ReAct facts

A fact sheet from ReAct – Action on Antibiotic Resistance, www.reactgroup.org

First edition 2007 – Last updated May 2008

Burden of Resistance to Multi-Resistant Gram-Negative Bacilli (MRGN)

◆ **Gram-negative bacilli like *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Acinetobacter* spp. are important pathogens and may cause blood stream, abdominal and urinary tract infections.**

◆ **Recent global surveillance data have shown an increasing resistance to antibiotics in these bacteria, resulting in risk of delayed or inadequate treatment of infections. Increased length of hospital stay, substantial increase in cost of care and increased risk of fatal outcome are serious consequences of antibiotic resistance.**

◆ **Estimates based on studies have shown that 3.1% of all in-hospital deaths in Israel are due to blood stream infection caused by multi-resistant Gram-negative bacilli. The risk of death is usually at least double when such bacilli are the cause of infection in comparison with infections caused by susceptible organisms.**

SCOPE OF THE PROBLEM

Escherichia coli

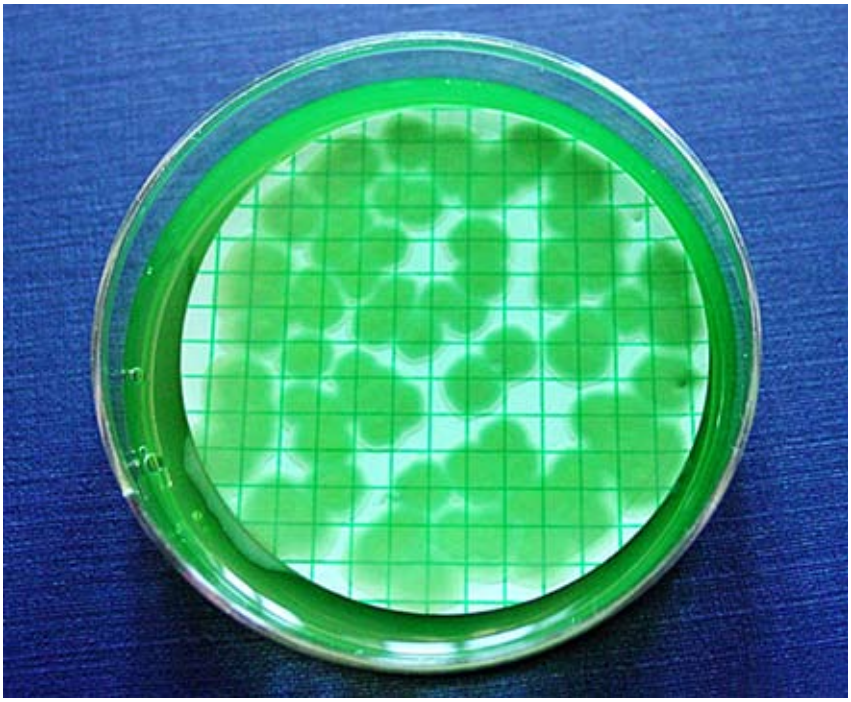
- Part of the bowel flora of healthy individuals.
- The main cause of urinary tract infection and one of the leading causes of blood stream infection as well as intra-abdominal infections.

Klebsiella pneumoniae

- Part of the bowel flora of healthy individuals.
- Among the most common agents causing nosocomial urinary tract and blood stream infections, as well as hospital-acquired pneumonia and intra-abdominal infections.

Pseudomonas aeruginosa

- Environmental pathogen with a high ability to survive in aqueous environments, including aqueous solutions such as disinfectants.
- Sometimes found as part of the normal flora of healthy individuals, and can easily colonise hospitalized patients and cause infections in immunosuppressed individuals.



Colonies of *Pseudomonas aeruginosa*. Photo: The Swedish Institute for Infectious Disease Control

Acinetobacter species

- Second most commonly isolated non-fermenter in human species (*P. aeruginosa* being the first), with the ability to survive on dry surfaces for several weeks, as well as on intact human skin.
- Can cause infections in debilitated individuals, particularly in the respiratory tract (ventilator-associated

pneumonia), the urinary tract, wounds, and central venous catheters.

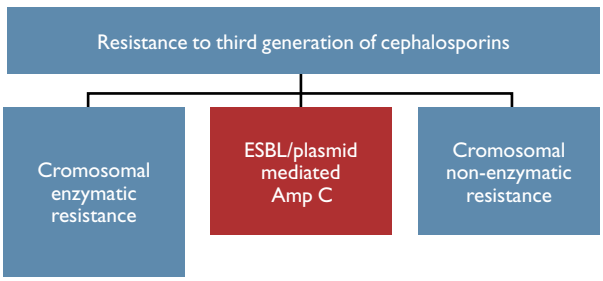
MULTI- RESISTANT GRAM-NEGATIVE BACILLI (MRGN)

- Global problem, adding to the overall burden of infectious diseases.
- Recent surveillance data shows an increasing incidence of resistance worldwide. [1]
- Apart from the above-mentioned bacteria, multi-resistance also occurs in Gram-negative bacilli like Enterobacter spp., Serratia spp. and *Citrobacter freundii*, but this factsheet focuses on the four Gram-negative pathogens recognized as the greatest public health threat. [2]

DEFINITIONS

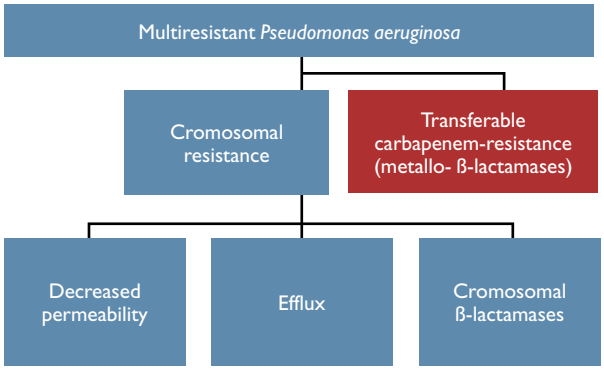
Third generation cephalosporin-resistant *E. coli* and *K. pneumoniae*

- Third generation cephalosporins (e.g. cefotaxime, ceftazidime, ceftriaxone and cefoperazone) are together with fourth generation cephalosporins (e.g. cefepime and cefpirome) referred to as extended-spectrum cephalosporins.
- The primary mechanism of resistance is the production of extended-spectrum ß-lactamases (ESBL), enzymes which can break down extended-spectrum cephalosporins and which are transmissible.
- Other less frequently observed resistance mechanisms are production of chromosomal ß-lactamases (only in *E. coli*) and non-enzymatic mechanisms such as decreased permeability of the outer bacterial membrane.
- Chromosomal ß-lactamases can also be mobilized on plasmids (plasmid-mediated AmpC), and should in such cases probably be considered as ESBLs.
- This factsheet will primarily focus on resistance conferred by ESBLs, and for practical reasons the term ESBL will often be used synonymously with resistance to third generation cephalosporins.



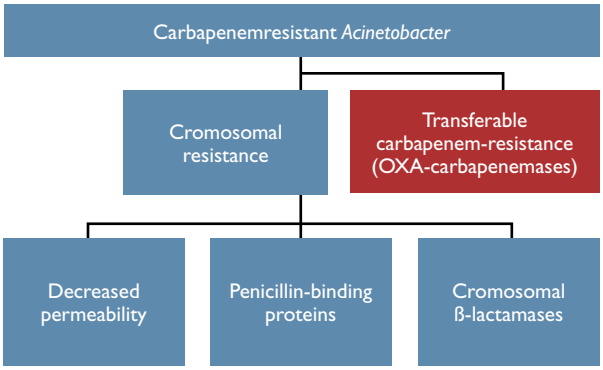
Multi-resistant *Pseudomonas aeruginosa* (MRPA)

- MRPA are usually defined as resistance to ≥3 antipseudomonal agents/groups of agents (third/fourth generation cephalosporins, piperacillin/tazobactam, imipenem, meropenem, fluoroquinolones, aminoglycosides).
- The resistance is usually conferred by several mechanisms such as decreased permeability, efflux (active extrusion), and production of chromosomal ß-lactamase.
- Some transferable ß-lactamases (carbapenemases) can by themselves confer a multi-resistant phenotype, and these ß-lactamases are called metallo-ß-lactamases because their activity is dependant on zinc.



Carbapenem-resistant Acinetobacter species (CRAB)

- Multi-resistant Acinetobacter isolates are often only susceptible to carbapenems (imipenem and meropenem).
- Carbapenem resistance is becoming increasingly common in Acinetobacter.
- Such isolates are often not susceptible to any of the regular antibiotics, and experimental or relatively toxic drugs with low efficacy are necessary for treatment.
- Mechanisms can be chromosomal and/or transferable, as displayed in the figure below.



EPIDEMIOLOGY

- True population-based estimates of the burden of the prevalence of resistance are largely lacking for MRGN. Resistance to extended-spectrum cephalosporins in *E. coli* and *K. pneumoniae* is highly variable in different parts of the world.
- According to published surveillance reports the prevalence of resistance world-wide is 2-30% for *E. coli* and 5-40% for *K. pneumoniae*. [3]
- Northern Europe and USA have the lowest resistance rates, but in intensive care units (ICU) in these regions the numbers are relatively higher.

Prevalence of MDR *P. aeruginosa*

- USA and Europe have reported resistance rates of 5-10%, whereas Japan has reported 2.8%. [4-6]
- Data from South America are relatively scarce, but indicate around 8% MRPA. [7]

Prevalence of carbapenem-resistant Acinetobacter

- Europe and Latin America have reported resistance rates of almost 30%, whereas the reported rates in USA are 5-10%. [7]
- Data from Australasia indicate resistance levels of around 5%, but the percentage is based on a relatively low number of clinical isolates. [1]

Escherichia coli: proportion of invasive isolates with resistance to third generation cephalosporins in 2006.
*These countries did not report any data or reported less than 10 isolates.
Source: http://www.earss.rivm.nl, March 2008

TREATMENT OPTIONS

Third generation cephalosporin-resistant *E. coli* and *K. pneumoniae*

- ESBLs are susceptible to carbapenems, the group of βlactam antibiotics with the broadest spectrum of activity, but resistance has started to emerge in USA, south-east Asia and southern Europe.
- Other possible treatment alternatives are fluoroquinolones and co-trimoxazole, but cross-resistance as well as treatment failure is frequently observed.
- Oral agents such as nitrofurantoin or fosfomycin may be treatment alternatives for lower urinary tract infections, but cannot be used to treat other infections caused by ESBLs.
- Some ESBLs are susceptible to aminoglycosides, but these drugs are relatively toxic and monitoring of serum levels is required during therapy.
- Tigecycline, a tetracycline derivate with improved activity against Gram-negatives, has emerged as a promising alternative, but unfortunately low-grade resistance to this agent has also been observed in ESBLs.

MDR *P. aeruginosa*

- MRPA are by definition resistant to ≥ 3 antipseudomonal agents, but may still be susceptible to 3-4 other antipseudomonal agents.
- A growing subgroup of MRPA are pan-resistant, susceptible only to the polymyxins.

Carbapenem-resistant Acinetobacter

- CRAB isolates are usually also resistant to fluoroquinolones, and in many cases also to aminoglycosides.
- Although tigecycline, rifampicin and sulbactam have been suggested for mono- or combination therapy, the polymyxins are the only agents with documented clinical effect against such pathogens.

QUALITATIVE CONSEQUENCES OF MRGN

Individual effect

- Treatment failure due to wrong empiric choice or adverse outcome due to delayed effective treatment.
- Treatment more 'troublesome' for patients due to the need for hospitalization of patients in the absence of oral treatment alternatives, and due to the need to monitor treatment.
- Use of more toxic alternatives (such as the polymyxins).
- Increased risk of getting infected when admitted to high-prevalence hospitals (e.g. for surgery).
- Increased morbidity and mortality.

Institutional impact for hospitals

- Antibiotic selection pressure due to the usage of alternative antimicrobial agents with broader spectrum of activity, leading to other types of resistance.
- Difficult & time-consuming cooperation between healthcare providers.
- Disruption of care.
- Bad hospital reputation, loss of confidence.
- Increased costs for empiric and directed antibiotic treatment.
- Infrastructural costs for effective surveillance programs.
- Increased hospitalization for non-severe infections due to lack of orally available drugs.

Societal impact

- Added burden of nosocomial infections.
- Effects on families & communities due, for example, to high costs of care and/or decreased incomes if patients are unable to work and pay tax.
- Increased overall healthcare expenditures.
- Loss of finite societal resource (antibiotics); future generations will not be able to benefit from active antibiotic treatment.
- Out-of-hospital, indirect and intangible costs, related to physical and psychological costs of leave-of-absence and discomfort.

QUANTITATIVE CONSEQUENCES OF RESISTANCE

- A recent report from Israel, based on several studies, has estimated the excess mortality caused by bacteremia due to multi-resistant Gram-negative bacilli to be 660 per year. This corresponds to 3.1% of all in-hospital deaths. [22]

ESBL-producing *E. coli* and *K. pneumoniae*

- The impact of ESBL-production on mortality in Enterobacteriaceae bacteriemia has been studied in a recent meta-analysis, and significantly increased mortality was found in the ESBL-group (pooled RR 1.85, 95% CI 1.39-2.47). [8]
- Four studies have demonstrated increased length of hospital stay (ranging from 1.56 to 2.47 times in patients infected with organisms resistant to third generation cephalosporins. [9-12]
- Increased hospital cost was documented in two studies (1.71 and 1.57 times increased cost, respectively). [9, 12]
- To date, no information is available on the number of excess deaths, the total number of additional hospital days and the economic cost attributable to infections caused by ESBL-producing bacteria.

MDR *P. aeruginosa*

- Six studies have demonstrated an impact on MRPA on mortality, with relative risk/odds ratio ranging from 1.6 to 5.0. [13–18]
- Direct comparisons between studies are often difficult to make, due to lack of a global consensus on the definition of MRPA, and in many of the studies the case definition has been resistance to more than three antibiotics.
- One study, in which MRPA was defined as resistance to ≥ 4 antipseudomonal agents, found an odds ratio of 2.0 for increased length of hospital stay in patients infected with MRPA. [18]

Carbapenem-resistant Acinetobacter

- One study of patients with Acinetobacter bacteriemia found a relative risk of mortality of 2.02 (95% CI 1.18-3.69) in patients infected with imipenem-resistant isolates. [19]
- One study has reported impact on mortality, two studies have reported impacts on length of hospital stay, and one study has reported higher hospital costs attributable to the presence of CRAB. [11, 20, 21]
- In general, studies conducted thus far have been relatively small, and additionally none of them have addressed the issue of infection versus colonizations, with the exception of the above-mentioned study of bacteriemia caused by CRAB.

PERSPECTIVES

Urgent need

- Improve statistics on the prevalence of MRGN, both for bloodstream infections (e.g. the European EARSS database) and for other types of infections.
- Establish a sound methodology for estimating, on a country-by-country basis, the mortality, burden of disease and economic burden arising from MRGN.
- Develop new drugs with activity against MRGN.
- Increase research on the prevention of emergence of MRGN organisms, such as development of mutant-preventive dosing schemes and selection of combination therapy for the treatment of certain pathogens, particularly those with high propensity to develop resistance.

A dark scenario

- Antibiotic selection pressure leading to high levels of carbapenem resistance among *E. coli* and *K. pneumoniae*, thus further compromising empirical therapy.
- Increased consumption of carbapenems leading to increased prevalence of MRPA and CRAB.
- Increasing proportion of infections due to MRPA and CRAB leading to increasing use of other agents, e.g. polymyxins, resulting in development of resistance to the few currently available alternative agents.
- Global emergence of pan-resistant bacteria leading to no available options for antimicrobial therapy.
- Dramatic increase in hospital costs due to the need for hospitalizing patients with non-severe infections, such as lower urinary tract infections, consequent to the lack of effective oral agents.

Although several countries are already experiencing some of the above concerns, it may be possible to prevent further deterioration of the situation through concerted efforts.

ReAct
Action on Antibiotic Resistance

◆ ReAct links a wide range of individuals, organisations and networks around the world taking concerted action to respond to antibiotic resistance.

◆ Our vision is that current and future generations of people around the globe should have access to effective treatment of bacterial infections.

◆ ReAct believes that antibiotics should be used appropriately, their use reduced when of no benefit and their correct and specific use increased when needed.

◆ ReAct believes that awareness of ecological balance is needed as part of an integral concept of health.

SUGGESTIONS FOR FURTHER READING

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- ☐ Schwaber MJ, Navon-Venezia S, Kaye KS, Ben-Ami R, Schwartz D, Carmeli Y. Clinical and economic impact of bacteremia with extended-spectrum-beta-lactamase-producing Enterobacteriaceae. Antimicrob Agents Chemother 2006; 50(4): 1257-62.
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- ☐ Laupland KB, Parkins MD, Church DL, Gregson DB, Louie TJ, Conly JM, et al. Population-based epidemiological study of infections caused by carbapenem-resistant *Pseudomonas aeruginosa* in the Calgary Health Region: importance of metallo-beta-lactamase (MBL)-producing strains. J Infect Dis 2005; 192(9): 1606-12.
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