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INPLASY

Prevalence, mortality, risk factors and treatment of carbapenem-resistant hypervirulentKlebsiella pneumoniae: An evidence mapping

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ADMINISTRATIVE INFORMATION

Support - MSD China.

Review Stage at time of this submission - Piloting of the study selection process.

Conflicts of interest - Jie Liu, Yue Liu and Yi Sun are employees of MSDChina. All authors declared that there were no conflicts of interest.

INPLASY registration number: INPLASY202470129

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 July 2024 and was last updated on 31 July 2024.

INTRODUCTION

Review question / Objective Primary objective: To estimate the global prevalence of CR-hvKP infection; To estimate the mortality of CR-hvKP infection. Secondary objective: To summarize the risk factors associated with CR-hvKP infection; To summarize the current treatment strategy and outcome of CR-hvKP infection.Primary objectives: Systematically collect susceptibility and drug resistance data for Aspergillosis (specifically Aspergillus fumigatus, Aspergillus flavus and Aspergillus niger) and mucormycosis (specifically Rhizopus spp., Mucor spp., and Rhizomucor spp.) against different types of antifungal agents (specifically Isavuconazole, Posaconazole, Amphotericin B, itraconazole, voriconazole).
Secondary objectives: Susceptibility and drug resistance data among different subgroups: 1. Between environmental and clinical isolates; 2. In different patient populations.

Background Klebsiella pneumoniae (KP) is a common Gram-negative bacterium in clinical practice, and its multiple resistance to antibiotics and high virulence have become important clinical issues. Multiple drug resistance (MDR) has led to KP becoming the main pathogen of hospital acquired infections, especially resistance to carbapenems. Hypervirulent KP (hvKP) often leads to life-threatening invasive infections, such as liver abscess and endophthalmitis. Early research suggests that high virulence and multidrug resistance belong to different evolutionary branches on the KP genome. Although hvKP exhibits high virulence, it is rarely resistant to commonly used antibiotics other than ampicillin. Carbapenem antibiotics against

extended-spectrum β-lactamase (ESBLs) and cephalosporin enzymes (AmpC) have strong stability and a wide antibacterial spectrum, making them first-line drugs for the clinical treatment of multidrug-resistant gram-negative bacteria. However, with the widespread use of broad-spectrum antibiotics and the spread of resistant plasmids, the resistance rate of hvKP continues to rise. In recent years, the carbapenem-resistant and hypervirulent Klebsiella pneumoniae (CR-HvKP) as a "super bacterium" has attracted global attention, posing great challenges to clinical treatment. Epidemiological investigation results show that there are significant differences in the distribution of different subtypes of carbapenem-resistant Klebsiella pneumoniae (CRKP) worldwide. Sequence type (ST) 11 clones aremainly seen in studies from China and South America, ST258 is mainly reported in the United States, ST512 is mainly seen in Italy and Greece, and ST147 is mainly seen in India and Tunisia. Epidemiological analysis of CR-hvKP in China shows that 80% of CR-hvKP strains belong to the ST11 type that produces KPC-2. ST11-CR-hvKP has high transmission, resistance, and virulence, posing a serious threat to human health. With the spread of virulence and resistance genes, the cloning background of strains presents
diversity. The reported sequence types (ST) of CR-hvKP include ST11, ST14, ST23, ST25, ST36, ST65, ST86, ST1797, ST43, ST231, ST147, ST15, ST383, ST268, ST595, ST375, ST48, and ST307, and the carbapenemases carried by them include KPC-2, NDM (NDM-1, NDM-5, and NDM-7), IMP, SIM, VIM (VIM-1 and VIM-2) and OXA-48 .
CR-hvKP has a strong ability to colonize the intestine, which poses a high risk of transmission and may lead to serious infections. In an epidemiological study targeting the gut carrying of Klebsiella pneumoniae among pregnant women in low-income countries, it was found that environmental exposure factors include food, animal contact, or hospitalization of family members, as well as intestinal colonization of MDR hvKP in
pregnant women, and even detection of ST23 CRKP strain in ready-to-eat vegetables. These results indicate that CRKP is not only a food safety issue, but also a public health threat. Zheng et al. screened patients hospitalized for diarrhea in a teaching hospital and found that the carrier rate of carbapenem producing Enterobacteriaceae (CPE) bacteria was 12.4%, with KP being the most common (65/87) and ST11 being the predominant type
(58/65; 89%). S1 nuclease PFGE (S1-PFGE) and Southern blot analysis showed that ST11-CR-HvKP isolates carried at least four types of rmpA - and rmpA2 - positive plasmids. The size ranges from approximately 146 kb to approximately 218 kb, and feces may be thesource of the ST11-CR-HvKP strain. The rapid spread and outbreak of CR-hvKP in the medical environment pose significant challenges to infection control. In 2016, Chinese scholar Gu et al. isolated 21 ST11 type CRKP strains producing KPC-2 from ICU wards. These strains were from the same clone and obtained pLVPK-like virulence plasmids, ultimately leading to the death of 5 patients during hospitalization.

Rationale CR-hvKP has become a popular clone that affects patients, but the development of targeted antibiotics lags far behind the emergence of drug-resistant bacteria, resulting in limited treatment options for carbapenem resistance. For CR-hvKP with gradually increasing detection rates, China mainly uses a combination therapy regimen based on tigecycline, polymyxin, and phosphomycin, as well as a new type of β-lactamase inhibitors such as ceftazidime/avibactam. Cefotaxime avibactam and tigecycline showed activity against all CR-hvKP strains in vitro testing. There are also research results indicating that the combination of tigecycline and polymyxin has a synergistic effect in vitro, which can be used as a potential choice for clinical treatment of CR-hvKP infection (18). However, in cases of fatal outbreaks of ST11 CR-hvKP infection in a hospital, polymyxin and tigecycline did not cure severely infected patients. Since the emergence of CR-hvKP strains poses a significant public threat, to comprehensively address related issues about CR-hvKP would increase our understanding of this new strains and identify current clinical gaps in this area. Thus, this evidence mapping aimed to summarize the incidence, mortality, risk factors, treatment pattern of CR-hvKP and CR-classic KP and CRKP.

METHODS

Strategy of data synthesis PubMed
#1. "Carbapenem-Resistant"[tw] OR "carbapenem non-susceptible"[tw] OR "carbapenem nonsusceptible"[tw] OR "Carbapenems-Resistant"[tw] OR "carbapenems non-susceptible"[tw] OR "carbapenems nonsusceptible"[tw] OR "Doripenem Resistant"[tw] OR "doribax Resistant"[tw] OR "Ertapenem Resistant"[tw] OR "invanz Resistant"[tw] OR "Thienamycine Resistant"[tw] OR "Thienamycin Resistant"[tw] OR "Meropenem Resistant"[tw] OR "Imipenem Resistant"[tw] OR "imipemide Resistant"[tw] OR "biapenem Resistant"[tw] OR "panipenem Resistant"[tw] OR "betamipron Resistant"[tw] OR ST11[tw] OR

(("Carbapenems"[mesh] OR "Carbapenems"[tw] OR "Carbapenem"[tw] OR "Doripenem"[tw] OR "Ertapenem"[tw] OR "Thienamycins"[tw] OR "Imipenem"[tw] OR "Meropenem"[tw]) AND ("beta-Lactam Resistance"[majr] OR "resistant"[ti] OR "resistance"[ti] OR "drug resistant"[tw] OR "drug resistance"[tw] OR "multidrug resistant"[tw] OR "multidrug resistance"[tw] OR "antimicrobial resistance"[tw]))
#2. (("Klebsiella pneumoniae"[Mesh] OR Klebsiella[tw] OR "K. pneumonia"[tw]) AND (Hypervirulen*[tw] OR "Hyper-virulen*"[tw] OR virulen*[tw] OR hypermucovisco*[tw] OR "hyper-mucovisco*"[tw] OR ST23[tw] OR ST25[tw] OR ST65[tw] OR ST1797[tw] OR KL1[tw] OR K1[tw] OR KL2[tw] OR K2[tw] OR KL64[tw] OR K64[tw])) OR "Hv-CRKP"[tw] OR "CR-HvKP"[tw] OR hvKP[tw] OR CRhvKP[tw] OR hvCRKP[tw] OR "MDR-hvKP"[tw]
#3. #1 AND #2 986
#4. "Review Literature as Topic"[Mesh] OR "Review" [Publication Type] OR Review[ti] OR "Meta-Analysis"[pt] OR "Meta-Analysis as Topic"[Mesh] OR "Systematic Review" [pt] OR "Systematic Reviews as Topic"[Mesh] OR "systematic"[Filter] OR "Systematic Review*"[ti] OR "Meta-Analysis"[ti] OR Metaanalys*[ti]
#5. #3 NOT #4
EMBASE
#1. 'carbapenem-resistant Enterobacteriaceae'/exp OR 'carbapenem resistance'/exp OR 'multidrug resistance'/exp OR ((Carbapenem* OR Doripenem OR Ertapenem OR Imipenem OR Meropenem OR biapenem OR multi-drug OR MRD OR multiple OR multidrug) NEAR/3 (Resistant OR nonsusceptible OR "non-susceptible")):ab,ti,kw OR ST11:ab,ti,kw
#2. 'carbapenem derivative'/exp OR 'carbapenem'/exp OR (Carbapenem* OR Doripenem OR Ertapenem OR Thienamycin* OR Imipenem OR Meropenem OR doribax OR invanz OR imipemide OR biapenem OR panipenem):ab,ti,kw
#3. 'beta-lactam resistance'/exp OR (Resistant OR resistance):ti OR ((drug OR multidrug OR antimicrobial) NEAR/3 (Resistant OR resistance OR nonsusceptible OR "non-susceptible")):ab,ti,kw
#4. #1 OR (#2 AND #3)
#5. 'Klebsiella pneumoniae'/exp OR (Klebsiella OR "K. pneumonia"):ab,ti,kw
#6. (Hypervirulen* OR "Hyper-virulen*" OR virulen* OR hypermucovisco* OR "hyper-mucovisco*" OR ST23 OR ST25 OR ST65 OR ST1797 OR KL1 OR K1 OR KL2 OR K2 OR KL64 OR K64):ab,ti,kw
#7. ("Hv-CRKP" OR "CR-HvKP" OR hvKP OR CRhvKP OR hvCRKP OR "MDR-hvKP"):ab,ti,kw
#8. (#5 AND #6) OR #7
#9. #4 AND #8
#10. [review]/lim OR 'review'/exp OR 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'systematic review'/exp OR 'systematic review (topic)'/exp OR (Review OR "Meta-Analysis"):ti
#11. #9 not #10
Wos
#1. TS=((Carbapenem* OR Doripenem OR Ertapenem OR Thienamycin* OR Imipenem OR Meropenem OR doribax OR invanz OR imipemide OR biapenem OR panipenem) NEAR/3 (Resistant OR nonsusceptible OR "non-susceptible")) OR TS=(ST11)
#2. TS=(Carbapenem* OR Doripenem OR Ertapenem OR Thienamycin* OR Imipenem OR Meropenem OR doribax OR invanz OR imipemide OR biapenem OR panipenem)
#3. TI=(Resistant OR resistance) OR TS=((drug OR multidrug OR antimicrobial) NEAR/3 (Resistant OR resistance OR nonsusceptible OR "non-susceptible"))
#4. #1 OR (#2 AND #3)
#5. TS=(Klebsiella OR "K. pneumonia") AND TS=(Hypervirulen* OR "Hyper-virulen*" OR virulen* OR hypermucovisco* OR "hyper-mucovisco*" OR ST23 OR ST25 OR ST65 OR ST1797 OR KL1 OR K1 OR KL2 OR K2 OR KL64 OR K64)
#6. TS=("Hv-CRKP" OR "CR-HvKP" OR hvKP OR CRhvKP OR hvCRKP OR "MDR-hvKP")
#7. #5 OR #6
#8. #4 AND #7
#9. TI=(Review OR "Meta-Analysis") OR Review Article (Document Types)
#10. #8 NOT #9
Cochrane
#1 ((Carbapenem* OR Doripenem OR Ertapenem OR Thienamycin* OR Imipenem OR Meropenem OR doribax OR invanz OR imipemide OR biapenem OR panipenem) NEAR/3 (Resistant OR nonsusceptible OR "non-susceptible" OR ST11)):ti,ab,kw
#2 (Carbapenem* OR Doripenem OR Ertapenem OR Thienamycin* OR Imipenem OR Meropenem OR doribax OR invanz OR imipemide OR biapenem OR panipenem):ti,ab,kw
#3 (Resistant OR resistance):ti
#4 ((drug OR multidrug OR antimicrobial) NEAR/3 (Resistant OR resistance OR nonsusceptible OR "non-susceptible")):ti,ab,kw
#5 #3 or #4
#6 #2 and #5
#7 #1 or #6
#8 MeSH descriptor: [Klebsiella pneumoniae] explode all trees
#9 (Klebsiella OR "K. pneumonia"):ti,ab,kw
#10 #8 OR #9
#11 (Hypervirulen* OR "Hyper-virulen*" OR virulen* OR hypermucovisco* OR "hyper-mucovisco*" OR

ST23 OR ST25 OR ST65 OR ST1797 OR KL1 OR K1 OR KL2 OR K2 OR KL64 OR K64):ti,ab,kw
#12 #10 AND #11
#13 ("Hv-CRKP" OR "CR-HvKP" OR hvKP OR CRhvKP OR hvCRKP OR "MDR-hvKP"):ti,ab,kw
#14 #12 OR #13
#15 #7 AND #14
Cnki（期刊、学位、会议，中英文扩展：是，中文）
(SU%=(碳青霉烯+碳青霉烯类+亚胺培南+美罗培南+美洛培南+帕尼培南+厄他培南+比阿培南多尼培南+多利培南+多力培南+多立培南+噻烯霉素+沙纳霉素+硫霉素+亚胺硫霉素+法罗培南)*(耐药+耐药性)+耐碳青霉烯+耐碳青霉烯类+耐亚胺培南+耐美罗培南+耐美洛培南+耐帕尼培南+耐厄他培南+耐比阿培南+耐多尼培南+耐多利培南+耐多力培南+耐噻烯霉素+耐沙纳霉素+耐硫霉素+耐亚胺硫霉素+ ST11 OR TKA % (碳青霉烯+碳青霉烯类+亚胺培南+美罗培南+美洛培南+帕尼培南+厄他培南+比阿培南多尼培南+多利培南+多力培南+多立培南+噻烯霉素+沙纳霉素+硫霉素+亚胺硫霉素+法罗培南)*(耐药+耐药性)+耐碳青霉烯+耐碳青霉烯类+耐亚胺培南+耐美罗培南+耐美洛培南+耐帕尼培南+耐厄他培南+耐比阿培南+耐多尼培南+耐多利培南+耐多力培南+耐噻烯霉素+耐沙纳霉素+耐硫霉素+耐亚胺硫霉素+ ST11) and (SU%=肺炎克雷伯氏菌病+肺炎克雷伯氏菌+肺炎克雷伯氏菌感染+肺炎克雷伯菌病+肺炎克雷伯菌+肺炎克雷伯菌感染+肺炎克雷伯杆菌病+肺炎克雷伯杆菌+肺炎克雷伯杆菌感染+肺炎克雷伯氏杆菌+肺克 TKA % 肺炎克雷伯氏菌病+肺炎克雷伯氏菌+肺炎克雷伯氏菌感染+肺炎克雷伯菌病+肺炎克雷伯菌+肺炎克雷伯菌感染+肺炎克雷伯杆菌病+肺炎克雷伯杆菌+肺炎克雷伯杆菌感染+肺炎克雷伯氏杆菌+肺克) AND (SU%=高毒力+高毒力株+毒力基因+毒力因子+ ST23+ ST25+ ST65+ ST1797+ KL1+ K1+ KL2+ K2+ KL64+ K64 OR TKA % 高毒力+高毒力株+毒力基因+毒力因子+ ST23+ ST25+ ST65+ ST1797+ KL1+ K1+ KL2+ K2+ KL64+ K64)
万方（期刊、学位、会议）
((主题:("碳青霉烯" OR "亚胺培南" OR "美罗培南" OR "美洛培南" OR "帕尼培南" OR "厄他培南" OR "比阿培南" OR "多尼培南" OR "多利培南" OR "多力培南" OR "多立培南" OR "噻烯霉素" OR "沙纳霉素" OR "硫霉素" OR "亚胺硫霉素" OR "法罗培南") AND 主题:(耐药)) OR 主题:("耐碳青霉烯" OR "耐亚胺培南" OR "耐美罗培南" OR "耐美洛培南" OR "耐帕尼培南" OR "耐厄他培南" OR "耐比阿培南" OR "耐多尼培南" OR "耐多利培南" OR "耐多力培南" OR "耐多立培南" OR "耐噻烯霉素" OR "耐沙纳霉素" OR "耐硫霉素" OR "耐亚胺硫霉素" OR ST11)) and 主题:("肺炎克雷伯" OR "肺克") and 主题:("高毒力" OR "高毒力株" OR "毒力基因" OR "毒力因子" OR "ST23" OR "ST25" OR "ST65" OR "ST1797" OR "KL1" OR "K1" OR "KL2" OR "K2" OR "KL64" OR "K64")
CBM
((("碳青霉烯"[常用字段:智能] OR "碳青霉烯类"[常用字段:智能] OR "亚胺培南"[常用字段:智能] OR "泰能"[常用字段:智能] OR "美罗培南"[常用字段:智能] OR "美洛培南"[常用字段:智能] OR "倍能"[常用字段:智能] OR "海正美特"[常用字段:智能] OR "中诺舒罗克"[常用字段:智能] OR "安吉利"[常用字段:智能] OR "联邦舒罗克"[常用字段:智能] OR "帕尼培南"[常用字段:智能] OR "克倍宁"[常用字段:智能] OR "厄他培南"[常用字段:智能] OR "厄他培南钠"[常用字段:智能] OR "怡万之"[常用字段:智能] OR "比阿培南"[常用字段:智能] OR "天册"[常用字段:智能] OR "安信"[常用字段:智能] OR "诺加南"[常用字段:智能] OR "多尼培南"[常用字段:智能] OR "多利培南"[常用字段:智能] OR "多力培南"[常用字段:智能] OR "多立培南"[常用字段:智能] OR "噻烯霉素"[常用字段:智能] OR "沙纳霉素"[常用字段:智能] OR "硫霉素"[常用字段:智能] OR "亚胺硫霉素"[常用字段:智能] OR "法罗培南"[常用字段:智能] OR "君迪"[常用字段:智能] OR "天显"[常用字段:智能]) AND ("耐药"[常用字段:智能] OR "耐药性"[常用字段:智能])) OR ("耐碳青霉烯"[常用字段:智能] OR "耐碳青霉烯类"[常用字段:智能] OR "耐亚胺培南"[常用字段:智能] OR "耐美罗培南"[常用字段:智能] OR "耐美洛培南"[常用字段:智能] OR "耐帕尼培南"[常用字段:智能] OR "耐厄他培南"[常用字段:智能] OR "耐比阿培南"[常用字段:智能] OR "耐多尼培南"[常用字段:智能] OR "耐多利培南"[常用字段:智能] OR "耐多力培南"[常用字段:智能] OR "耐多立培南"[常用字段:智能] OR "耐噻烯霉素"[常用字段:智能] OR "耐沙纳霉素"[常用字段:智能] OR "耐硫霉素"[常用字段:智能] OR "耐亚胺硫霉素"[常用字段:智能])) AND ("肺炎克雷伯氏菌病"[常用字段:智能] OR "肺炎克雷伯氏菌"[常用字段:智能] OR "肺炎克雷伯氏菌感染"[常用字段:智能] OR "肺炎克雷伯菌病"[常用字段:智能] OR "肺炎克雷伯菌"[常用字段:智能] OR "肺炎克雷伯菌感染"[常用字段:智能] OR "肺炎克雷伯杆菌病"[常用字段:智能] OR "肺炎克雷伯杆菌"[常用字段:智能] OR "肺炎克雷伯杆菌感染"[常用字段:智能] OR "肺炎克雷伯氏杆菌"[常用字段:智能] OR "肺克"[常用字段:智能]) AND ("高毒力"[常用字段:智能] OR "高毒力株"[常用字段:智能] OR "毒力基因"[常用字段:智能] OR "毒力因子"[常用字段:智能] OR "ST23"[常用字段:智能] OR "ST25"[常用字段:智能] OR "ST65"[常用字段:智能]

OR "ST1797"[常用字段:智能] OR "KL1"[常用字段:智能] OR "K1"[常用字段:智能] OR "KL2"[常用字段:智能] OR "K2"[常用字段:智能] OR "KL64"[常用字段:智能] OR "K64"[常用字段:智能]).

Eligibility criteria Population(s): Infections caused by carbapenem-resistant hypervirulent Klebsiella pneumoniae (CR-hvKP);
Outcomes: 1. General prevalence, 2. Prevalence by regions, 3. Mortality rate, 4. Risk factors, 5. Treatment and outcome by different strategy;
Study design: For CR-hvKP: RCTs, CCTs, cohort studies, case-control studies, case series, cross-sectional studies. For carbapenem-resistant -classic
Klebsiella pneumoniae (CR- classic Kp) and carbapenem-resistant -Klebsiella pneumoniae (CR-Kp): systematic review.
Studies that did not report in English or Chinese will be excluded.

Source of evidence screening and selection Two reviewers will screen studies after reading titles and abstracts of the search results. And the third party will be responsible for resolving the inconsistency. All potentially relevant citations will be requested and inspected in detail using the full-text version where available. Disagreements will be resolved by discussion, with assistance from a third party if necessary. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram will be constructed to show the full study-selection process.

Data management All data collected for the study should be recorded accurately, promptly, and legibly. For primary data collection, the investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. For data not obtained from a primary source (i.e., secondary data, such as claims and electronic health records), the investigator is responsible for reviewing data quality and relevance to the best of the investigator's knowledge. By signing this protocol either electronically or written, the investigator confirms that the quality and relevance of data has been assessed to meet the minimum requirements for all study objectives.

Language restriction No restriction.

Country(ies) involved China.

Keywords carbapenem-resistant and hypervirulent Klebsiella pneumoniae; prevalence; mortality; risk factors; treatment strategy.

Contributions of each author

Author 1 - Xiaoyu Chai - Xiaoyu Chai will draft the papper.
Email: klmytchristy@163.com
Author 2 - Qianyi zhou - Qianyi zhou will perform data collection, extraction and reviewe the manuscript.
Email: zhouqy316@163.com
Author 3 - Wei Jiang - Wei Jiang will perform data collection, extraction and reviewe themanuscript.
Email: nankaidoc@nankai.edu.cn
Author 4 - Jie Liu - Jie Liu obtained the funding and will provide the administrative, technical and logistic support.
Email: jie.liu3@merck.com
Author 5 - Yue Liu - Yue Liu obtained the funding and will provide the administrative, technical and logistic support.
Email: yue.liu3@merck.com
Author 6 - Yi Sun - Yi Sun obtained the funding and will provide the administrative, technical and logistic support.
Email: yi.sun3@merck.com
Author 7 - Wenjie Yang - Wenjie Yang will conceive the ideas and design the study.
Email: yangm8006@sina.com