Carbapenemase-producing *Klebsiella pneumoniae* in elderly frail patients admitted to medical wards

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ABSTRACT

Carbapenemase-producing *Klebsiella pneumoniae* (CPKP) is rapidly emerging as a leading nosocomial infection in many countries, especially in Italy where it is considered endemic. In this paper we briefly summarize the main characteristics of this outbreak, focusing on its recent spread to elderly frail patients admitted to internal medicine and geriatric wards. Severity of disease, clinical complexity and a large number of comorbidities seem to be major risk factors in clinical practice, although scientific evidence is still lacking, since until now studies have been carried out mainly in intensive care settings. We also discuss the possible role of gut microbiota in CPKP colonization onset and the possible role of pre-probiotics in promoting eradication.

Introduction

Nosocomial infections by multi-drug resistant Gram-negative bacteria have nowadays become a worldwide threat for the health of hospital inpatients.[1] In this scenario, carbapenemase-producing *Klebsiella pneumoniae* should be considered a major health concern, since it has the capacity of causing large pandemic foci in different hospital settings.[2] Carbapenemases are special types of β-lactamase that show high genetic variability and relevant hydrolyzing capacity for carbapenems. *K. pneumoniae* is the most frequent species where the production of carbapenemases has been documented, even if reports of other bacterial species showing this mechanism of resistance to carbapenems, like *Acinetobacter baumannii* and *Citrobacter freundii*, are constantly rising.[2-5]

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Epidemiology

The first *in vivo* isolation of a carbapenemase-producing *K. pneumoniae* (CPKP) strain dates back to 2000 in North Carolina in an intensive care unit patient.[6] In the following years, many CPKP-related cases of severe septic shock have been described in Intensive Care Units (ICUs) of Northeastern United States.[7] By the end of 2000s, CPKP had reached all developed countries worldwide, but characteristically affecting different countries in a non-homogeneous way. In fact, there are some countries in Europe, like Greece, where CPKP infection is endemic by now, while, for example, in Portugal and Sweden it has been detected only sporadically.[2,3]

Italy has faced CPKP later than other European countries, but, if possible, in a more serious way. The first isolation is dated 2009 in Florence in a patient with a complicated intra-abdominal infection[8] and, since then, CPKP has quickly spread all over the country with a large number of pandemic outbreaks, so that Italy has been recently upgraded to an endemic country status.[2]

Clinical features

CPKP primarily colonizes lower intestinal tract and inguinal or perineal skin of hospital inpatients. Colo-

nization is generally asymptomatic and does not require specific treatment. However, in some cases, CPKP can enter bloodstream and cause systemic infections, mainly complicated urinary tract infections or septic shock, whose prognosis is generally unfavorable even when an adequate intensive medical treatment is instituted. Mortality rates of about 41-80% have been reported in literature when infection occurs.[9,10] Given the high degree of antibiotic resistance by these bacteria, therapeutic options are indeed very limited, including variable combinations of aminoglycosides, tigecycline, colistin and fosfomycin. There is much debate in literature about the possible use of carbapenems at high dosage or in combination therapy when *K. pneumoniae* minimum inhibitory concentrations for imipenem are <4 mg/L. Pros of this approach are the drug-sparing policy and the low risk for further resistance induction, cons are the controversial efficacy and the low tolerability of high-dose regimens.[11] However, there is also growing evidence that combination therapy, for example with meropenem, colistin and tigecycline, is the only effective way to diminish mortality.[12,13]

Transmission

CPKP transmission is mainly by contact, either direct or indirect. Subjects with a normal intestinal microbiota, like healthcare professionals but unlike hospital inpatients, are generally protected against colonization, even if they may act as vehicles and thus transmit bacteria to susceptible patients. Sanitary measures such as contact isolation, cohorting of positive patients and epidemiologic surveillance with weekly rectal swabs performed to all high-risk patients of the same ward of the index case have proven to be effective in limiting CPKP transmission.[14,15]

Few studies have evaluated risk factors for colonization or infection so far. In ICU-admitted patients, the importance of prior antibiotic exposure, prior hospitalization, severe illness and respiratory failure has been emphasized,[16,17] together with bacterial genotype and phenotype.[18]

New clinical scenarios and perspectives

In the existing literature, CPKP infection is mainly described as an ICU-setting concern. However, clinical practice, at least in Italy, is rapidly changing. CPKP outbreaks are seen more and more often also in internal medicine and geriatric wards, especially in frail elderly subjects with multiple comorbidities. There are actually some epidemiological reports showing that most CPKP patients are not infected in an ICU-setting, but instead in common internal medicine wards, and data seem to show that this phenomenon is continuously rising as the diffusion of CPKP spreads.[19-21] As a matter of fact, besides published data, CPKP is rapidly emerging as one of the leading nosocomial infections in internal medicine practice and rectal colonization is more and more often recognized anywhere an epidemiologic surveillance program is instituted.

Susceptibility to nosocomial infections and immunologic rearrangements globally known as immunosenescence are well-known features of frailty.[22] On the other side, CPKP isolates in everyday clinical practice do more and more often belong to elderly with a high degree of clinical complexity, a large number of comorbidities and frequently bedridden or cognitively impaired. Thus we may hypothesize that frailty and comorbidity themselves are a strong risk factor for CPKP colonization, together with the ones already described in literature (Table 1).

Table 1. Well-established and possible risk factors for carbapenemase-producing *Klebsiella pneumoniae* colonization and infection in clinical practice.

	Risk factors well established in literature	Possible risk factors
Disease-related	Severe illness High APACHE-II score Need for mechanical ventilation Respiratory failure	High number of comorbidities Chronic disease Immunodeficiency
Healthcare-related	Prior hospitalization Intensive Care Unit admission Prior antibiotic exposure Prior therapy with carbapenems	Internal Medicine or Geriatric Unit admission Prolonged hospital stay Nursing home residency Prolonged bed rest High number of medical devices High number of diagnostic invasive procedures
Patient-related		Advanced age Frailty Movement disability
Bacteria-related	Genotype and phenotype of *Klebsiella pneumoniae* strain	

Moreover, frail elderly usually have a different fecal microbiota composition than adults.[23,24] This may cause a lower bacterial competition at an intestinal level, making rectal colonization easier for CPKP strains. In fact, once a CPKP-positive patient is discharged from hospital, a normal gut microbiota is restored as he or she recovers, and therefore CPKP can be spontaneously eradicated. Thus one may hypothesize that restoring a normal gut flora through probiotics might be an effective way to treat CPKP colonization and to prevent systemic infection onset.

Our experience

In our clinical experience at Parma University Hospital we observed 133 cases of CPKP positivity from August 2011 to May 2012. In most cases patients were frail elderly with many comorbidities admitted to internal medicine wards. Rectal swab performed for epidemiologic surveillance was the most frequent means of detection, so that simple enteric colonization was more common than actual infection. However, when infection occurred, it was extremely serious with development of a sometimes fatal septic shock.

In a subgroup of 36 CPKP-positive patients we also carried out a pilot study to detect the possible role of high-dose symbiotic probiotic in achieving CPKP eradication. Patients randomly received usual care alone (18 patients) or usual care plus a common commercial symbiotic supplement [5 high-dose (24×10^9 colony forming units) probiotic strains alive and psyllium fiber, 18 patients] for 14 days. Patients in both treatment and control group did not differ for general baseline features, even if patients who had developed a CPKP-related infection before randomization were 26% in treatment group and 6% in control group (P=0.186). In the treatment group we observed a significantly higher incidence of rectal swab negativization than in control group (53% *vs* 12%, P=0.0094, χ^2 test). Mortality was not statistically different (31% treatment group *vs* 12% control group, P=0.236). These preliminary results seem to confirm the assumption that gut microbiota is crucial in CPKP colonization in elderly patients and that probiotic therapy may be effective for eradication.

Conclusions

As our experience confirms, carbapenemase-producing *K. pneumoniae* is becoming a major health concern also in internal medicine and geriatric settings, especially for those patients who already have serious diseases and a complex clinical course. Raising clinicians' awareness about the importance of CPKP screening and management will be crucial to limit the pandemic spread, especially in endemic countries like Italy. We also hope that further research will clarify risk factors for CPKP colonization and the possible role of gut microbiota in the onset and management of the infection.

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