J Antimicrob Chemother 2022; **77**: 1140–1145
https://doi.org/10.1093/jac/dkab495 Advance Access publication 19 January 2022

Journal of Antimicrobial Chemotherapy

Spread of hypervirulent multidrug-resistant ST147 *Klebsiella pneumoniae* in patients with severe COVID-19: an observational study from Italy, 2020–21

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Received 6 November 2021; accepted 15 December 2021

Objectives: To report an outbreak of hypervirulent *Klebsiella pneumoniae* (hvKp) in COVID-19 patients.

Methods: Prospective, observational study including consecutive COVID-19 patients with hvKp infections admitted to the University Hospital of Pisa (Italy). Clinical data and outcome of patients were collected. All patients were followed-up to 30 days from the diagnosis of infection. Mortality within 30 days of the diagnosis of hvKp infection was reported. The hypermucoviscous phenotype was determined by the 'string test'. Molecular typing was performed on three strains collected during different periods of the outbreak. The strains underwent whole genome sequencing using the Illumina MiSeq instrument. The complete circular assemblies were also obtained for the chromosome and a large plasmid using the Unicycler tool.

Results: From November 2020 to March 2021, hvKp has been isolated from 36 COVID-19 patients: 29/36 (80.6%) had infections (15 bloodstream infections, 8 ventilator-associated pneumonias and 6 complicated urinary tract infections), while 7/36 (19.4%) had colonization (3 urine, 2 rectal and 2 skin). The isolates belonged to ST147 and their plasmid carried three replicons of the IncFIB (Mar), IncR and IncHI1B types and several resistance genes, including the *rmpADC* genes encoding enhancers of capsular synthesis. The hvKp isolates displayed an ESBL phenotype, with resistance to piperacillin/tazobactam and ceftolozane/tazobactam and susceptibility only to meropenem and ceftazidime/avibactam. The majority of patients were treated with meropenem alone or in combination with fosfomycin. Thirty-day mortality was 48.3% (14/29).

Conclusions: ST147 ESBL-producing hvKp is associated with high mortality in COVID-19 patients. Strict microbiological surveillance and infection control measures are needed in this population.

Introduction

Hypervirulent (hypermucoviscous) *Klebsiella pneumoniae* (hvKp) is a concerning organism because it may cause life-threatening diseases. Although not specific for hvKp, an atypical trait of hvKp strains is the hypermucoviscous phenotype defined by a positive string test.[1]

Bacterial superinfections have been increasingly reported in patients with COVID-19 and may lead to poor outcome in these patients.[2] Prolonged hospitalization, widespread use of broad-spectrum antibiotics, use of steroids and immunomodulators are factors that increase the risk of multidrug-resistant organisms (MDRO) in these patients.[2] Recently, a fatal case of hvKp infection in a Japanese patient with COVID-19 has been reported.[3] Here, we describe a cluster of hvKp infections observed in COVID-19 patients in the University Hospital of Pisa (Italy).

Patients and methods

This single-centre, prospective, observational study included consecutive COVID-19 patients with hvKp infections admitted to the tertiary care University Hospital of Pisa (Italy) from November 2020 to March 2021. Epidemiological and demographic information, medical history, symptoms at admission and treatment details were collected. The use of steroids was classified as low- or high-dose based on the cutoff of 1 mg/kg/day of methylprednisolone or equivalents, as previously described.[4]

Patients were followed-up to 30 days from the diagnosis of infection. Thirty-day mortality was defined as death occurring within 30 days from the diagnosis of hvKp infection.

The hypermucoviscous phenotype was determined by the 'string test',[5] a positive reaction being defined as a bacteriological loop being able to generate a viscous filament ≥5 mm in length by stretching bacterial colonies growth at 37°C by 18–24 h on a blood agar plate (see Figure S1, available as Supplementary data at *JAC* Online). Susceptibility tests were performed with Merlin microdilution panels on a Tecan automated platform.

Molecular typing was performed on three strains (arbitrarily named PA, ZO and VA, Bioproject PRJNA746575) representative of three different periods of the outbreak November 2020, January 2021 and March 2021). The strains were analysed by WGS performed on genomic DNA purified using the Macherey Nagel DNA extraction kit (Düren, Germany), preparing paired-end libraries sequenced using the Illumina MiSeq instrument (Illumina Inc). *De novo* assembly of Illumina reads was performed using the SPADES 3.8 software (https://w3.iss.it/site/aries/). The PA strain, selected as representative of the outbreak clone, was also subjected to nanopore sequencing on the MinION Flow Cell (R9.4.1) following SQK-RBK004 sequencing procedures on an Mk1C MinION platform.[6]

The complete circular assemblies (Bioproject PRJNA746592; Acc no.s CP084984–CP084985) were obtained for the chromosome (5 379 443 bp) and a large plasmid (382 377 bp) by using the Unicycler tool (https://usegalaxy.eu). *In silico* analysis of antimicrobial resistance, replicons, and virulence gene content was performed on the chromosome and the plasmid of the PA strain, using Plasmid Finder, ResFinder and Kleborate online tools, respectively.[7–9]

The study was approved by the local Ethics Committee (Number 17681).

Results

During the study period, 1037 patients with COVID-19 were admitted to our hospital. We isolated hvKp from 36 COVID-19 patients. Of these, 29 (80.6%) patients had infections caused by hvKp [15 with bloodstream infection (BSI), 8 with ventilator-associated pneumonia (VAP), and 6 with complicated urinary tract infection (cUTI)], while 7 (19.4%) had colonization (3 urine, 2 rectal and 2 skin). Demographics and clinical features of patients with infections caused by hvKp are reported in Table 1.

Overall, 21/29 (72.4%) patients were cared for in ICU and underwent invasive mechanical ventilation (MV), 3/29 (10.3%) received non-invasive MV. The median time from admission to hvKp infection was 17 days (IQR 9.5–20). All patients received low molecular weight heparin and 27/29 (93.1%) steroids. Immunomodulatory drugs were administered in 7 (24.1%) patients. Twenty-six (89.7%) patients received intravenous antibiotics before the occurrence of hvKp infection: the majority received piperacillin/tazobactam with or without linezolid (16, 55.2%), followed by ceftriaxone with or without azithromycin (5, 17.2%), azithromycin alone (2, 6.9%), ceftobiprole (1, 3.4%), levofloxacin (1, 3.4%) and meropenem (1, 3.4%). Among the 26 patients who received antibiotics before the occurrence of hvKp infection, 18 (69%) had a previous documented infection: 2 patients had a documented respiratory coinfection (due to *Streptococcus pneumoniae*), 10 patients a documented VAP (4 *Pseudomonas aeruginosa,* 4 *K. pneumoniae*, 2 *K. pneumoniae* plus *Staphylococcus aureus*), 6 (23%) patients had a urinary tract infection. Eight patients received antibiotic therapy without a documented isolate.

All hvKp strains (100%) were resistant to third-generation cephalosporins, aminoglycosides, and fluoroquinolones and the majority (94.4%) were resistant to piperacillin/tazobactam, ceftolozane/tazobactam, and trimethoprim/sulfamethoxazole. The hvKp isolates were fully susceptible to meropenem and ceftazidime/avibactam (Table S1). *In silico* WGS studies performed by Kleborate demonstrated that the three isolates were ST147. Single nucleotide polymorphism (SNP) analysis demonstrated that they were closely related to each other (3–4 SNPs of

Table 1. Demographics and clinical characteristics of COVID-19 patients ($N = 29$) with infection caused by hvKp

Characteristic	Value
Age, years, median (IQR)	73 (65.5–77.5)
Male sex, *n* (%)	25 (86.2)
Coexisting comorbidities, *n* (%)	
COPD	3 (10.3)
Diabetes mellitus	5 (17.2)
Cardiovascular disease	20 (68)
Solid cancer	3 (10.3)
Ward of hospitalization (at time of infection), *n* (%)	
Intensive care unit	21 (72.4)
Sub-intensive care unit	3 (10.3)
Medical ward	5 (17.2)
Charlson Comorbidity Index, median (IQR)	3 (3–5)
SOFA score (at time of hvKp infection), median (IQR)	8.5 (0.75–11.25)
Septic shock (at time of hvKp infection), *n* (%)	8 (27.6)
Previous antibiotic therapy, *n* (%)	26 (89.7)
Source of infection, *n* (%)	
Bloodstream infection	15 (51.7)
Ventilator-associated pneumonia	8 (27.6)
Urinary tract infection	6 (20.7)
Concomitant medications, *n* (%)	
Remdesivir	6 (20.7)
Steroids	27 (93.1)
Dexamethasone 6 mg daily	8 (27.6)
Steroids high dose[a]	19 (65.5)
Low-molecular-weight heparin	29 (100)
Immunomodulatory drugs[b]	7 (24.1)
Respiratory support (at time of hvKp infection), *n* (%)	
Invasive mechanical ventilation	21 (72.4)
Non-invasive mechanical ventilation	3 (10.3)
Supplementary oxygen therapy	5 (17.2)
Time from admission to hvKp infection, days, median (IQR)	17 (9.5–20)
Time from hvKp infection to death, days, median (IQR)	5.5 (2–22.5)
30 day mortality, *n* (%)[c]	14 (48.3)

COPD, chronic obstructive pulmonary disease; hvKp, hypervirulent *K. pneumoniae*.

[a]High dose of steroids was defined as use of 1 mg/kg/day of methylprednisolone or equivalents

[b]Immunomodulatory drugs included baricitinib or tocilizumab.

[c]30 day mortality was defined as occurrence of death within 30 days from diagnosis of hvKp infection.

difference across 4283 core genes, data not shown).The plasmid carried three replicons of the IncFIB (Mar), IncR and IncHI1B types and several resistance genes [*aac(6′)-Ib, aadA1, bla*$_{OXA-9}$, *bla*$_{TEM-1A}$,*aph(3′)-Ia, mph(A), sul1, dfrA5, mph(E), sul2*], including *armA*, which encodes the 16S rRNA methyltransferase conferring resistance to all aminoglycosides, and the *bla*$_{CTX-M-15}$ extended-spectrum β-lactamase gene. No carbapenemases genes were detected on the plasmid. However, the plasmid carried the *iucA-D-iutA* hydroxamate siderophore aerobactin virulence determinant, and the *rmpADC* (allele 27) genes (*rmpA2* is

Table 2. Genetic features deduced from whole genome sequencing of the hypervirulent ST147 *K. pneumoniae* isolates

Locus	Location[a]	Positions[b]		Description/phenotype
IncFIB(Mar)	Plasmid	646	208	Replicon
IncR	Plasmid	35 322	35 072	Replicon
aac(6')-Ib	Plasmid	52 273	52 878	Amikacin, gentamicin, kanamycin resistance
aadA1	Plasmid	52 948	53 736	Streptomycin resistance
bla$_{OXA-9}$	Plasmid	53 781	54 620	Ampicillin resistance
bla$_{TEM-1A}$	Plasmid	55 320	56 180	Ampicillin resistance
rmpA	Plasmid	162 998	163 630	Enhancer of *cps* synthesis
iucA	Plasmid	180 751	182 541	Hydroxamate siderophore aerobactin
iucB	Plasmid	182 542	183 489	
iucC	Plasmid	183 489	185 222	
iucD	Plasmid	185 226	186 503	
iutA	Plasmid	186 585	188 786	
rmpA2	Plasmid	193 677	194 314	Enhancer of *cps* synthesis
aph(3′)-Ia	Plasmid	240 342	239 527	Kanamycin resistance
mph(A)	Plasmid	242 200	241 298	Erythromycin, azithromycin resistance
sul1	Plasmid	249 689	248 850	Sulfisoxazole resistance
dfrA5	Plasmid	250 687	250 214	Trimethoprim resistance
mph(E)	Plasmid	258 500	257 616	Erythromycin, azithromycin resistance
msr(E)	Plasmid	260 031	258 556	Erythromycin, azithromycin resistance
armA	Plasmid	263 103	262 330	Amikacin, gentamicin, kanamycin, streptomycin resistance
sul2	Plasmid	265 585	266 400	Sulfisoxazole resistance
IncHI1B	Plasmid	279 395	278 826	Replicon
bla$_{CTX-M-15}$	Plasmid	369 187	370 062	Ampicillin, ceftriaxone resistance
mrkA	Chromosome	876 941	877 549	Type 3 fimbriae synthesis
mrkB	Chromosome	877 645	878 346	
mrkC	Chromosome	878 358	880 844	
mrkD	Chromosome	880 835	881 830	
mrkF	Chromosome	881 844	882 479	
mrkJ	Chromosome	882 514	883 230	
mrkH	Chromosome	883 964	884 668	
bla$_{CTX-M-15}$	Chromosome	1 597 014	1 597 889	Ampicillin, ceftriaxone resistance
bla$_{CTX-M-15}$	Chromosome	1 671 695	1 672 570	Ampicillin, ceftriaxone resistance
fyuA	Chromosome	1 863 698	1 865 719	Yersiniabactin receptor resistance
ybtE	Chromosome	1 865 850	1 867 427	Yersiniabactin biosynthetic operon
ybtT	Chromosome	1 867 431	1 868 234	
ybtU	Chromosome	1 868 231	1 869 331	
irp1	Chromosome	1 869 328	1 878 819	
irp2	Chromosome	1 878 907	1 885 014	
ybtA	Chromosome	1 885 205	1 886 164	
ybtP	Chromosome	1 886 421	1 888 133	
ybtQ	Chromosome	1 888 120	1 889 922	
ybtX	Chromosome	1 889 915	1 891 195	
ybtS	Chromosome	1 891 223	1 892 527	

[a]Plasmid refers to location in the single large plasmid of 382 377 bp with FIB(Mar)-R-HI1B replicons, identified in the PA strain, carrying both virulence and resistance genes.

[b]Nucleotide positions refers to start and stop codon of each gene of the plasmid and chromosome complete circular sequences, respectively (Bioproject PRJNA746592; Accession no.s CP084984–CP084985).

frameshifted) encoding the enhancers of capsular synthesis, known to be responsible for the hypervirulent phenotype observed in this hvKp clone (Table 2 and Figure 1). On the chromosome, two other relevant virulence genetic determinants were identified, including the *mrkA-H* type 3 fimbriae synthesis cluster and the complete *fyu-ybt-irp* yersiniabactin biosynthetic operon. Two additional the $bla_{CTX\text{-}M\text{-}15}$ genes were identified in the chromosome, contributing to resistance to cephalosporins (Table 2).

Patients were treated with meropenem with or withou fosfomycin (17/29, 58.6%), ceftazidime/avibactam (4/29, 13.8%), and colistin/tigecycline (1/29, 3.4%). Seven patients did not receive any *in vitro* active therapy. Fourteen (48.3%) patients died within 30 days of hvKp infection: two had a cUTI, five a VAP and seven a BSI.

Discussion

We describe an outbreak of infections caused by hvKp in patients with SARS-CoV-2 pneumonia. To date, only one case of hvKp in a patient with COVID-19 has been reported.[3] Remarkably, all the hvKp strains belonged to ST147 and produced some specific virulence factors. Our study highlights some concerns.

First, ST147 is a high-risk Kp clone with the potential to become a major threat to public health. ST147 consists of multiple clades/clusters associated with various carbapenemases (KPC, NDM, OXA-48-like, and VIM), and has been responsible for several outbreaks in India, Italy, Greece, North Africa and, more recently, Spain.[10,11] In our hospital, NDM-producing Kp belonging to ST147 has been endemic since November 2018.[11–13] In patients with rectal colonization by this strain, we observed an increased risk of developing bacteraemia caused by the same organism, a fact that highlights its high propensity to cause severe infections.[12] The hypervirulent phenotype poses a serious therapeutic problem, since this hvKp remains fully susceptible only to meropenem and new β-lactams/β-lactamases inhibitors (ceftazidime/avibactam and meropenem/vaborbactam). Resistance of hvKp isolates to piperacillin/tazobactam and ceftolozane/tazobactam represents a major concern. Susceptibility to these two β-lactam/β-lactamase inhibitor combinations may be impaired in ESBL-producing organisms carrying the $bla_{CTX\text{-}M\text{-}15}$ gene, especially in high-inoculum infections.[14,15] In line with these findings we found that hvKp in our study carried $bla_{CTX\text{-}M\text{-}15}$ both in plasmid and chromosomal locations. This

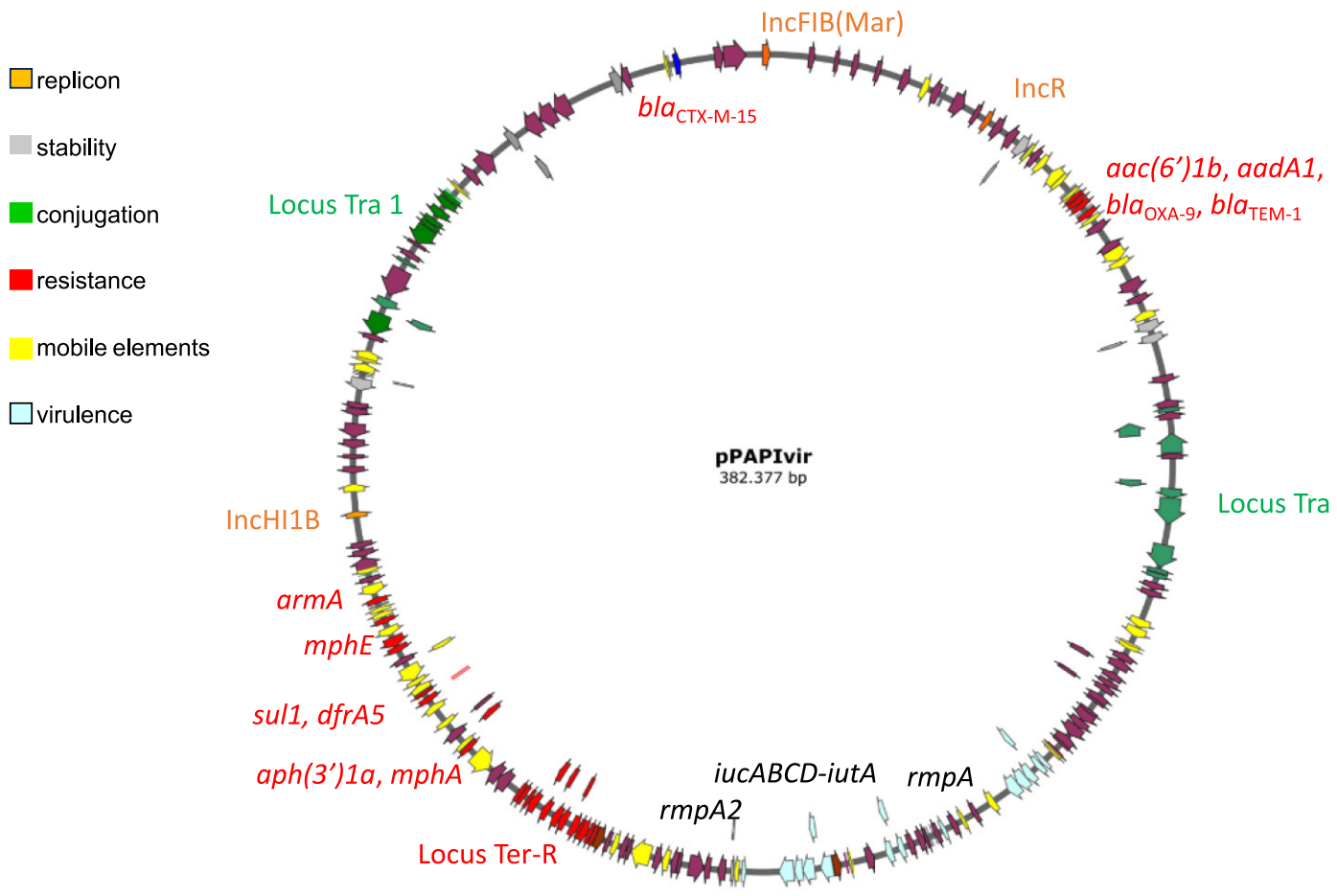

Figure 1. Major structural features of the FIB(Mar)-R-HI1B resistance and virulence plasmid identified in the hypervirulent outbreak ST147 clone, Pisa 2020–2021. Predicted coding sequences are indicated by coloured arrows oriented in the direction of transcription of each respective gene. Important plasmid features (virulence, resistance, replicons, transfer loci) are coloured as indicated in the key.

MDR phenotype makes necessary the use of carbapenems or, alternatively, of drugs such as ceftazidime/avibactam with increased costs and risk of induction of resistance.[16]

The second important point is the high mortality associated with hvKp infections (48.3%), which is significantly higher than that we detected in COVID-19 patients who had superinfections in our hospital (18.8%) during the first wave.[2] This finding suggests a role for the virulence factors associated with the hypervirulent phenotype, such as the aerobactin cluster, already found to be associated with increased virulence in mice,[1,17] and with the hypermucoviscous phenotype, such as *rmpA* genes that reduce binding affinity of the strain to macrophage cells and cause resistance to phagocytosis.[18]

Finally, a significant proportion of patients in our cohort received broad-spectrum antibiotics before the occurrence of hvKp infections because of suspected or confirmed infection. It should be underlined that the majority of patients in our cohort were hospitalized in ICU and received antibiotics because of documented superinfections. In any case, the use of antibiotics remains unacceptably high in hospitalized patients with COVID-19. A recent study found that 37% and 85% of patients with COVID-19 received an antibiotic before they were admitted and during their hospital stay, respectively.[19] Antimicrobial stewardship programmes and adherence to current guidelines should be implemented in COVID-19 patients.[20]

The spread of hvKp in our hospital reinforces the importance of adhering to standard infection prevention and control precautions in COVID-19 patients, to prevent the cross-transmission between patients and dissemination of MDRO. To this end we implemented strict surveillance cultures in COVID-19 wards, contact precautions and isolation procedures for infected/colonized patients, which has been followed by a decline of the isolation rate during the last 6 months (March to September 2021). As reported in a recent study, in our centre we performed a systematic surveillance for rectal colonization by carbapenem-resistant Enterobacteriaceae (CRE) but not by ESBL-producing organisms.[12] Thus, we did not know the rectal colonization status for hvKp. After the outbreak of hvKp in COVID-19 patients, we implemented our surveillance system and we now search for hvKp on rectal swabs in specific high-risk patients, such as solid organ transplant recipients admitted to ICU.

In conclusion, hvKp superinfections may represent a significant cause of mortality in patients with severe COVID-19. Strict microbiological surveillance and infection control measures are needed.

Funding

This study was supported by internal funding.

Transparency declarations

M.F. received grants and/or speaker honoraria from MSD, Angelini, Shionogi, Pfizer, Menarini, Gilead and Nordic Pharma. F.M. has participated in advisory board and/or received speaker honoraria from Angelini, Correvio, Merck Sharp &Dohme (MSD), Nordic Pharma, Pfizer, Astellas, Gilead, Bristol-Myers Squibb (BMS), Janssen, ViiV, bioMérieux, Biotest, Becton Dickinson, Pfizer, and Shionogi. The remaining authors have none to declare.

Author contributions

M.F. conceived the study and wrote the manuscript; G.T. collected data and wrote the manuscript; G.A., G.B. and A.C. coordinated experimental design, performed data analysis and wrote the manuscript; A.L., C.G. and S.B. performed experiments; S.T. collected data; R.M. was involved in patient assistance; F.M. was involved in patient assistance and revised the manuscript.

Data availability

The three *Klebsiella pneumoniae* (PA, ZO and VA) genomes have been released under Bioproject PRJNA746575.

Supplementary data

Figure S1 and Table S1 are available as Supplementary data at *JAC* Online.

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