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The burden of infections caused by Metallo-Beta-Lactamase-Producing Enterobacterales in Italy: epidemiology, outcomes, and management

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SUMMARY

Metallo-β-lactamase (MBL)-producing Enterobacterales represent a growing public health threat due to their intrinsic resistance to several antibiotics. In Italy, the burden of infections caused by these organisms has been steadily increasing. In recent years, MBL-producing *Klebsiella pneumoniae*, particularly those carrying New Delhi metallo-β-lactamase (NDM) enzyme, have emerged across multiple Italian regions, frequently associated with high-risk clones such as ST147. These infections are associated with high morbidity, mortality, and healthcare costs. While advances in diagnostic techniques have improved the detection of MBLs, underreporting and heterogeneous practices are common. Therapeutic options remain limited.
The rising incidence and clinical complexity of MBL-producing Enterobacterales in Italy underscore the urgent need for coordinated actions to improve surveillance, diagnostics, infection control, and optimize antimicrobial stewardship. The development of novel therapeutic agents and the implementation of strategies for managing MBLs are crucial to reduce their clinical and public health impact. This review aims to provide a comprehensive overview of the current epidemiology, clinical outcomes, and management challenges of infections caused by MBL-producing Enterobacterales in Italy.

Keywords: Antimicrobial resistance, Epidemiology, *Klebsiella pneumoniae* NDM, Metallo-β-lactamase-producing Enterobacterales.

INTRODUCTION

Carbapenem-resistant Enterobacterales (CRE), including *Klebsiella pneumoniae* (*K. pneumoniae*) and *Escherichia coli (E. coli)*, represent a great challenge worldwide [1]. Their resistance is largely mediated by the production of carbapenemases, as reported in Table 1 [2]. However, this is not a unique resistance mechanism. Multiple mechanisms including efflux pump overexpression and porin loss have been implicated in carbapenem resistance among Enterobacterales. These co-existing resistance determinants, often harbored within the same strain, significantly complicate phenotype of resistance.
MBL-producing CRE pose a global health threat due to limited therapeutic options and high attributable mortality, especially in elderly and immunocompromised patients [3-7]. The economic bur-

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Table 1 - Molecular classification of the ß-lactamases enzymes (Ambler classification).

Class	*Mechanism of action of the hydrolytic domain*	*Representative enzymes*	*Target*
A	Serine-based inactivation mechanism	Narrow-spectrum (PSE, CARB)	Carboxypenicillins
		ESBL (CTX-M, TEM, SHV)	Cephalosporins
		Class A Carbapenemase (KPC, IMI/NMC-A, GES, SME, SHV-38, SFC-1)	Carbapenems, cephalosporins
B	Metallo-β-lactamases, inactivation mediated by zinc ion(s)	NDM, VIM, IMP, CphA	Carbapenems
C	Serine-based inactivation mechanism	AmpC	Cephalosporins
D	Serine-based inactivation mechanism	OXA CHDL	Carbapenems

AmpC: Ampicillin C-type β-lactamase; CARB: Carbenicillinase; CHDL: carbapenem-hydrolizing Class D β-lactamase; CphA: Carbapenem-hydrolyzing metallo-β-lactamase A; CTX-M: cefotaximase, Munich; ESBL: extended-spectrum b-lactamases; GES: Guiana Extended-Spectrum β-lactamase; IMI: Imipenem-hydrolyzing β-lactamase; IMI/NMC-A: Imipenemase/non-metallocarbapenemase-A; IMP: Imipenemase; KPC: *Klebsiella pneumoniae* carbapenemase; NDM: New Delhi metallo-β-lactamase; OXA: Oxacillinase; PSE: Pseudomonas-specific enzyme; SFC: Serratia fonticola carbapenemase; SHV: Sulfhydryl-variable; SME: Serratia marcescens enzyme; TEM: Temoniera; VIM: Verona integron-encoded metallo-β-lactamase.

den of these infections is also considerable, since they are associated with prolonged hospital stays and increased healthcare costs [8]. The global spread of these resistant pathogens, mainly driven by dominant clonal complexes, is largely facilitated by horizontal gene transfer which promotes the persistence and diversification of resistance genes across different bacterial hosts [9]. With regards to species, both carbapenem-resistant *K. pneumoniae* and *E. coli* represent a threat for human health. However, recent studies have highlighted the growing clinical concern posed by MBL-producing *E. coli*, particularly in the context of urinary tract infections (UTI) [10-12]. In fact, uropathogenic *E. coli* are characterized by substantial genetic heterogeneity, high prevalence of carbapenemase-encoding genes (including bla_{NDM} and bla_{OXA} variants), and enhanced biofilm-forming capacity [10-11]. This pathogen is increasingly detected in immunocompromised patients, such as kidney transplant recipients, and can be related to poor clinical outcome [10].

In recent years, the epidemiological landscape is changing with a global increase in the MBL detection among CRE. Until 2018, *K. pneumoniae* carbapenemase (KPC) was the predominant carbapenemase in the United States and Europe, including Italy [13-15]. However, the ATLAS study (2018-2019) showed regional variation in MBL prevalence, with rates of 59.4% in Asia–Pacific and 49% in Africa/Middle East [16]. In the US, KPC prevalence declined from 73.8% in 2019 to 57.1% in 2021, whereas MBLs increased from 3.8% to 20.4% [17]. Moreover, 7.8% of meropenem-nonsusceptible Enterobacterales co-produced two carbapenemases, most commonly NDM and OXA-48-like carbapenemases [16]. Although outbreaks of MBL-producing Enterobacterales have been reported in Italy, national surveillance data remain limited, highlighting the need for updated epidemiological insight [5, 14, 18-20].

This review aims to provide an updated summary of the epidemiology, infection outcomes, and clinical impact of MBL-producing Enterobacterales in Italy.

METHODS

A comprehensive literature search was conducted using PubMed to identify relevant studies on infections caused by MBL-producing Enterobacterales in Italy published in the last 15 years. The studies were retrieved using the logical combinations of the search terms "Infections", "*Metallo-beta-lactamase*", "*Klebsiella pneumoniae*", "Enterobacterales", "Enterobacteriaceae", "*carbapenem-resistant Enterobacterales*", "CRE" and "Italy". Inclusion criteria focused on epidemiology, treatment outcomes, management and surveillance of MBL-producing Enterobacterales in Italy. Data from these studies were summarized in this narrative review to provide an overview of the burden, transmission, and clinical management of these infections.

EPIDEMIOLOGY

The recently published risk assessment by the European Centre for Disease Prevention and Control (ECDC) reported a 10.2% increase in the incidence of bloodstream infections (BSI) caused by carbapenem-resistant *K. pneumoniae* in Italy between 2019 and 2023 [21]. The most recent Italian National Surveillance report describes 3,867 cases of BSI caused by CRE in 2023 compared to 2,183 in 2016, with the highest incidence observed in Central Italy, followed by the South and Islands, and the North [6]. These infections are predominantly linked to urinary tract and central/peripheral venous catheters [6].

In 74.9% of cases, KPC was identified as the enzyme responsible for carbapenem resistance, whereas MBL enzymes were detected in 13.8% of cases, marking an increase from 8.4% reported in 2022. NDM and VIM represented 89% and 9% of the total MBL respectively [6]. NDM-producing *K. pneumoniae* was mostly identified in Lombardy, Tuscany, Piedmont, Sicily, and Apulia, where multiple hospitals have reported outbreaks [5, 6, 22, 23].

The first outbreak of NDM-1-producing sequence type (ST) 147 *K. pneumoniae* emerged in the North-Western area of the Tuscany region in late 2018 and was associated with an increase in BSI during 2019–2020 [19, 22, 23]. Subsequently, other outbreaks have been documented from 2020 to 2022 in Apulia (22.6% of isolates with NDM-producing *K. pneumoniae*), and more recently in Pavia area, where an NDM-producing *K. pneumoniae* clone ST6668 rapidly spread across hospitals [19, 24].

The NDM-producing *K. pneumoniae* ST147 linked to the Tuscany outbreak has been extensively characterized [23, 25]. Susceptibility to aztreonam-avibactam was reported in 99.7% of cases, whereas susceptibility to aminoglycosides, fosfomycin and tigecycline was detected in 30%, 67% and 70.9% of isolates, respectively [5]. Fully susceptibility to cefiderocol according to 2023 EUCAST breakpoints was detected in 33.2% of cases, whereas the 69.2% of isolates had an alone of inhibition in the area of technical uncertainty [5].

Co-existence of different resistance genes encoding carbapenemases within the same strain has been reported [26-30]. The simultaneous presence of multiple carbapenemases in invasive isolates is increasing, suggesting an evolutionary advantage [26-30]. Co-infections involving NDM and OXA-48 are becoming more frequent, particularly in *K. pneumoniae* strains [18, 29, 31]. In Italy, 3.4% cases of BSIs with simultaneous carbapenemase were reported in 2023 with respect to 2.6% in 2022 [8]. Recently, NDM-1/OXA-48 coproducing- *K. pneumoniae* isolates from BSI have been reported in Calabria region [31]. In all the strains, beta-lactamases resistance genes, bla_{OXA-48}, bla_{NDM-1}, $bla_{CTX-M-15}$, and bla_{SHV}, were found. Most of the NDM-1/OXA-48 producing *K. pneumoniae* strains belonged to the high-risk clone ST147 [31].

Another study reported the first documented case in Italy of a *K. pneumoniae* strain carrying three different carbapenemases, NDM-1/5, and OXA-48, on separate plasmids, isolated in Milan in 2019 [18]. All isolates were resistant to almost all antibiotics available at that time, except for colistin and tigecycline [18]. Co-expression of multiple carbapenemases was found also in a study from Apulia, with 11 isolates out of 459 displaying NDM + KPC, and one isolate KPC + VIM [23] (Figure 1).

Resistance genes such as bla_{NDM}, often carried on mobile genetic elements like Inc_{X3} plasmids, can spread easily between bacteria. The presence of multiple plasmids and the rapid transfer of resistance genes increase the risk of spreading resistance to other *K. pneumoniae* strains or different Enterobacterales. This amplifies the potential for outbreaks in intensive care units (ICUs) and hospital wards, making infections more difficult to treat, and underscoring the need for infection control measures to prevent transmission [32].

Of importance, MBL are increasingly detected not only among *K. pneumoniae* isolates [7, 33-35]. A recent study reported a nosocomial outbreak of VIM-producing Enterobacterales that occurred in an Italian medical unit from November 2021 to December 2023. The spread involved several different species of Enterobacterales, including *K. oxytoca*, *Enterobacter cloacae*, *Citrobacter freundii* [35]. These reports highlight the evolving epidemiological landscape beyond *K. pneumoniae.*

Although most infections caused by CRE occur in the hospital settings, community-acquired infections are alarmingly increasing becoming a threat especially in frail patients. For instance, residents in long-term facilities are at higher risk for the potential broad antibiotic use [36-39]. Long-term care facilities were identified as hotspots for the spread of CRE, emphasizing the need for implementing

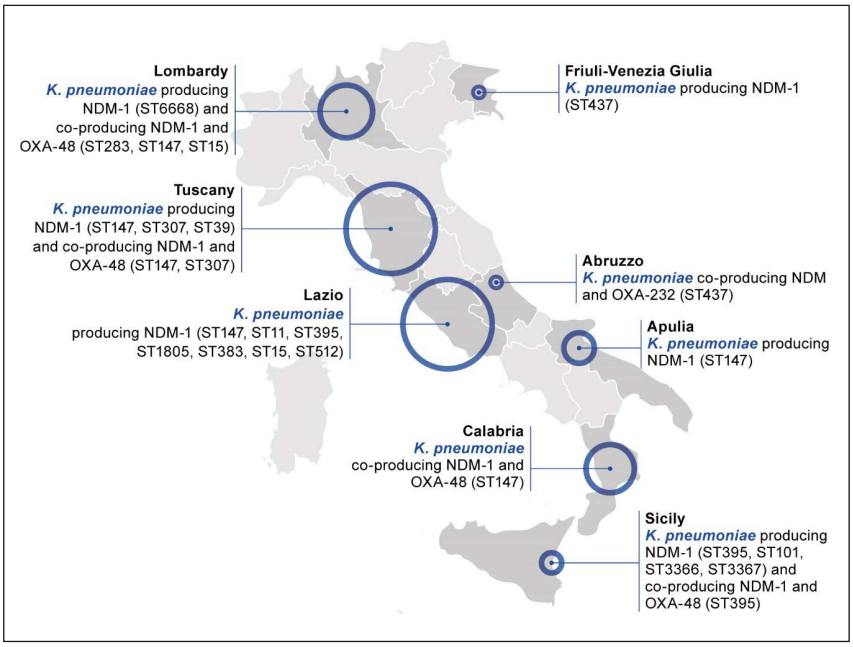

Figure 1
Geographic distribution of selected outbreaks of NDM-1 producing *K. pneumoniae* across Italy (2018-2023).*
The figure includes only isolates for which clone type (ST) was specified according to [5, 18, 19, 23, 27, 28, 31, 41, 61].

*ST147 NDM1-producing *Klebsiella pneumoniae* is endemic in the Tuscany region, whereas other clones have been sporadically detected.

infection control measures, including efficient disinfection protocols and systematic rectal screening in hospitals as well as in nursing homes to reduce patients' transmission [36-39].
According to national surveillance data, 18.7% of BSI caused by CRE in Italy in 2023 had their onset at home, and 6.9% occurred in residential care facilities, confirming that a significant proportion of CRE-BSI originate outside of hospitals [6]. Some studies showed that NDM-producing CRE spread in the community and may be responsible for incident cases of infections in patients admitted to Emergency Department [40].

ENVIRONMENTAL SOURCES

Environmental reservoirs play a critical role in the transmission of MBL-producing Enterobacterales, particularly in the context of prolonged or recurring outbreaks. Environmental surfaces can harbor biofilm-associated populations of CRE. These niches support bacterial survival and promote horizontal gene transfer, making them ideal settings for sustained colonization by multidrug-resistant strains. Environmental contamination can lead to indirect patient-to-patient transmission through splashes, aerosols, or contaminated hands and equipment, even in the absence of direct contact. Environmental niches, such as sink drains or water systems, can sustain long-term colonization by CRE, facilitating indirect patient-to-patient transmission and contributing to the transition from epidemic to endemic spread.
Environmental persistence can favor hospital dissemination of MBL-CRE, in particular of VIM-producing isolates. In fact, the study by Oliveri et al highlighted the role of environmental persistence in the spread of MBL-CRE in hospital settings [35]. In this study, the implementation of increasingly aggressive infection control practices was apparently able to temporarily mitigate the spread of VIM-CRE but not to eradicate the phenomenon, which was likely supported by an environmental reservoir of VIM-positive strains [35]. Environmental VIM-positive isolates were ubiquitous in sinks in the ward but with a prevalent distribution in the rooms most distant from the waste disposal, potentially indicating an improper use of sinks for the disposal of body fluids from colonized patients [35]. Therefore, routine environmental screening and targeted interventions, including enhanced cleaning protocols, water system decontamination and implementation of infection control measures should be considered integral components of infection prevention and control strategies.

COLONIZATION AND RISK OF PROGRESSION TO INFECTION

Intestinal colonization with carbapenem-resistant *K. pneumoniae* represents a critical precursor to invasive infections in hospitalized patients [40, 41]. Among patients in high-risk units (i.e., Intensive Care and Neonatal Intensive Care Units, Haematology Unit, Emergency Room, and Neurological Clinic), 4.9% developed BSI caused by the same intestinal colonizing strains [41]. The concordance between rectal and blood samples strains was confirmed by whole genome sequencing through analysis of sequence type, resistance and virulence genes, and plasmid profile [41]. This detailed analysis allowed the recognition of the ST101 and ST395 as emerging invasive clones over the conventional ST258/ST512. Moreover, this study reinforced asymptomatic gastro-intestinal colonization as a reservoir for potential subsequent invasive infections, especially in ICU and immunocompromised patients [40, 41].

The risk of progression from intestinal colonization to invasive infection is a key concern in patients with colonization by MBL-producing Enterobacterales. A recent national systematic review estimated an overall progression rate from colonization to infection among CRE carriers of 11% [42]. Notably, the risk varied substantially across bacterial species and healthcare settings, with higher rates reported for *K. pneumoniae* and among patients in intensive care units and onco-hematology wards. Moreover, intestinal colonization by CRE can be associated with different risk of BSI depending on the carbapenemase type [40]. The CHIMERA study, which included 677 rectal carriers of carbapenemase-resistant *K. pneumoniae* of whom 56.4% were NDM, 36.5% KPC, 5.8% VIM, and 1.8% OXA-48, found that the risk of BSI differed by carbapenemase type. Specifically, patients with rectal colonization by NDM–producing *K. pneumoniae* had higher risk of BSI compared to KPC rectal carriers (59/382, 15.4% versus 20/247, 8.1%, respectively, p=0.004) [40]. The incidence rates of BSI per 100 patients per month was significantly higher in the NDM group (22.33, 95% CI 17.26-28.88) than in the KPC group (9.56, 95% CI 6.17-14.82), suggesting that the type of carbapenemase may influence the risk of subsequent BSI [40]. This higher incidence of BSI in the NDM group seems to be mainly related to an increased virulence of the ST147 NDM clone [40].

The knowledge of colonization status may be useful to identify carriers and, consequently, implement infection control measures and guide the choice of an appropriate empirical therapy when septic shock occurs [12]. Although universal colonization screening is not routinely implemented, routine rectal screening for CRE may be useful in high-risk hospital wards, e.g. onco-hematology and ICUs, in subjects with immunosuppression (e.g. transplant and oncological patients), in patients with septic shock, and in epidemiological setting endemic for different carbapenemases (KPC vs NDM vs OXA-48) [40]. Further studies are needed to better delineate the contexts in which molecular rectal screening should be implemented.

OUTCOMES

BSI by MBL-producing CRE are associated with poor patients' outcomes [3-5, 21, 38-40]. The highest mortality rates have been reported in elderly patients hospitalized in internal medicine units and in ICU [43-45]. A recent study including 30 patients with NDM-Kp BSI hospitalized in internal medicine reported a 30-day mortality rate as high as 46.7% [43]. Of importance, urinary tract infections by NDM-producing CRE are associated with treatment failure in elderly patients, underscoring the impact of antimicrobial resistance in this high-risk population [44]. In ICU setting, patients with infections due to NDM-producing Enterobacterales had both a mortality rate and a treatment failure rate of 37.5% in the ICU [45].

In the ALARICO study, which included more than 1000 cases of BSI due to carbapenem-resistant Gram-negative bacilli in Italy, the highest attributable mortality was observed in patients with MBL-producing Enterobacterales (35%), followed by carbapenem-resistant *A. baumannii* (16%), carbapenem-resistant *P. aeruginosa* (19%), and KPC-producing *K. pneumoniae* (5%) [3] (Table 2). These data highlight the poor prognosis associated with MBL-related infections. In the ALARICO study nearly two-thirds of patients with NDM received colistin-containing regimens, that may have contributed to the high mortality rates in this group [3]. On the contrary, most of KPC received ceftazidime/avibactam, highlighting that the choice of

Table 2 - Summary of time from hospital admission to BSI, time from BSI to outcome and 30-day mortality of infections caused by different carbapenem-resistant Gram-negative bacilli from the ALARICO Study [3].

Pathogen	*Time (days) from hospital admission to BSI (median, IQR)*	*Time (days) from BSI to outcome (median, IQR)*	*30-day mortality*	*Excess mortality*
CS-GNB	2 (IQR 0–13)	14 (IQR 9–21)	13.7%	Reference
KPC-CRE	14 (IQR 2–30)	19 (IQR 11–30)	26.6%	5%
MBL-CRE	13 (IQR 5–24)	18 (IQR 8.5–30)	36.4%	35%
CRPA	17 (IQR 2–26)	21 (IQR 12–30)	32.8%	19%
CRAB	11 (IQR 3–24)	16 (IQR 9–24)	43.2%	16%

CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacterales; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CS, carbapenem-susceptible; GNB, gram-negative bacilli; IQR, interquartile range; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamases.

antibiotic may contribute to the clinical outcome of patients with CRE BSI. Moreover, these findings reflect the broader challenge in managing MBL-BSI in the absence of effective targeted therapies during the study period. Delays in appropriate treatment and limited access to active agents likely played a key role in the high mortality rates observed. These results reinforce the clinical need for early identification of MBL-producing strains and access to novel therapeutic agents, which can offer promising activity against these difficult-to-treat pathogens. Recent evidence supports this observation. A multicenter retrospective cohort study conducted in seven hospitals in Italy and Israel investigated the association between carbapenemase type (NDM vs KPC vs OXA-48) and 30-day mortality in patients with BSIs caused by CRE [46]. The authors found no difference in mortality rates between carbapenemase groups, suggesting that differences in clinical outcomes may be more strongly influenced by host factors and treatment appropriateness than by the specific carbapenemase type itself [46].

One of the major determinants of outcome in patients with BSI by CRE is represented by the timing of appropriate antibiotic therapy, that should be started as early as possible, ideally within the first 24 hours following blood culture collection [47]. Thus, inadequate molecular diagnostics, relying solely on phenotypic resistance information, further complicates treatment and contributes to delayed therapy [48].

DIAGNOSTIC TESTS IN ITALY

Improved laboratory capabilities for detecting carbapenemase types have advanced understanding of CRE epidemiology and colonization, enabling targeted interventions. However, underreporting and inconsistencies in surveillance protocols across Italy may influence the actual burden of MBL-producing Enterobacterales [6].

Detection of carbapenemases is required for patient management, rapid implementation of infection prevention and control protocols, and epidemiologic purposes. Therefore, microbiology laboratories must be able to detect and report carbapenemases among Gram-negative organisms from both cultured isolates and directly from clinical specimens for treatment and surveillance purposes.

Detection methods for β-lactamase can be classified into three groups: those based on phenotypic detection, those based on the hydrolysis by β-lactamase, and β-lactamase gene detection. For a detailed description of these methods refer to review papers [2, 49].

Rapid immunochromatographic methods, such as lateral flow assays, designed to detect specific carbapenemase enzyme family, have been increasingly used and in some cases they are applied to accurately detect these enzymes from positive blood cultures and direct rectal swabs [50-52]. CLSI guidelines emphasize the importance of using phenotypic assays to identify and differentiate specific carbapenemase types and suggest a stepwise approach for carbapenemases detection, prioritizing phenotypic methods for initial screening and then using genotypic methods for confirmation and identification of specific carbapenemase types.

The modified carbapenem inactivation method (mCIM) and EDTA-modified carbapenem inactivation method (eCIM) are indicated to distinguish serine-beta-lactamases from MBLs [53]. EUCAST un-

derlines the importance of screening for resistance mechanisms of epidemiological and infection control importance [54]. Molecular methods and lateral flow assays for the rapid identification and characterization of carbapenemase types are recommended. These methods offer faster results compared to traditional culture-based methods. Sullivan E and colleagues compared the NG-Test Carba-5 lateral flow assay against a PCR-based molecular method (Cepheid Xpert Carba-R) for detecting carbapenemase genes (bla_{KPC}, $bla_{NDM,}$ bla_{VIM}, bla_{IMP}, bla_{OXA-48}) [55]. The results showed 98.2% overall agreement and a significantly faster turnaround time [55].

Moreover, matrix-assisted laser desorption ionization-time of flight mass spectroscopy (MALDI-TOF MS) is emerging as a promising tool for direct CRE detection from blood samples and epidemiological surveillance [48].

In many Italian hospitals, molecular testing for the detection of carbapenemase genes, primarily targeting the five major ones (bla_{KPC}, bla_{NDM}, bla_{OXA-48}-like, bla_{IMP}, bla_{VIM}) is a key diagnostic tool used both at hospital admission and during hospitalization [40, 56]. Automated commercial molecular assays have the advantage of simplified workflow and procedures that can be performed with minimal molecular expertise and many of them demonstrated good performance with excellent sensitivity and specificity [57].

EMERGING LANDSCAPE OF THERAPEUTIC STRATEGIES AGAINST MBL-CRE

Effective management of CRE infections requires coordinated regional efforts to improve surveillance and implement robust infection control measures [6]. At the same time, the evolution of treatment options plays a critical role in improving patient outcomes [58, 59].

Very limited therapeutic options are currently available for the treatment of infections caused by MBL-CRE. They include old (colistin, fosfomycin or tigecycline) and new (aztreonam/avibactam and cefiderocol) antibiotic regimens.

Historically, colistin was the cornerstone of treatment, but its use has decreased due to toxicity and suboptimal efficacy [3]. Cefiderocol is a potential option, but concerns about reduced susceptibility, in particular against NDM-1 producing Enterobacterales, may limit its use, especially as empirical treatment [5, 60-63].

A recent epidemiological study showed that, using the EUCAST breakpoints, the prevalence of cefiderocol-non susceptible strains is higher among CRE compared to non-fermenting Gram negative bacilli, such as *P. aeruginosa* [64]. More specifically, cefiderocol non-susceptibility was exceedingly high in NDM-producing Enterobacterales (38.8%) [64]. In Italy, an outbreak reported in Florence involved 21 strains of NDM-1-producing Enterobacterales resistant to cefiderocol out of a total of 52 recorded between August 2021 and July 2022 [60]. This occurred regardless of prior exposure to the drug, thus demonstrating that cefiderocol-resistant strains do not necessarily exhibit fitness defects and can spread even in the absence of direct selective pressure [60]. The largest observational study on MBL conducted in Pisa reported that up to 66.8% of MBL-producing Enterobacterales were resistant to cefiderocol [5]. A recent publication from Udine described the emergence of cefiderocol resistance in an NDM-1-producing *K. pneumoniae* strain following treatment, along with its subsequent intra-hospital spread [61]. In Genoa, cefiderocol resistance was also reported in clinical isolates from pediatric patients with no prior exposure to the drug: 16 out of 30 tested Enterobacterales strains (mostly MBL producers) were found to be resistant [65].

Aztreonam-avibactam (ATM-AVI) is an emerging option for treating MBL infections recently approved by EMA [66-70]. This treatment combines the stability to MBLs of aztreonam with the inhibition ability of avibactam against wide range of beta-lactamases, including extended-spectrum beta-lactamases (ESBLs) that are often co-expressed by MBL-producing bacteria [10, 71]. The molecule showed an *in vitro* broad activity against multi-resistant Enterobacterales, including MBL-producing strains, with a lower prevalence of resistant strains compared to other combined compounds and cefiderocol [72-74]. A multicenter *in vitro* study conducted in 21 European countries, which included meropenem-resistant Enterobacterales strains collected in 2020, showed susceptibility rate to cefiderocol of 75% and to ATM-AVI of 99% [75]. Notably, among cefiderocol-resistant strains (one third of which originated from Italy and frequently harbored multiple resistance mechanisms) 94.6% remain susceptible to ATM-AVI, underscoring both the possible differences in susceptibility profiles between the two agents,

and the clinical value of retaining both as therapeutic options [75].
Another agent undergoing evaluation is cefepime-taniborbactam, which combines a
cephalosporin with a β-lactamase inhibitor, that demonstrates potent activity against a broad range of β-lactamases, including class A (e.g., KPC), class C, class D, and several class B β-lactamases such as NDM [76]. However, its activity does not extend to all MBLs, as it shows limited or no activity against IMP-type carbapenemases, highlighting the importance of molecular characterization when selecting targeted therapy [59]. Other two investigational β-lactam/β-lactamase inhibitor combinations, cefepime/zidebactam and cefepime/nacubactam, have shown promising *in vitro* activity against MBL-producing Enterobacterales. Zidebactam acts both as a β-lactamase inhibitor and as a β-lactam enhancer by binding to PBP2, which enhances the activity of cefepime even in the presence of MBL. Similarly, nacubactam also inhibits serine β-lactamases (including ESBLs and AmpC) and enhances cefepime activity by PBP2 binding [59].
Of particular concern is the emerging co-production of VIM and mobilized colistin resistance (*mcr*) genes in Enterobacterales, which significantly limits therapeutic options [77]. The simultaneous presence of carbapenemase- and colistin-resistance mechanisms confers resistance to two major last-resort antibiotic classes, leaving few or no effective treatments available.
Overall, data from clinical studies on MBL-producing Enterobacterales are still limited and studies to investigate further therapeutic options are warranted [78, 79].

CONCLUSIONS

The rising prevalence of MBL-producing Enterobacterales in Italy, once confined to localized outbreaks, now demands broader clinical awareness. Rectal colonization remains the main risk factor, supporting the implementation of rectal screening in high-risk wards and, when possible, its extension to other healthcare settings. Hospital-level surveillance, with timely data sharing, is essential to guide infection management.
The rising prevalence and complexity of MBL-producing Enterobacterales infections in Italy highlight the urgent need for integrated infection prevention strategies. These should combine routine molecular surveillance, including whole-genome sequencing, with environmental diagnostics to detect hidden reservoirs, and targeted antimicrobial stewardship to guarantee the optimal therapeutic options in infected patients. Coordinated efforts at both the hospital and national level are essential to prevent the further spread of these difficult-to-treat organisms and to mitigate their clinical and public health impact.

Author contribution
All authors conceived the study, analyzed the literature, wrote, edited, and critically revised the manuscript. All authors approved the current version for submission

Conflicts of interest
GT received speaker honoraria by Shionogi, Gilead, Menarini, Pfizer and honoraria for participation on a scientific board from MSD and Advanz Pharma. MF received unconditional grants from Gilead and speaker honoraria from Shionogi, Pfizer, Menarini, MSD, Gilead, GSK, MundiPharma, and Thermo Fisher.
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