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REVIEW

The global epidemiology of carbapenemase-producing Enterobacteriaceae

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ABSTRACT

Carbapenemase-producing Enterobacteriaceae (CPE) are an important and increasing threat to global health. Both clonal spread and plasmid-mediated transmission contribute to the ongoing rise in incidence of these bacteria. Among the 4 classes of β-lactamases defined by the Ambler classification system, the carbapenemases that confer carbapenem resistance in Enterobacteriaceae belong to 3 of them: Class A (K. pneumoniae carbapenemases, KPC), Class B (metallo-β-lactamases, MBL including New Delhi metallo-β-lactamases, NDM) and Class D (OXA-48-like carbapenemases). KPC-producing CPE are the most commonly occurring CPE in the United States. MBL-producing CPE have been most commonly associated with the Indian Subcontinent as well as with specific countries in Europe, including Romania, Denmark, Spain, and Hungary. The epicenter of OXA-48-like-producing is in Turkey and surrounding countries. Detailed knowledge of the epidemiology and molecular characteristics of CPE is essential to stem the spread of these pathogens.

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Introduction

Resistance against antibacterials in clinically relevant bacteria is one of the most imminent threats to public health and especially to our most vulnerable patient populations. The World Health Organization has recognized antimicrobial resistance (AMR) as "a global health security threat that requires action across government sectors and society as a whole." [1] The Centers for Disease Control and Prevention (CDC) has estimated the excess direct healthcare costs associated with AMR to be as high as $20 billion, and additional costs to society for lost productivity as high as $35 billion a year in the United States alone.[2] Reliable global estimates are needed for the proportion of total infections that are caused by multidrug resistant (MDR) bacteria, and the proportion for each bacterial species isolated from clinical samples that displays an MDR phenotype. However, obtaining the data to calculate these proportions is hampered by incomplete reporting, practice variance in diagnostics and changing definitions for the MDR phenotype. Nonetheless, important progress in this respect has been made by organizations such as various tracking programs led by the CDC (www.cdc.gov), the Centers for Disease Dynamics, Economics and Policy (CDDEP, www.cddep.org), the Antibacterial Resistance Leadership Group (ARLG, www.arlg.org), and in Europe by the European Centers for Disease Control and Prevention (eCDC, ecdc.europa.eu) and the Combatting Bacterial Resistance in Europe project (COMBACTE, www.combacte.com).

Enterobacteriaceae are a family of bacteria that encompass many bacteria that are commonly isolated from clinical cultures, including *Escherichia coli, Klebsiella* spp., and *Enterobacter* spp. From the perspective of antimicrobial resistance, Enterobacteriaceae are especially important as they are a common cause of community-associated as well as healthcare-associated infections.[3]

In recent years, we have witnessed the emergence of carbapenemase-producing Enterobacteriaceae (CPE). For now, infections caused by CPE in the US are generally healthcare-associated, although community-associated infections are beginning to emerge.[3,4] The threat of CPE is substantial as carbapenems have traditionally been used in the treatment of infections caused by extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E), and are still considered a last-line of defense against Enterobacteriaceae to date. Few antibiotics retain activity against CPE due to the ability of carbapenemases to hydrolyze most other β-lactam antibiotics as well as the frequent coexistence in CPE isolates of additional mechanisms of resistance against other antibiotic classes such as fluoroquinolones and aminoglycosides. The remaining therapeutic options are less than

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desirable secondary to concerns over the lack of efficacy and their toxicity profiles.[5] In addition, rates of resistance to these agents of last resort such as tigecycline and polymyxins are increasing.[6-9] Recently, ceftazidime-avibactam has become available and other novel agents with anti-CPE activity are in phase 3 clinical trials.[10] Nonetheless, it is likely that history will repeat itself and resistance against these newer agents will also develop in time.

In this review, we describe the current epidemiology of CPE.

Definitions and terminology

In the past, the field of antibacterial resistance research has been plagued by the lack of standardized definitions for resistance phenotypes. In 2012, Magiorakos and colleagues proposed consensus definitions for MDR, extensively-drug-resistant (XDR) and pandrug-resistant (PDR) bacteria, generated by experts representing the CDC and eCDC.[11] Using these criteria, almost all currently encountered CPE would be considered MDR, and a substantial subset of CPE would be considered XDR.

Additional issues with terminology have been introduced by the concurrent use of the terms carbapenem-resistant Enterobacteriaceae (CRE), CPE and carbapenemase-producing carbapenem-resistant Enterobacteriaceae (CP-CRE). Also, the terms carbapenem-resistant organisms (CRO) and carbapenemase-producing organisms (CPO) are occasionally used. The CDC had initially defined CRE as those Enterobacteriaceae which were non-susceptible to $\geq$ 1 carbapenem and were resistant to 3rd generation cephalosporins. In their November 2015 update, this definition was revised. CRE are now defined as any Enterobacteriaceae which are *resistant* (excluding intermediate resistance) to any carbapenem antimicrobial or are documented to produce a carbapenemase. In addition, for those Enterobacteriaceae which may have intrinsic reduced susceptibility to imipenem such as *Proteus mirabilis*, resistance to a non-imipenem carbapenem is required.[12] The CDC acknowledges that this definition lacks specificity for CPE, especially in low-prevalence areas. The CDC Toolkit therefore recommends that laboratories confirm carbapenemase production by performing molecular testing for the presence of carbapenemases. In this review, we will specifically focus on the epidemiology of CPE.

Horizontal gene transfer and clonal expansion

An important question that remains largely unresolved is whether the main driver of spread of carbapenemases within Enterobacteriaceae is clonal expansion and transmission of successful CPE clonal lineages that stably maintain carbapenemase genes, or whether horizontal transfer of carbapenemase genes through mobile genetic elements such as plasmids containing them is primarily responsible. The global spread of sequence type (ST) 258 KPC-producing *K. pneumoniae* is an argument in favor of the former.[13,14] ST258 *K. pneumoniae* is considered a "high risk international clone," similar to ST131 *E. coli*.[15] In addition, specific clades within ST258 have been associated with carriage of specific bla_{KPC} genes: ST258A – corresponding to clade I – is found to be highly associated with bla_{KPC-2} whereas ST258B (clade II) tends to carry bla_{KPC-3}.[16] This suggests that through recombination events and transference of mobile genetic elements, including transposons and plasmids, bla_{KPC-2} and bla_{KPC-3} have become associated with specific clones of *K. pneumoniae*, and that this association has remained intact as bacteria spread from one person to the next. These subtypes also differ in the genetic region responsible for capsular polysaccharide biosynthesis.

However, evidence for outbreaks primarily related to horizontal gene transfer has also been reported. In a 5-year single center CPE outbreak investigation, bla_{KPC} was found in 66 different strains of Enterobacteriaceae. These 66 strains consisted of 13 different species, including *Klebsiella, Enterobacter*, and *Citrobacter*.[17] In addition to person-to-person spread of bla_{KPC} carrying bacteria, they found evidence for the transfer of plasmids between various bacteria, as well as for the transfer of bla_{KPC} containing transposons between plasmids.[17] In addition, an outbreak investigation from Norway revealed that intergenous spread mediated through a bla_{KPC-2} containing plasmid was responsible for transmission of carbapenem resistance from *K. pneumoniae* to *Enterobacter asburiae*.[18]

It is clear that there is continuous interplay between bacterial clones and mobile genetic elements that carry resistance genes. In contrast to the close association between ST258 and bla_{KPC}, bla_{OXA-48} is is more closely associated with IncLM type plasmids irrespective of ST type.[15] In conclusion, both plasmid-mediated spread that involves horizontal transmission of resistance genes between bacteria, as well as clonal expansion and transmission likely contribute to the ongoing global CPE epidemic. Evidence is strong that clonal expansion is responsible for a substantial portion of transmitted cases. However, plasmid-mediated transmission is harder to detect and may have been underestimated in reports to date.

Where are CPE found?

Among the 4 classes of β-lactamases defined by the Ambler classification system, the carbapenemases that confer carbapenem resistance in Enterobacteriaceae

belong to 3 of them: Class A, Class B, and Class D.[19] Class A enzymes include the *Klebsiella pneumoniae* carbapenemase (KPC) family, as well as much less commonly encountered nonmetallocarbapenemase type A (NMC-A) and SME enzymes, which may be found in *E. cloacae* and *S. marcescens*, respectively. KPC enzymes are the most commonly encountered enzymatic cause for carbapenem resistance in the US. The closely related genes $bla_{\text{KPC-2}}$ and $bla_{\text{KPC-3}}$ account for most of bla_{KPC}. Class B enzymes include the metallo-β-lactamases (MBL), such as the New-Delhi-metallo-β-lactamases (NDM), the IMP family of carbapenemases, and the Verona integron–encoded metallo-β-lactamases (VIM). In a zinc-dependent manner, these enzymes hydrolyze a broad variety of β-lactams, but are unable to hydrolyze monobactams such as aztreonam. Class D carbapenemases produced by Enterobacteriaceae include the oxacillinase (OXA)-48-like β-lactamases. OXA-48-like carbapenemases in isolation induce a relatively weak hydrolysis of penicillins and carbapenems but not cephalosporins. As a consequence they may be more difficult to detect, and have been called "the phantom menace."[20] Unfortunately, high level carbapenem resistance may occur when these enzymes are found in combination with other β-lactamases such as ESBL, or with porin changes leading to permeability defects.

Where are KPC-producing CPE found?

Carbapenemases of the KPC family have the most extensive global distribution of all carbapenemases associated with Enterobacteriaceae. The first KPC-producing CPE in the United States was isolated from a patient in North Carolina.[21] This strain was identified through the Project Intensive Care Antimicrobial Resistance Epidemiology (ICARE) of the CDC, another example of the importance of such surveillance programs.[22] This initial report was followed by a large number of cases of KPC-producing CPE reported from New York City area hospitals.[14] In a New York-based multicenter survey, the prevalence of bla_{KPC} within *K. pneumoniae* isolates peaked at 36% in 2006.[23] Of great interest, a notable decline has since been recorded to 25% in 2009 and 13% in 2013–2014.[23] Spread to the Great Lakes region of the United States has been described. The Consortium on resistance against carbapenems in *Klebsiella* and other Enterobacteriaceae (CRACKLE) is a prospective, multicenter, observational study of hospitals in Ohio, Pennsylvania and Michigan.[16] Data from CRACKLE showed endemicity of KPC-producing CPE, primarily *K. pneumoniae* of ST258, in the region. The carbapenemase genes responsible for carbapenem resistance were $bla_{\text{KPC-2}}$ and $bla_{\text{KPC-3}}$ in more than 90% of all CPE in this study.[16] Patients with CPE infection and/or colonization have been recognized in both community hospitals as well as tertiary care hospitals in the CRACKLE study.

In the most recent assessment from the CDC, KPC-producing CPE have been reported from every state in the United States except for Maine and Idaho.[24] Nonetheless, infections caused by KPC-producing CPE remain a very small subset of all infections caused by Enterobacteriaceae in the US. In a CDC study spanning 2012–2013, the incidence of CRE in 7 US communities was estimated between 0.35 and 4.80 annual incident CRE cases/100,000 population, with an overall estimate of 2.94 annual incident CRE cases/100,000 population.[25] However, these data are limited by the small number of CRE isolates that were confirmed to be CPE. Less than a third of CRE isolates were available for testing. Of these 188 isolates, 47% tested positive for a carbapenemase and the only identified carbapenemases were part of the KPC family.[25] Detailed data on the incidence of KPC-producing CPE in the US remain scarce.

KPC-producing CPE are also widespread in South and Central America. Several studies have described their epidemiology in Colombia.[26-28] For example, a recent 2 y (2012–2014) surveillance study in 5 hospitals – sized between 140 and 754 beds – in Medellin revealed that 166 patients had KPC-producing CPE during the study period. Of interest, a high frequency of non-ST258 (62%) was found in this study.[29] In a multi-national observational study spanning 7 Latin American nations (Argentina, Colombia, Ecuador, Guatemala, Mexico, Peru and Venezuela), 255 patients with bloodstream infections caused by Enterobacteriaceae were included. Of these patients, 21% had a CPE, which were mostly KPC producers (83%).[30] As in most series of CPE infections, *K. pneumoniae* was the most commonly isolated Enterobacteriaceae species. Similar to the US, it is difficult to reliably estimate the exact incidence of CPE infections in various Latin American countries.

In Europe, the highest incidence of KPC-producing CPE is found in Mediterranean countries, especially Italy and Greece.[31] These 2 countries were the only 2 European countries reported to have an "endemic situation" for KPC in 2014–2015.[31] While other carbapenemases are present in Italy and Greece, KPC remains the most common etiology of carbapenem resistance.[31] In a single-center study from Italy that reported on CPKP during 2012–2014, 432 of a total of 436 carbapenemase-producing strains were found to produce KPC.[32] In a large, retrospective, multi-center study conducted in 5 Italian hospitals, 661 patients with KPC-producing *K. pneumoniae* were included over a 4 y period. Of these, the majority carried $bla_{\text{KPC-3}}$ (75%), and the remainder carried $bla_{\text{KPC-2}}$.[33] These were selected from a total of

3,449 patients with culture positivity for KPC-producing *K. pneumoniae*. In other words, on average around 170 patients had positive cultures for KPC-producing *K. pneumoniae* per participating hospital per year.[33] The impact of KPC in Greece has been similarly dramatic. In a 10-year single-center study, a large increase in the number of KPC-producing *K. pneumoniae* cases was reported.[34] Prior to 2008, no KPC producers were found. From 2008 onwards, the prevalence of KPC producers increased and by 2014 the majority of *K. pneumoniae* isolates carried a bla_{KPC} gene.[34] In addition, the overall rate of carbapenemase-producing *K. pneumoniae* bloodstream infection (BSI) increased from 0.5 cases per 10,000 patient-days in 2005 to 4.2 cases per 10,000 patient-days, while non-carbapenemase-producing *K. pneumoniae* BSI rates did not decrease.[34]

In the Middle East, a significant epidemic of KPC-producing CPE has evolved. Of note, a national interventional strategy to contain the spread of CPE within Israel was started in 2007 after a large spike in the number of such cases was detected nationwide. This successful intervention resulted in a dramatic drop of hospital-acquired CPE cases from 55.5 to 4.8 cases/100,000 patient-days.[35] Unfortunately, ongoing unrest in the Middle East threatens these advances, as exemplified by the finding of CPE in wounded Syrian patients admitted to northern Israeli hospitals.[36]

KPC enzymes have also been reported in Asia, especially China. In a study of carbapenem-resistant *E. coli* strains from Shanghai, the majority of CPE (13/16) produced KPC.[37] When patients at a Chinese tertiary care hospital were screened for CRE rectal carriage in a 2011–2012 study, 4 of 303 were found to have KPC-producing Enterobacteriaceae.[38] In a study from 2011, bla_{KPC-2} was present in 71% of 109 ertapenem-resistant *K. pneumoniae* isolates, often in combination with CTX-M type ESBL enzymes.[39] The Chinese report of bla_{KPC-2} in a hypervirulent K1 strain is especially concerning as it may be the harbinger of the spread of strains that combine hypervirulence with carbapenem resistance.[40] In contrast, bla_{KPC} has been infrequently found in Enterobacteriaceae from patients in India, where NDM-type MBL is the predominant carbapenemase.[41,42]

Few data are available regarding the epidemiology of KPC in Africa. A single-center study from Tanzania indicated that KPC was an unusual etiology for carbapenem resistance; among 29 carbapenemase-producing *K. pneumoniae*, only 3 were KPC producers.[43] KPC producers have also been reported from South Africa.[44]

Where are MBL-producing CPE found?

The substantial burden of carbapenemases in the MBL class appears to lie in Asia. Especially, the New Delhi Metallo-β-lactamases (NDM) are of concern in this region. The first patient in whom bla_{NDM-1} was detected was a Swedish patient who traveled to India in 2007, and acquired a *K. pneumoniae* urinary tract infection. This isolate displayed carbapenem resistance that was mediated through production of a novel carbapenemase designated NDM-1.[45] A follow-up study showed that NDM-1-mediated carbapenem resistance was widespread in India, Pakistan, and Bangladesh.[46] Since then, bla_{NDM}-positive Enterobacteriaceae have become increasingly common in India. Of note, bla_{NDM-1} carrying CPE were not only isolated from patients in India, but importantly also in public tap water and seepage water.[47] In a recent study from Mumbai, out of 111 CPE, 106 were NDM producers. In addition, 21 NDM producers were found to produce additional carbapenemases as well (17 isolates were positive for OXA-48-type carbapenemase and 4 for VIM-type MBL).[41] Of great concern, they have also been recognized as a source of community-associated infections.[48] NDM producers have also been described in Enterobacteriaceae in China, but appear to be less widespread as compared to India. In a multicenter study looking at 90 patients with *E. coli* BSI in Shanghai between 2013–2014, no NDM producers were found.[49] Similarly, in an evaluation of 71 CRE from Hong Kong from 2010–2012, only 9 were confirmed to be CPE. Of these 9 isolates, 3 produced IMP-4, 3 NDM-1 and 3 KPC-2.[50] A recent worrying observation is the co-localization of bla_{NDM-9} and the plasmid-mediated colistin resistance gene *mcr-1* within an *E. coli* strain recovered from chicken meat sold in Guangzhou, China.[51]

In Europe, NDM producers are most commonly found in Romania, Poland and Denmark, where "inter-regional spread" (epidemiological stage 4) is deemed to be present.[31] A large national Polish study from 2012–2014 identified 374 patients with NDM-producing CPE.[52] Most of these cases were epidemiologically linked and thought to be part of a large multi-regional, multi-center outbreak. Outbreak isolates included *K. pneumoniae* and *E. coli*, and several contained similar transposons.[52] In Spain, Italy and Hungary, VIM is the predominant MBL; in these countries, "inter-regional spread" (epidemiological stage 4) of VIM producers has been documented.[31] In addition, contact with healthcare in countries that are endemic for NDM-producers such as India, has been linked to cases presenting in the UK and other European countries.[53]

In the US and Canada, MBL have remained an uncommon etiology for carbapenem resistance in Enterobacteriaceae.[54] In 2012, an outbreak of blaNDM-1 producing *K. pneumoniae* was reported from Denver. Routes of transmission were speculated to include colonized patients who went undetected. The route of introduction into the Denver healthcare system was not established.[55] As of April 2016, 157 NDM-producing

CPE from 25 states were reported to the CDC.[24] A recent outbreak from Illinois of NDM-producing CPE was found to be associated with the use of endoscopes.[56] VIM-producing and IMP-producing CPE are even less common; per the CDC, only 17 isolates from 7 states; and 10 isolates from 5 states have been reported as of April 2016, respectively.[24]

MBL-producing Enterobacteriaceae isolates have also been reported from several Latin American countries. In a multinational survey spanning 2012–2014, VIM-producing CPE were recovered from Mexico and NDM-1-producing CPE from Venezuela.[57] As noted above, KPC enzymes are the most common etiology of carbapenem resistance in Latin America; in the observational multi-national study on CPE BSI in 7 Latin American nations, 9% and 8% of CPE harbored bla_{VIM} and bla_{NDM}, respectively.[30] Similarly, in a multi-center Colombian study of 193 carbapenem-resistant *K. pneumoniae* isolates, only 1 isolates was found to be positive for an MBL gene (bla_{VIM}).[29] MBL-producing CPE have also been reported from Brazil.[58] Of concern, bla_{NDM-1} was found in the water near Rio de Janeiro in the time period leading up to the 2016 Olympics.[59]

MBL enzymes have been reported in CPE recovered from patients in various African countries for the past decade or so. However, the current magnitude of the MBL-mediated CPE epidemic in Africa is difficult to estimate due to scarcity of data. In a multinational survey spanning 2012–2014, NDM-producing CPE were recovered from Kenya, Nigeria and South Africa and VIM-producing CPE from Nigeria and South Africa.[57] In an early report from Tunisia, 11 patients admitted in 2005 with VIM-4-producing CPE were described.[60] A more recent study evaluating bacteria recovered from 2 polluted Tunisian rivers in 2010 documented the frequent occurrence of VIM and IMP enzymes in *K. pneumoniae* isolates.[61] The first recognized occurrence of NDM-1 in South Africa was in 2010.[62] This first case has been followed by several others from South Africa, raising concerns that NDM-producing CPE are becoming endemic.[63,64] Risk factors for acquisition of NDM-producing CPE in South Africa were similar to other reports and included comorbid conditions, mechanical ventilation, and prior use of piperacillin-tazobactam.[64] Of note, both local and imported cases of NDM-1 producing CPE seem to occur in South Africa.[63] VIM-1-producing CPE have also been described from South Africa.[65] In addition, NDM enzymes have been reported from several other African countries including Egypt, Morocco, Algeria, Kenya, Cameroon and Tanzania.[43,66-70]

Where are OXA-producing CPE found?

OXA-48-like carbapenemases remain extremely rare as a cause of carbapenem resistance in Enterobacteriaceae in the US.[71] Per CDC data, OXA-48-like-producing CPE were detected only in 43 patients from 19 states as of August 2015.[71] In contrast, they are relatively commonly found in Europe, especially in Mediterranean countries.[20] The first reported OXA-48-producing Enterobacteriaceae was a *Klebsiella pneumoniae* strain that was isolated in Turkey in 2001.[72] OXA-48-like producing *Klebsiella pneumoniae* clones have persisted in Turkey as a cause of nosocomial infections. Turkey was reported as having the highest epidemiologic level (stage 5 "endemic situation") of these strains in 2014–2015.[31] In a recent study from Turkey, 92% of CPE were OXA-48-like producers.[73] In Spain, France, Belgium and Romania, the epidemiologic stage was deemed "inter-regional spread," or stage 4, in 2014–2015.[31] In addition to Europe, OXA-48-like enzymes have been found worldwide in Enterobacteriaceae. Examples of areas with spread of OXA-48-like producing CPE include the Middle East (e.g., United Arab Emirates, Saudi Arabia, Lebanon, Israel), Africa (e.g., Libya, Egypt, Algeria, Morocco, South Africa), Asia (e.g., Russia, India, China, Taiwan, Thailand), and South America (e.g., Argentina, Brazil, Colombia).[29,74-89] It is important to note that, since most clinical microbiology laboratories do not test for the presence of OXA-48-like enzymes and the associated phenotype (i.e., low-level carbapenem resistance) may be difficult to recognize, the incidence of OXA-48-like-producing CPE is likely underestimated.

Who is at risk for acquiring CPE?

Safdar and Maki outlined a framework for the commonality of risk factors for the acquisition of MDR organisms in their landmark article.[90] This framework applies to the acquisition of CPE as well. Similar to other MDR bacteria, important risk factors for colonization with CPE include prior antibiotic usage, healthcare and long term care exposure, chronic comorbid conditions, and the presence of invasive catheters and drains.[16,25,91-95] A potential common pathway for these risk factors – in addition to the obvious increased risk of exposure to other patients and/or healthcare workers who are colonized with CPE – is the disturbance of the microbiome.[96]

Accordingly, in the CRACKLE study patients were elderly; the median age of patients with carbapenem-resistant *K. pneumoniae* was 70 y (interquartile range [IQR] 58–81 years).[16] A slight female predominance was observed; 60% of patients were women. Comorbid conditions were common; 56% had a documented history of diabetes mellitus, 57% had heart disease, 26% of patients carried the diagnosis of renal insufficiency. The median Charlson Comorbidity Index was 4 (IQR 2–6).[16] Similarly, patients with CDC-defined CRE had a median age of 66 (with a range of <1 to 100), 59% were female. In

the CDC study, a lower Charlson Comorbidity Index was noted (a median of 2, with a range of 0–12), perhaps as a consequence of a lower percentage of patients included in the study who had carbapenemase-producing CRE. Still only 9% of patients did not have any underlying condition. Indwelling devices were also common in this CDC study, 75% of patients had a urinary catheter in place, 43% a central venous catheter, and 39% a feeding tube.[25] In addition to these traditional risk factors, travel to endemic areas is obviously an important risk factor.[97] Especially healthcare exposure in endemic areas including "medical tourism" plays an important role in the spread of CPE.[97]

Conclusions

Carbapenemases have a global distribution, but substantial variability exists on the continental, national, regional, and even center-to-center levels. Awareness of the prevalence and incidence of the specific mechanisms of carbapenem resistance within Enterobacteriaceae is crucial in the prevention of their spread and selection of appropriate treatment options.

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