EDITORIAL

The new threat to carbapenems, and antibiotics in general, is now widely recognised as NDM-1. Bacteria possessing NDM-1 also carry with it a plethora of other antibiotic resistance genes (often co-hosted on plasmids) including those mediating resistance to aminoglycosides, macrolides, sulphamethoxazole, quinolones and other beta-lactams. Accordingly, most strains present with a multi-drug resistant (MDR) phenotype and some a pan-drug resistant (PDR) phenotype. Thus, there now looms an urgent need to use existing drugs more wisely by optimising dosing, thereby maximising patient outcome and preventing resistance. Such prudence will also ensure good practice for newly released compounds and those currently in the pharmaceutical pipeline.

This issue synergistically combines the topical story of NDM-1 and provides solutions for overcoming MDR and PDR bacteria.

Although the name, and alleged etiology of NDM-1, is still being vigorously disputed, the genetic pool would suggest that it began somewhere in India, Pakistan or Bangladesh. In this region, sanitation is desperately poor with a high risk of dissemination of NDM-1, and medical resources can vary considerably. Microbiologists must therefore apply whatever means (automated methods VITEK®, Etest® and/or disk diffusion) available to ascertain the growing problem of MDR phenotypes and provide useful information on individual patient isolates ensuring appropriate treatment. If laboratories are not large enough to warrant automation, the Etest can provide an accurate MIC for selected antibiotics, and its storage, application and readability is ideally suited for such regions.

The Minimum Inhibitory Concentration (MIC) is the most basic requirement for tailoring antibiotic therapy to maximise outcome. The site of infection, type of bacteria, patient immune status and organ function are all factors that will affect therapeutic outcome and whilst laboratories cannot control these variables, they can ensure that one parameter, an accurate MIC, is professionally delivered – particularly for critically ill patients.

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STATE-OF-THE-ART

NDM-1, the emerging carbapenemase

DEFINITION

New Delhi metallo β-lactamase (NDM-1) is a resistance protein belonging to the unusual group of β-lactamases capable of hydrolyzing all β-lactams including carbapenems, except monobactam aztreonam (1). This group includes well-known metallo-β-lactamases (MBLs), such as IMP and VIM MBLs, which all possess zinc ions in their active site, hence their name (2). NDM-1 was identified as early as 2008 in Sweden from an Indian patient hospitalized in a New Delhi hospital in 2007 (1). NDM-1 was first detected in a Klebsiella pneumoniae isolate as a source of urinary tract infection, and simultaneously from an Escherichia coli isolate as faecal normal flora (1). The spread of NDM-1 producers corresponds to the transmission of a single gene, the NDM-1 gene, in different genetic and species backgrounds (3).

WORLDWIDE EPIDEMIOLOGY AND CLINICAL INFECTIONS

After the first identification of NDM-1, many other NDM-1 isolates were identified during an extended survey performed in the UK, India, Pakistan and Bangladesh mostly reporting NDM-1 producers in K. pneumoniae and E. coli and published mid-August 2010 (3). A total of 37 NDM-1...
producers were identified in the UK and 143 NDM-1 producers from countries located on the Indian subcontinent. This extended survey reported that the emergence of NDM-1 producers in the UK could be traced back to 2008. The current number of cases identified in the UK is now over one hundred (D. Livermore, personal communication).

Additional cases of NDM-1 producers have been identified in India, mostly reported from a Mumbai hospital in E. coli and K. pneumoniae. Since mid-August 2010, additional NDM-1 producers have been identified worldwide except for Central and South America; Austria (n=3), Canada (n=4) (9), Belgium (n=4) (10), Denmark (n=1) (11), China (n=3) (Y. Yunsong, personal communication), France (n=2), Germany (n=1) (12), Hong Kong (n=1) (Health Authorities, public announcement), Israel (n=1) (D. Ben David, personal communication), Italy (n=2) (G. Rossolini, personal communication), Japan (n=1) (Y. Yamamoto, personal communication), Singapore (n=1) (13), the Netherlands (n=2), Norway (n=2), South Korea (n=2) (official public announcement), Sweden (n=2) (1), Taiwan (n=1) the United States (n=5) (15, 16) (Figure 1). We have personally identified additional cases, including the first cases in Australia (n=1) (15), France (n=2) (15, 16), Kenya (n=7) (15), and Sultanate of Oman (n=2) (16) in 2009 and 2010 for which detailed published data are available. Most of the identified cases of NDM-1 producers worldwide have been from patients hospitalized in 2009 and 2010.

In most, but not all cases, the origin of patients or a patient hospitalization can be traced to the Indian subcontinent. Of the first 29 UK patients reported to be positive for NDM-1 producers, 17 had previously travelled to the Indian subcontinent, and 14 had been hospitalised there (10). Therefore, the source of contamination of 12 UK patients could not be traced back to the Indian subcontinent and may correspond to acquisition in the UK. Several cases have also revealed the origin of patients or hospitalization stay as being in different Balkan countries (Montenegro, Kosovo, Serbia, Bosnia-Herzegovnia) and in the Middle East (Dubai, Sultanate of Oman) with no relationship to the Indian subcontinent (Figure 1) (10). This is the case for patients from Austria, Belgium, Denmark, Italy and Germany. In addition, one of the four cases identified in France was a patient transferred from an Iraqi hospital who had never been to the Indian subcontinent (P. Nordmann, unpublished data). For several cases (at least mainland China, Kenya and several UK cases), patient travel abroad could not be identified.

NDM-1 has been identified in Enterobacteriaceae (mostly in K. pneumoniae and E. coli), and also in enterobacterial species such as K. oxytoca, Proteus mirabilis, Enterobacter cloacae, Citrobacter freundii, Providencia spp. This gene has also been reported in at least several Acinetobacter baumannii isolates from India, Germany, the UK, and mainland China (15). Therefore, evidence of exchange of the NDM-1 gene between unrelated Gram-negative species is well-established.

The type of infections associated with NDM-1 producers are mostly hospital-acquired infections, since most of the studies on NDM-1 producers so far originate from hospital-based studies. As suggested in the large study reporting NDM-1 producers from India, Pakistan, Bangladesh and the UK (4), we were able to clearly establish the community acquisition of an NDM-1 producer by identification of a colonized woman after a three-month stay in the Indian state of Darjeeling (16). This raises concern about the spread of NDM-1 producers in the environment - at least on the Indian subcontinent. Indirect fecal-oral transmission may therefore be likely to play a major role in community settings, via contaminated hands, food and water. Isolates of Enterobacteriaceae producing NDM-1 have caused a range of infections typical for organisms of this genus, including urinary tract infections, diarrhoea, septicaemia, pulmonary infections, peritonitis, device-associated infections and soft tissue infections (15, 16). No evidence is available indicating that NDM-1 producers are more virulent than non-NDM-1 producers.
GENETICS

The epidemic of NDM-1 producers does not correspond to the spread of a single bacterial isolate. The NDM-1 gene has been identified in many different enterobacterial and non-enterobacterial species and in different isolates belonging to the same enterobacterial species. In India, NDM-1-positive K. pneumoniae were clonally related in a given area (Haryana), whereas they were not in other areas of India and in Pakistan. We have identified the same NDM-1-producing K. pneumoniae ST14 clone from isolates from India, the Sultanate of Oman and Kenya indicating, as reported for ESBL producers, that a specific clone may be geographically widespread. NDM-1 has been identified in unrelated plasmid structures differing in both size and structure. Interestingly, the plasmids identified in the UK were not the same as those identified on the Indian subcontinent.

Therefore, genetic vectors of the NDM-1 gene are multiple. In addition, the few data we have concerning the surrounding genetic structures bracketing the NDM-1 gene indicate that unrelated transposon-like structures may be associated with the spread of this gene. No published data are yet available showing the in-vivo mobility of the NDM-1 gene, although the chromosome and plasmid location of the gene has been identified. It is possible that the surrounding structures may be also associated with variation of expression of the NDM-1 gene as recently identified by our team (P. Nordmann, personal communication).

RESISTANCE PATTERN OF NDM-1 PRODUCERS

NDM-1 is commonly found in isolates that exhibit resistance to a wide range of β-lactam and non-β-lactam antibiotic molecules, and are highly multi-resistant, in some instances to virtually all clinically-available antibiotics. Many NDM-1 producers remain susceptible only to colistin and tigecycline. A few isolates, mostly E. coli, retain a degree of susceptibility (or of intermediate resistance) to antibiotics such as chloramphenicol, tetracycline, fosfomycin, a few aminoglycoside molecules, furanes and aztreonam. Most of the NDM-1 producers expressed an ESBL determinant such as CTX-M-15, whereas some of them also contained a plasmid-mediated cephalosporinase. In the very first study that identified a NDM-1 K. pneumoniae producer, NDM-1 was associated with resistance determinants such as those encoding for ESBL, plasmidmediated cephalosporinase, aminoglycoside methylase and macrolide esterase gene. In addition, in an NDM-1-positive C. freundii isolate, we have identified nine β-lactamasms including three carbapenemases (NDM-1, VIM-4 and OXA-181) (Figure 2). Such multi-drug resistance patterns explain why identification of NDM-1 producers based only on a phenotypic-based analysis is difficult.

DETECTION

To stem the onset of NDM-1 producers, early identification of cases of NDM-related infections and of the carriers is essential. NDM-1 susceptibility to carbapenemas varies, and many isolates may be considered susceptible to several carbapenemas, even though the recently updated CLSI breakpoints for carbapenemas are followed. As observed for producers of other types of carbapenemas, such as KPC, ertapenem may also be the most appropriate molecule for detecting NDM-1 producers with low-level resistance to carbapenemas. Automated susceptibility testing systems, such as the VITEK™ 2 (bioMérieux, France), correctly flag NDM-1 producers as carbapenemase producers. Further phenotypic identification of MBL production may then be based on the use of a combined test (IMP/IMP + EDTA) and the Etest™ MBL (bioMérieux). The Etest MBL strip is a method specifically designed for detecting MBL producers based on inhibition of the enzyme activity by EDTA. We do not recommend the Hodge test for detecting MBL activity, as it is time-consuming and may lack specificity. Molecular-based techniques such as PCR are the gold standard for identification of NDM-1 producers (best followed by sequencing analysis of the PCR products). We have developed a multiplex PCR assay for detecting the main types of clinically-significant carbapenemase genes, including NDM-1.

The efficient prevention of the spread of NDM-1 producers also requires a rapid screening technique that is able to detect NDM-1 producers at the carriage state (mostly in the gastrointestinal tract), when severely-ill patients are hospitalized in at-risk hospitalization units (ICU, surgery, transplantation…). Screening of NDM-1 carriers may be based on culture media such as chromId™ ESBL (bioMérieux), which contains a cephalosporin. This medium has been designed for screening extended spectrum β-lactamase producers, and gives excellent results at low detection limits ranging from 8 x 100 to 5 x 102 CFU/ml. The CHROMagar KPC culture medium (CHROMagar Ltd, France) contains a carbapenem molecule, and has shown much higher limits of detection (1 x 101 to 5 x 105 CFU/mL). It may be proposed for the follow-up of out-breaks with NDM-1 producers, after checking that the epidemic strain grows on that selective medium.

Colonies growing on screening media may be tested for NDM-1 producers by determining their carbapenem susceptibility level followed by molecular methods (Figure 3). This is the screening strategy that we have recommended to the French Health authorities, and which has been implemented for all patients transferred to a French hospital from a foreign hospital on the day of admission. A similar strategy could be implemented on a worldwide scale.
At the local level, detection of NDM-1 producers as agents of infection should be made for any infected patient, whereas detection of the carriage state should be done for severely-ill patients. Detection of NDM-1 producers should be combined with the implementation of hygiene measures. Such hygiene measures have been known for years (no need to reinvent the wheel!) for the containment of hospital-based multi-drug resistant Gram-negatives rods (for example ESBL producers) and may simply be translated to the containment of NDM-1 producers. They will prevent the development of nosocomial outbreaks, and identification of the carriage state may help to guide the choice of the most adequate antibiotic therapy should the colonized patient develop an infection. Diagnostic tools and extended medical knowledge on the management of Gram-negative outbreaks are already available, enabling immediate action at the local level for efficient prevention of nosocomial outbreaks with NDM-1 producers. There is no need to wait! 

At the international level, the response to the growing issue of multi-drug resistance in Gram-negatives is based on the implementation of a worldwide surveillance network designed to discover and provide online reporting of emerging broad-spectrum antibiotic resistance trends. Such a network should be managed by the World Health Organization, and should be based only on established laboratories already existing in both developed and emerging countries.

In addition, there is an urgent need for designing (or redirecting) research programs in big pharma, as well as in small biotechs, in order to discover novel molecules for treating Gram-negative infections. Based on the analysis of the discovery of novel antibiotic molecules over the past sixty years and on the knowledge of Gram-negative genetics, our belief is that totally novel chemically-based products could be a solution to this emerging resistance issue, at least in the short- and mid-term. Finally, let’s be bear in mind that E. coli is the most common human bacterial pathogen and that the window of opportunity is rapidly closing. 

It is difficult to predict the true spread rate (months, years?) of NDM-1 producers worldwide. There is no reason to believe that this outbreak may stop spontaneously. It appears that at least two reservoirs have been already identified in the Indian subcontinent (Bangladesh, India, Pakistan) and in the Balkan states, as well as in several countries in the Middle East. So far, there is no evidence of community-based acquisition of NDM-1 producers outside the Indian subcontinent, which will remain a main reservoir of NDM-1 producers simply because of the size of its population.

It seems that in the case of NDM-1, E. coli could be an important source of isolates, whereas the other carbapenemases (IMP, VIM, KPC) are mostly located in the hospital-based K. pneumoniae species. One of the most important threats would be that dissemination of the NDM-1 gene may mirror the spread of CTX-M ESBLs, as observed in E.coli and then in K. pneumoniae. The rate of ESBL producers is already very high in many countries in the world, including those known to be reservoirs for NDM-1 producers (30). E. coli is responsible for easily transmissible infections (mostly community-acquired infections such as diarrhoea and urinary tract infections) and may be the reservoir for transmission of the NDM-1 gene to other bacterial species such as K. pneumoniae in the hospital environment. K. pneumoniae is known to be the most powerful pathogen for dissemination of multi-drug resistance in Gram negatives in hospitals.

Antibiotic stewardship and antibiotic control, surveillance studies on antibiotic consumption, risk assessment studies are excellent examples for trying to reduce antibiotic resistance, but their effect, if any, will only produce results in the long term. However, we believe that there should be an urgent response to the emergence of carbapenemase producers in Enterobacteriaceae at both local and international levels.

**PERSPECTIVES**

- At the local level, detection of NDM-1 producers as agents of infection should be made for any infected patient, whereas detection of the carriage state should be done for severely-ill patients. Detection of NDM-1 producers should be combined with the implementation of hygiene measures. 
- At the international level, the response to the growing issue of multi-drug resistance in Gram-negatives is based on the implementation of a worldwide surveillance network designed to discover and provide online reporting of emerging broad-spectrum antibiotic resistance trends. 
- There is an urgent need for designing (or redirecting) research programs in big pharma, as well as in small biotechs, in order to discover novel molecules for treating Gram-negative infections. 
- It is difficult to predict the true spread rate (months, years?) of NDM-1 producers worldwide. 

**REFERENCES**

Antimicrobial chemotherapy is arguably the most important medical breakthrough of the last 100 years. Unfortunately, over the last decade there has been an explosion of resistance. Indeed, there are infections with *Pseudomonas aeruginosa*, *Acinetobacter* spp. and some *Klebsiella pneumonia* that are virtually untreatable. This has been identified as a crisis by the Infectious Diseases Society of America (1), leading to a series of whitepapers and their “10 for 20” program (2), where IDSA pushes for pharmaceutical companies to generate 10 new molecules active against resistant pathogens, with an emphasis on Gram-negative pathogens, by the year 2020.

Such a program will help, but is only part of the answer. In addition, we must treat patients in a way that minimizes the probability of resistance emergence. The timely knowledge of the Minimal Inhibitory Concentration (MIC) for a variety of agents and NOT just “S”, “I” or “R” is central for decision-making in choice of drug, drug dose and schedule of administration that will generate a favorable clinical outcome and minimize emergence of resistance. Further, this understanding will prolong the useful lifetime for the drugs that emerge from the “10 for 20” program.

**TABLE 1**

<table>
<thead>
<tr>
<th>Information Required for Optimal Management of Infections</th>
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<tbody>
<tr>
<td>1. Infection site</td>
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<tr>
<td>2. Antibiotic choices (e.g. drugs on formulary)</td>
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<tr>
<td>3. Identity of infecting pathogen</td>
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<td>4. MIC of different drugs for the infecting pathogen</td>
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<td>5. Protein binding for the different drugs</td>
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<tr>
<td>6. Population pharmacokinetics for the different drugs, including site penetration data</td>
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<tr>
<td>7. Exposure targets for differing amount of bacterial kill or for resistance suppression* or targets derived from clinical data</td>
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</tbody>
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* generally derived with preclinical animal models or in vitro hollow fiber infection models

**FIGURE 1**

Only non-protein-bound drug is microbiologically active.

The MIC, Clinical Outcome and Suppression of Emergence of Resistance

When evaluating a patient for treatment of infection, the first and most critical step is to **identify the locale of the infection**. Different doses of drug are required for different locals (e.g. bacterial skin and skin structure infections versus meningitis versus pneumonia). These differences are driven mainly by differing degrees of drug penetration to the infection site. Importantly, the true difference in site penetration between patients is also a highly important factor.

Once the infection site is identified, there are a number of pieces of information required to make an informed choice of drug, dose and schedule. These are shown in Table 1.

Once the site and the causative organism are identified, we need to be cognizant of the **drugs available for therapeutic choice**. For each of the drugs that may be useful, key pieces of information drive the recommendations for dose and dosing schedule. First, we need the protein binding for each of those agents (as generally only free or non-protein bound drugs are microbiologically active). The demonstration of this principle was made by Menniken, Briant and Rolinson (3) and is shown in Figure 1. As the free fraction of drug increases, lower doses are required.

A critical step is to **identify the MIC values for the infecting pathogen for the drugs in question**. The MIC value provides a straightforward way to normalize the between-pathogen difference in terms of drug interaction with primary effect site (e.g. penicillin binding proteins for β-lactams or topoisomerases 2 and 4 for quinolones). For any drug dose, as the MIC increases, successful therapy becomes less likely.

Another critical issue is identifying the true between-patient variability in drug pharmacokinetics, as the drug concentration-time profile will be quite different. Some of this difference will be explained by factors such as weight, sex and organ function (e.g. differences in glomerular filtration rate). However, even after all of these factors are accounted for, there will still be true between-patient variability in drug pharmacokinetics. Such differences will have a major impact on the ability to reach any particular exposure target. We deal with these differences by employing Monte Carlo simulation.
For this we need to have a population pharmacokinetic analysis that provides a measure of central tendency for the pharmacokinetic parameters as well as a measure of dispersion in the population. As an example, a drug may have a mean value of drug clearance of 10 L/h, but also have a standard deviation of 5 L/h. In a population of 10,000 patients drawn from such a distribution, the range of drug clearance would be from 1.431 L/h to 50.36 L/h. The 5th and 95th percentiles of this distribution would be 4.096 and 19.34 L/h. The Area Under the concentration-time Curve (AUC) range would then be 19.86 to 698.8 mg*h/L, a greater than 35-fold range. Potentially patients at the high end of the range may respond differently than patients at the low end.

The most important piece of information required for optimization of therapy is knowledge of the amount of drug exposure, indexed to the MIC, which is required to attain the desired microbiological effect.

This approach of linking exposure to microbiological effect was pioneered by Drs. Harry Eagle and William Craig (4-6). In Figure 2, the relationship between drug exposure and the ability to kill Pseudomonas aeruginosa in a granulocyte-replete mouse thigh infection model is shown (7). In panel a, a low inoculum was employed (ca. 10^6 CFU), while in panel b, the challenge is 10 times higher at 10^7 CFU. The markedly increased amounts of drug exposure required to mediate the same amount of bacterial effect is due to the increase in the bacterial challenge. In one instance, the challenge had a total bacterial burden just below the inverse of the mutational frequency to resistance, so that there was a high probability of having virtually no resistant mutants in the population a priori. In contrast, increasing the burden 10-fold exceeded the inverse of the mutational frequency to resistance and therefore had a high probability of having two populations at the outset of therapy, a fully susceptible population and a less susceptible subpopulation. A higher drug exposure is necessary to attain the desired antimicrobial effect because at lower exposure, the drug would kill the fully susceptible population, but would amplify the less susceptible subpopulation.

In this same paper, the exposure required to suppress amplification of resistant subpopulations was calculated, with a total drug value of an AUC/MIC ratio of 157 (free drug AUC/MIC of 110). A prospective validation study was performed with a regimen designed to maximally amplify the resistant subpopulation (total drug AUC/MIC ratio = 52) and one to prevent amplification (total drug AUC/MIC ratio = 157), as shown in Figure 3.
These experiments allowed us to set targets for exposure for levofloxacin in the blood for stasis, 1, 2 or 3 Log$_{10}$(CFU/g) bacterial cell kill or resistance emergence. For the larger bacterial burden, these AUC/MIC ratios were 28, 58, 88, 161 and 157, respectively. Note that the AUC/MIC ratios for 3 Log$_{10}$(CFU/g) bacterial cell kill and resistance suppression are identical.

These targets allow us to examine variability in the drug pharmacokinetics for man and the distribution of MIC values to begin to understand how well a specific drug and dose will perform to achieve the desired endpoint.

**USE OF MONTE CARLO SIMULATION TO GENERATE TARGET ATTAINMENT PLOTS FOR DRUG DOSES**

When clinicians choose a dose, it is important to recognize how well that dose will perform with respect to the achievement of the desired endpoint. The data from above were evaluated with respect to a 750 mg dose of levofloxacin and the endpoint of resistance suppression. The ability to attain the target (total drug AUC/MIC ratio of 157) for this type of infection is displayed in Figure 4. It is important to recognize that the independent variable in this plot is MIC. As can be seen, the likelihood of suppressing resistant subpopulation amplification exceeds 90% up to an MIC of 0.25 mg/L and exceeds 80% at an MIC of 0.5 mg/L. At an MIC of 1.0 mg/L, the likelihood of target attainment falls below 50%. Consequently, for a severe Pseudomonas aeruginosa infection, a 750 mg levofloxacin dose will be adequate up to an MIC of 0.5 mg/L.

Another example can be found from deriving exposure targets directly from clinical data. In Figure 5, Panel a, we show the pharmacodynamics relation for the probability of organism persistence in patients with nosocomial pneumonia treated with 750 mg of levofloxacin. The probability of failure to eradicate the causative organism (persistence) is affected by drug exposure (ability to achieve an AUC/MIC ratio of 87 or not) and increasing age, where increasing age provides a lower probability of pathogen eradication. The median age of the patients in this trial of nosocomial pneumonia was 53 years. For patients with this age who did achieve an AUC/MIC ratio of 87, there is a 19% likelihood of failure of eradication, while patients of this age who did not attain the target of 87 had a 48% probability of persistence. Overall, failure to achieve the exposure target increases the likelihood of failure by more than 2.5 fold at the median age of 53.

Figure 5, Panel b, shows the target attainment plot for an AUC/MIC ratio of 87 by MIC value for a distribution of both Pseudomonas aeruginosa and Enterobacter cloacae. Because the target is lower here for attainment of pathogen eradication than it was above for resistance suppression and because we are dealing here with nosocomial pneumonia, there are minor differences in the adequacy of a 750 mg levofloxacin dose. Here, the likelihood of target attainment remains above 90% up to an MIC value of 0.5 mg/L but at 2.0 mg/L, the probability of target attainment is circa 40%.
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When we examine Figures 4 and 5, it is clear that achieving the two different desired endpoints (resistance suppression in Figure 4 and pathogen eradication in Figure 5) falls below an acceptable probability between 0.5 mg/l and 1.0 mg/l. These data suggest that current CLSI breakpoints may be suboptimal for fluoroquinolones.

**SUMMARY**
When we choose drugs, doses and schedules to treat seriously ill patients, the MIC value is a critical determinant of the likelihood of successful outcome. Since we would like to optimize clinical outcome and preserve the utility of currently available drugs by suppressing resistance emergence, it is clear that knowing the true MIC value and NOT just S, I and R is critically important.

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