Acquired Metallo-β-Lactamases: An Increasing Clinical Threat

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(See the article by Peleg et al. on pages 1549–56)

Production of β-lactamase was the first recognized mechanism of bacterial resistance to β-lactam antibiotics and remains the major cause of β-lactam resistance in gram-negative pathogens [1]. Two different families of β-lactamases, evolutionarily and mechanistically unrelated to each other, have evolved in bacteria: the serine-β-lactamases and the metallo-β-lactamases (MBLs). The latter enzymes, which open the β-lactam ring with the help of a metal cofactor, can degrade all classes of β-lactams except monobactams and are notable for their constant and efficient carbapenemase activity. This is a most worrisome feature because carbapenems, which are stable against the vast majority of serine-β-lactamases produced by resistant pathogens, are the antibiotics with the broadest spectrum of activity and are among the few backup agents for use against multidrug-resistant gram-negative pathogens. Moreover, MBLs are not susceptible to therapeutic β-lactamase inhibitors (such as clavulanate and penicillanic acid sulphones), and no new inhibitor of these enzymes is yet in the pipeline [2, 3]. In spite of these threatening properties, the MBLs (discovered in the mid-1960s) were initially regarded as resistance determinants of low clinical importance, compared with serine-β-lactamases, because they were detected in only a few species of minor pathogenic potential (e.g., *Bacillus cereus, Stenotrophomonas maltophilia,* some *Aeromonas* species, a cluster of strains of *Bacteroides fragilis,* and some flavobacteria). That view abruptly changed with the appearance of acquired MBLs, encoded by genes carried on mobile DNA elements, among major gram-negative pathogens, including members of the family Enterobacteriaceae, *Pseudomonas aeruginosa,* and *Acinetobacter* species [1, 2]. IMP-1 was the first acquired MBL to be identified; it was discovered in the early 1990s in Japanese hospitals in carbapenem-resistant isolates of *Serratia marcescens, P. aeruginosa,* and other gram-negative pathogens. During the past decade, both the global dimension of this problem and an unanticipated diversity of enzymes have been revealed, as acquired MBLs have been detected in clinical isolates from Asia as well as from Europe and North and South America [3]. Currently, the most prevalent and widespread acquired MBLs are the IMP-type and VIM-type enzymes, of which several variants are known. However, 3 additional types of acquired MBLs—SPM-1, GIM-1, and SIM-1—have recently been identified [3, 4] which suggests that the capture by bacteria of similar resistance genes in the clinical setting could be an ongoing, relatively common, and rapidly increasing phenomenon.

Although the potential threat of acquired MBLs is no longer questioned [1, 2], the extent of their future clinical impact remains an open issue. In fact, only a few relatively large outbreaks of strains that produce MBLs have been reported [3, 5], and although studies that describe the clinical characteristics of patients from whom MBL-producing organisms were isolated have shown relatively high rates of colonization [6–8], no major epidemic of clinical infection has thus far been traced to similar strains.

Peleg et al. [9] provide us with new insight into this issue, supporting the view that acquired MBLs should be considered an increasing clinical threat. The article describes the emergence and rapid dissemination of an acquired MBL determinant in a hospital setting in Australia, a continent where this resistance mechanism had not previously been reported. The MBL gene involved in the outbreak was $bla_{\text{IMP-4}}$, an allelic variant of the $bla_{\text{IMP-1}}$ gene previously identified in clinical isolates of *Acinetobacter* species and *Citrobacter youngae* from Hong Kong and the People's Republic of China [10, 11]. It was likely imported to Australia from those areas via international travelers. During a 7-month period, following the first detection in a *P. aeruginosa* isolate, the MBL gene was found in hospital-acquired isolates of gram-negative pathogens of 5 different species, including *P. aeruginosa, S. marcescens, Klebsiella pneumoniae, Enterobacter cloacae,* and *Escherichia coli.* This is the first study to report such a rapid emergence in a single hospital of the same ac-

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quired MBL determinant in several different species, as well as in different strains of the same species (clonal diversity was observed among the MBL-positive isolates of *K. pneumoniae* and *S. marcescens*). A similar scenario suggests that intraspecific and interspecific gene transfer played a major role in the dissemination of the MBL determinant within the hospital setting after its first introduction in the intensive care unit (ICU). The ICU was clearly the "melting pot" for this dissemination, since most MBL-positive isolates were from ICU patients (or were related to ICU admission), and MBL-positive isolates of different species were also sequentially detected in the same ICU patient. Clonal expansion of some IMP-4–producing strains was also evident, denoting the spreading potential for individual clones. Another notable finding by Peleg et al. [9] is the high rate of clinical infections (75%) associated with the MBL-positive strains, compared with the lower infection-versus-colonization rates reported in previous studies [6–8]; serious infections such as ventilator-associated pneumonia and septicemia were the most common [9]. Overall, this is an alarming report: (1) it underscores the propensity of acquired MBL determinants to intercontinentally disseminate; (2) it highlights the possibility that introduction of similar resistance genes in the nosocomial setting can be followed by a rapid dissemination among the different species of gram-negative pathogens which can cause nosocomial infections in that hospital; and (3) it emphasizes the importance of surveillance also in those hospital settings where acquired MBL determinants are known or presumed to be absent or uncommon.

Acquisition of an MBL determinant can significantly reduce the number and type of antimicrobial agents to which the microorganism is susceptible. In fact, MBL producers usually exhibit complex multidrug-resistant phenotypes because of their nosocomial origin and because of the frequent links between MBL genes and other resistance genes on the mobile DNA elements that are involved in their dissemination [3]. The strains from the Australian outbreak were no exception, which left only a few therapeutic options, and some of these (e.g., therapy with aztreonam or colistin) have uncertain roles [9].

In their study, Peleg et al. noticed that only a low number of MBL-producing isolates appeared to be carbapenem-resistant by conventional susceptibility testing [9]. This was apparently related to the high prevalence of Enterobacteriaceae among the MBL producers. In fact, it is known that, unlike *P. aeruginosa* and *Acinetobacter* species, Enterobacteriaceae with acquired MBL genes tend to exhibit carbapenem MICs that remain lower than the breakpoint for resistance, unless permeability is also impaired [3, 12]. This phenomenon has major implications for the detection of similar isolates (and consequently for surveillance) and also for the selection of antimicrobial chemotherapy. Concerning detection, specific diagnostic tests are necessary to assess MBL production by clinical isolates because the antimicrobial susceptibility profile obtained by conventional testing is neither a specific nor a sensitive indicator [3]. Concerning antimicrobial selection, despite some controversy that still exists, current knowledge strongly suggests that MBL-producing organisms should be considered biologically resistant to carbapenems (regardless of the results of susceptibility testing) and these drugs should not be used to treat infections with such organisms. This view is supported by the findings of Peleg et al. [9] that most patients (including those with clinical infections) were receiving a carbapenem prior to the isolation of an MBL-producing organism.

In conclusion, there is mounting evidence that acquired MBLs are emerging as resistance determinants of increasing clinical importance, and they should be carefully monitored. The emergence of MBL-producing organisms with complex multidrug-resistant phenotypes in a nosocomial setting can be a formidable therapeutic challenge, especially in view of the dearth of new drugs active against multidrug-resistant gram-negative pathogens, and should be considered a matter of major concern for infection control management.

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