highlights that a high prevalence of KPC enteric carriage was found in patients prior to intensive care unit admission. Concurrently, duration of preceding hospitalization prior to ICU admission and number of comorbidities were both risk factors predicting enteric carriage. Therefore, ASP interventions can focus effort on several key checkpoints in CRE transmission. ASP can mobilize active surveillance of high risk patients upon transfer to intensive care units and facilitate infection control measures. Additionally, another key target is ensuring that inter-unit transfers do not allow for prolonged unnecessary, or unnecessarily broad spectrum antimicrobial therapies which may be lost during hand-off between unit transfers.

As expected, the burden of CRE carriage is highest in patients with significant healthcare exposures and in particular long-term acute care hospitals (LTACH). A companion study found that patients with a prior stay at an LTACH had an elevated risk (OR, 4.75) of CRE infection as compared with patients with other MDROs. Similarly, a 2013 study found that in Chicago, LTACH patients had a 9.2-fold increased prevalence ratio for KPC-expressing K. pneumoniae. Similar findings in Los Angeles County noted an 8-fold higher incidence of CRE rates in patients residing in LTACHs compared to acute-care hospitals. Findings in additional studies showed 50% of all patients with carbapenem-resistant Gram-negative organisms were admitted from a post-acute care facility. These findings all add to a growing body of evidence that a significant reservoir and source of transmission of CRE is present in LTACH facilities. Despite the burden of CRE at urban centers and long-term facilities, community and rural facilities are still at risk. Thus, optimally ASP effects can exert an influence across the full range of a health system. Evidence suggests that even with limited resources, ASPs, in all types and sizes consistently result in a reduction antimicrobial use, improve patient outcomes, and control the emergence of antimicrobial-resistant organisms.

Due to the complexity and comorbidities of patients at risk for CRE, a reduction in the rate of these lethal organisms relies on a multi-disciplinary approach. ASPs serve as a key component, and in many ways should serve as integrative nexus of a collaborative approach. ASP need to have consistent communication and facilitate the integration of care between facility-wide surveillance and
infection control teams, medical teams, and infectious disease specialist consultants. Finally, ASP should be progressive, focusing on areas of concern that are facility specific. This can be accomplished by tailoring activities based on data of local antimicrobial usage rates, antibiogram resistance patterns over time, and collection of a database of patients with prior MDR isolates for early identification, isolation, or cohorting as necessary in the setting of rehospitalization.

Improvement of appropriate antimicrobial usage, thusly, can be seen as a core tenet in prolonging the lifespan of our current available therapeutics and reducing the proliferation of resistant organisms. Leveraging ASPs into this outcome will require a strong commitment from leadership and the collaborative efforts of clinicians, infection prevention epidemiologists, pharmacists, nursing teams, laboratory personnel, and IT staff. As such, effective antimicrobial stewardship requires a multidisciplinary team approach incorporating multiple elements of simultaneous proactive interventions, surveillance, direct feedback, and education. The integration of culture surveillance, drug expertise, timely communication, and receptive and focused intervention is necessary to achieve effective results.

Ultimately, outcome assessment and clinician feedback are equally important in order to modify each ASP to the particular needs of each facility. The exact role and model of each program should be tailored to the available resources, local resistance patterns, and unique challenges of each institution. Antimicrobial stewardship, in its optimal form, results in reduction of unnecessary antimicrobial use, optimization of appropriate use, but most critically, in all studies have not resulted in any increase in patient mortality. In a survey of physician attitudes toward ASP at a tertiary care hospital, clinicians agreed that there was a decrease in inappropriate use (84%), improved quality of care (82%), and felt that ASP intervention provided education regarding up to date guidelines on appropriate antibiotic use (91%). Equally important, the majority of clinicians (94%) did not find ASP an impediment to clinical autonomy.

Acute care hospitals and intensive care units offer the unique position of being a leader in setting best practice standards. In the future, ASPs must continue to be at the forefront in maximizing the impact of new diagnostics. They must also adapt to local epidemiology. Future ethical questions may also arise about the role of patients as an active partner in changing the medical-model of antimicrobial use and in guiding individualized care. Future goals should also be in extending and integrating the role of stewardship programs to LTACH and Assisted-Living Facilities to better address the threat of highly resistant pathogens on a longitudinal scale.

Disclosure of potential conflicts of interest
No potential conflicts of interest were disclosed.

References
[1] Pollack LA, Srinivasan A. Core elements of hospital antibiotic stewardship programs from the Centers for Disease Control and Prevention. Clin Infect Dis 2014; 59 Suppl 3: S97-100; PMID:25261548; https://doi.org/10.1093/cid/ciu542
[2] Camins BC, King MD, Wells JB, Goole HL, Patel M, Kourbatova EV, Blumberg HM. Impact of an antimicrobial utilization program on antimicrobial use at a large teaching hospital: a randomized controlled trial. Infect Control Hosp Epidemiol 2009; 30:931-8; PMID:19712032; https://doi.org/10.1086/605924
[3] Report to the President on Combating Antibiotic Resistance. Executive Office of the President: President’s Council of Advisors on Science and Technology, 2014
[4] Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, Srinivasan A, Delitt TH, Falck-Ytter YT, Fishman NO, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016; 62:e51-77; PMID:27080992; https://doi.org/10.1093/cid/ciw118
[5] Nowak MA, Nelson RE, Breidenbach JL, Thompson PA, Carson PJ. Clinical and economic outcomes of a prospective antimicrobial stewardship program. Am J Health Syst Pharm 2012; 69:1500-8; PMID:22899745; https://doi.org/10.2146/ajhp110603
[6] Kitchel B, Rasheed JK, Patel JB, Srinivasan A, Navon-Venezia S, Carmeli Y, Brolund A, Giske CG. Molecular epidemiology of KPC-producing Klebsiella pneumoniae isolates in the United States: clonal expansion of multilocus sequence type 258. Antimicrob Agents Chemother 2009; 53:3365-70; PMID:19506063; https://doi.org/10.1128/AAC.00126-09
[7] Kitchel B, Sundin DR, Patel JB. Regional dissemination of KPC-producing Klebsiella pneumoniae. Antimicrob Agents Chemother 2009; 53:4511-3; PMID:19687250; https://doi.org/10.1128/AAC.00784-09
[8] Wendt C, Schütt S, Dalpke AH, Konrad M, Mieth M, Trierweiler-Hauke B, Weigand MA, Zimmermann S, Biehler K, Jonas D. First outbreak of Klebsiella pneumoniae carbapenemase (KPC)-producing K. pneumoniae in Germany. Eur J Clin Microbiol Infect Dis 2010; 29:563-70; PMID:20213255; https://doi.org/10.1007/s10096-010-0896-0
[9] Qi Y, Wei Z, Ji S, Du X, Shen P, Yu Y. ST11, the dominant clone of KPC-producing Klebsiella pneumoniae in China. J Antimicrob Chemother 2011; 66:307-12; PMID:21313234; https://doi.org/10.1093/jac/dkq431
[10] Villegas MV, Lolans K, Correa A, Suarez CJ, Lopez JA, Vallejo M, Quinn JP, Colombian Nosocomial Resistance Study
Group. First detection of the plasmid-mediated class A carbapenemase KPC-2 in clinical isolates of Klebsiella pneumoniae from South America. Antimicrob Agents Chemother 2006; 50:2880-2; PMID:16870793; https://doi.org/10.1128/AAC.00186-06

[11] Zarkotou O, Pournaras S, Tselioti P, Dragoumanos V, Pitiriga V, Ranelou K, Prekates A, Themeli-Digalaki K, Tsakris A. Predictors of mortality in patients with bloodstream infections caused by KPC-producing Klebsiella pneumoniae and impact of appropriate antimicrobial treatment. Clin Microbiol Infect 2011; 17:1798-803; PMID:21595793; https://doi.org/10.1111/j.1469-0691.2011.03514.x

[12] Gupta N, Limbugo BM, Patel JB, Kallen AJ. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clin Infect Dis 2011; 53:60-7; PMID:21653305; https://doi.org/10.1093/cid/cir202

[13] Gasink LB, Edelstein PH, Lautenbach E, Synnestvedt M, Fishman NO. Risk factors and clinical impact of Klebsiella pneumoniae carbapenemase-producing K. pneumoniae. Infect Control Hosp Epidemiol 2009; 30:1180-5; PMID:19860564; https://doi.org/10.1086/648451

[14] Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resistant Klebsiella pneumoniae acquisition among hospitalized adults and effect of acquisition on mortality. Antimicrob Agents Chemother 2008; 52:1028-33; PMID:18086836; https://doi.org/10.1128/AAC.01020-07

[15] Patel G, Huprikar S, Factor SH, Jenkins SG, Cafée DP. Outcomes of carbapenem-resistant Klebsiella pneumoniae infection and the impact of antimicrobial and adjunctive therapies. Infect Control Hosp Epidemiol 2008; 29:1099-106; PMID:18973455; https://doi.org/10.1086/592412

[16] Spellberg B, Blaser M, Guidos RJ, Boucher HW, Bradley JS, Eisenstein BI, Gerding D, Lynfield R, Reiner LB, Rex J, et al. Combating antimicrobial resistance: policy recommendations to save lives. Clin Infect Dis 2011; 52 Suppl 5:S397-428; PMID:21475858

[17] Spellberg B, Bartlett JG, Gilbert DN. The future of antibiotic use and resistance. N Engl J Med 2013; 368:299-302; PMID:23343059; https://doi.org/10.1056/NEJMp1215093

[18] Falagas ME, Rafaillidis PI, Kofferdis D, Vrzitli S, Chelvatzoglou FC, Papaioannou V, Maraki S, Samonis G, Michalopoulos A. Risk factors of carbapenem-resistant Klebsiella pneumoniae infections: a matched case-control study. J Antimicrob Chemother 2007; 60:1124-30; PMID:17884829; https://doi.org/10.1093/jac/dkm356

[19] Kritsotakis EI, Tsoulis T, Roumelaki M, Christidou A, Gikas A. Antibiotic use and the risk of carbapenem-resistant extended-spectrum-β-lactamase-producing Klebsiella pneumoniae infection in hospitalized patients: results of a double case-control study. J Antimicrob Chemother 2011; 66:1383-91; PMID:21454344; https://doi.org/10.1093/jac/dkr116

[20] Caballero S, Carter R, Ke X, Susac B, Leiner IM, Kim GJ, et al. Distinct but Spatially Overlapping Intestinal Niches for Vancomycin-Resistant Enterococci faecium and Carbapenem-Resistant Klebsiella pneumoniae. PLoS Pathog 2015; 11:e1005132; PMID:26334306; https://doi.org/10.1371/journal.ppat.1005132

[21] Patel N, Harrington S, Dihmess A, Woo B, Masoud R, Martis P, Fiorenza M, Graffunder E, Evans A, McNutt LA, et al. Clinical epidemiology of carbapenem-intermediate or -resistant Enterobacteriaceae. J Antimicrob Chemother 2011; 66:1600-8; PMID:21508008; https://doi.org/10.1093/jac/dkr156

[22] Lai CC, Shi ZY, Chen YH, Wang FD. Effects of various antimicrobial stewardship programs on antimicrobial usage and resistance among common gram-negative bacilli causing health-care-associated infections: A multi-center comparison. J Microbiol Immunol Infect 2016; 49:74-82; PMID:26586483; https://doi.org/10.1016/j.jmii.2015.05.011

[23] Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N. Impact of antimicrobial stewardship in critical care: a systematic review. J Antimicrob Chemother 2011; 66:1223-30; PMID:21460369; https://doi.org/10.1093/jac/dkr137

[24] Kochar S, Sheard T, Sharma R, Hui A, Tolentino E, Allen G, Landman D, Bratu S, Augenbraun M, Quale J. Success of an Infection Control Program to Reduce the Spread of Carbapenem Resistant Klebsiella pneumoniae. Infect Control Hosp Epidemiol 2009; 30:447-52; PMID:19301985; https://doi.org/10.1086/596734

[25] Munoz-Price LS, Hayden MK, Lolans K, Won S, Calvert K, Lin M, Stermer A, Weinstein R. Successful control of an outbreak of Klebsiella pneumoniae carbapenemase producing K. pneumoniae at a long-term acute care hospital. Infect Control Hosp Epidemiol 2010; 31:341-7; PMID:20175685; https://doi.org/10.1086/651097

[26] Ben-David D, Maor Y, Keller N, Regev-Yochay G, Tal I, Shachar D, Zlotkin A, Smollan G, Rahav G. Potential role of active surveillance in the control of a hospital wide outbreak of carbapenem resistant Klebsiella pneumonia infection. Infect Control Hosp Epidemiol 2010; 31:620-6; PMID:20370465; https://doi.org/10.1086/652528

[27] Safdar N, Maki DG. The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant Staphylococcus aureus, enterococci, gram-negative bacilli, Clostridium difficile, and Candida. Ann Intern Med 2002; 136:834-44; PMID:12044132; https://doi.org/10.7326/0003-4819-136-11-20020604-00013

[28] Brown K, Valenta K, Fisman D, Simor A, Daneman N. Hospital ward antibiotic prescribing and the risks of Clostridium difficile infection. JAMA Intern Med 2015; 175:626-33; PMID:25705994; https://doi.org/10.1001/jamainternmed.2014.8273

[29] Ohl CA, Dodds Ashley ES. Antimicrobial stewardship programs in community hospitals: the evidence base and case studies. Clin Infect Dis 2011; 53 Suppl 1:S23-8; quiz S9-30; https://doi.org/10.1093/cid/cir365

[30] Pakyz AL, Oinonen M, Polk RE. Relationship of carbapenem-necin restriction in 22 university teaching hospitals to carbapenem use and carbapenem-resistant Pseudomonas aeruginosa. Antimicrob Agents Chemother 2006; 50:2880-2; PMID:16870793; https://doi.org/10.1128/AAC.00186-06
[33] Bauer KA, Perez KK, Forrest GN, Goff DA. Review of rapid diagnostic tests used by antimicrobial stewardship programs. Clin Infect Dis 2014; 59 Suppl 3:S134-45; PMID:25261540; https://doi.org/10.1093/cid/ciu547

[34] Papadimitriou-Olivgeris M, Marangos M, Fligou F, Christodidou M, Bartzavali C, Anastasiou ED, et al. Risk factors for KPC-producing Klebsiella pneumoniae enteric colonization upon ICU admission. J Antimicrob Chemother 2012; 67:2976-81; PMID:22927316; https://doi.org/10.1093/jac/dks316

[35] Perez F, Endimiani A, Ray AJ, Decker BK, Wallace CJ, Hujer KM, Ecker DJ, Adams MD, Toltzis P, Dul MJ, et al. Carbapenem-resistant Acinetobacter baumannii and Klebsiella pneumoniae across a hospital system: impact of post-acute care facilities on dissemination. J Antimicrob Chemother 2010; 65:1807-18; PMID:20513702; https://doi.org/10.1093/jac/dkq191

[36] Chopra T. Effective Antibiotic Stewardship Programs at Long-Term Care Facilities: A Silver Lining in the Post-Antibiotic Era. In: Rivard CM, ed. Annals of Long Term Care: HMP Communications, 2015

[37] Marquez P, Terashita D, Dassey D, Mascola L. Population-based incidence of carbapenem-resistant Klebsiella pneumoniae along the continuum of care, Los Angeles County. Infect Control Hosp Epidemiol 2013; 34:144-50; PMID:23295560; https://doi.org/10.1086/669087

[38] Perez F, Van Duin D. Carbapenem-resistant Enterobacteriaceae: a menace to our most vulnerable patients. Cleve Clin J Med 2013; 80:225-33; PMID:23547093; https://doi.org/10.3949/ccjm.80a.12182

[39] Stach LM, Hedican EB, Herigon JC, Jackson MA, Newland JG. Clinicians’ attitudes towards an antimicrobial stewardship program at a children’s hospital. J Ped Infect Dis 2012; 1:190-7; https://doi.org/10.1093/jpids/pis045