XDR ACINETOBACTER: HOW TO EXIT FROM AN ENDEMIC SITUATION

Garyphallia Poulakou
Consultant, Infectious Diseases
4th Dept Internal Medicine, Athens Medical School
Attikon University Hospital of Athens
Conflicts of Interest

• Research grants from Pfizer
• Travel grants from Pfizer, Astellas, Gilead, Novartis, Abbott
Definitions of Resistance Acronyms

1. **“Pandrug Resistant (PDR):** All classes of antibiotics, since in the Greek language the prefix “pan-” means “all” or “whole”

2. **Extensively Drug Resistant (XDR):** All classes of antibiotics except 1 or 2 (usually colistin ± tigecycline)

3. **Multidrug Resistant (MDR):**
   Resistant in at least one agent in ≥3 antimicrobial categories

*Magiorakos AP, et al. CMI 2011*
More definitions……..

• Endemic: A baseline rate established by ongoing surveillance of the usual frequency of an organism, infection or disease in a given setting.

• Epidemic: A higher incidence than usual of an organism, infection or disease in a defined population in a given period of time.

• Contact Precautions: Transmission-based Precautions method recommended by the Centers for Disease Control and Prevention (CDC). This method requires barrier precautions and personal protective equipment (PPE) for direct contact with residents/patients or contaminated equipment.

What is *Acinetobacter* spp?

- In 1911 Beijerinck, a Dutch microbiologist, described an organism named *Micrococcus calco-aceticus* that was isolated from soil by enrichment in a calcium-acetate-containing medium.
- The Greek word “ακίνητος” [akinetos], i.e., nonmotile, was initially proposed by Brisou and Prévot in 1954 to separate the non-motile from the motile microorganisms within the genus *Achromobacter*.
- Long taxonomic history...
- Gram-negative, strictly aerobic, nonfermenting, nonmotile, catalase-positive, oxidase-negative coccobaccilus.

*Clin Microbiol Rev* 2008;21(3):538-582
Natural Habitats

- Members of the genus *Acinetobacter* are considered ubiquitous organisms since they can be recovered from virtually all samples obtained from soil or surface water.

- *A. baumannii* although has been found in soil samples in Hong Kong and on vegetables in the UK, does not appear to be a typical environmental organism.


*Seifert H, J Clin Microbiol 1997; 35:2819-2825*
Acinetobacters are part of the human skin flora

- Up to 43% of non-hospitalized individuals were found to have their skin and mucous membranes colonized with *Acinetobacter* spp
- Fecal carriage of non-baumannii *Acinetobacters* was found at a rate of 25% among healthy individuals
- In a study from Hong Kong 53% of medical students and new nurses were colonized with acinetobacters in summer versus 32% in winter

Mc Donald L, *Clin Infect Dis* 1999; 29:1133-1137
From human flora to disease

• In patients hospitalized on a regular ward, the carriage rate of *Acinetobacter* species was reported ~75%.

• However, *A. baumannii*, the most important nosocomial *Acinetobacter* species, was found only rarely on human skin (0.5% -3%) and in human feces (0.8%).

Seifert H, J Clin Microbiol 1997; 35:2819-2825
Peleg A, Clin Microbiol Rev 2008;21(3):538-582
Mc Donald L, Clin Infect Dis 1999; 29:1133-1137
From colonization to disease

• This organism is unique among gram-negative bacilli in its ability to persist in the environment for prolonged periods of time

• Environmental contamination has been linked to hospital outbreaks suggesting a role in nosocomial transmission

• The main clinical syndromes reported include pneumonia and bacteraemia, along with surgical site infection, skin and soft tissue infections, urinary tract infections

• *A baumannii* can also be the cause of secondary meningitis, particularly in patients with ventricular draining tubes or of peritonitis in patients undergoing peritoneal dialysis

Villegas MV, ICHE 2003;24:284-95
Modes of transmission through the inanimate environment

• The organism has been isolated throughout the inanimate environment—on the beds of colonized patients and on nearby surfaces (e.g., on mattresses and bedside equipment), in hospital rooms (e.g., on floors, sinks, countertops, and door handles), and in room humidifiers.

• Spread of *A. baumannii* via droplets has been suggested by the results of air sampling with culture plates.

• Healthcare workers or mobile medical equipment can be the vehicles for transmission.

---

Hota B, Clinical Infectious Diseases 2004; 39:1182–9
Impact on Patient Outcomes

- *MDR Acinetobacter* infection usually occurs in severely ill patients in the ICU, therefore associated crude mortality rate is high, (26% to 68%)
- The estimation of attributable mortality of these infections is extremely difficult
- Recent studies and a systematic review concluded that *Acinetobacter* infection or colonization is associated with increased mortality
  - Many methodological diversities (mostly in control for patients' severity of illness)
  - Other studies that rigorously controlled for severity of illness did not find *Acinetobacter* infection to be independently associated with increased mortality
- *Acinetobacter* infection might be a marker of increased mortality in patients with severe underlying illness but not an independent predictor of mortality

Mechanisms of resistance

• The most prevalent mechanism of β-lactam resistance in *A. baumannii* is enzymatic degradation by β-lactamases.

• However, in keeping with the complex nature of this organism, multiple mechanisms often work in concert to produce a multi-resistant phenotype.

• Of the β-lactamases, those with carbapenemase activity are most concerning and include the serine oxacillinases (Ambler class D OXA type) and the metallo-β-lactamases (MBLs) (Ambler class B).
Other mechanisms of resistance

- Non-enzymatic
  - changes in outer membrane proteins (OMPs)
  - multidrug efflux pumps
  - alterations in the affinity or expression of penicillin-binding proteins
- Aminoglycoside-modifying enzymes
- Modifications to DNA gyrase or topoisomerase IV through mutations in the gyrA and parC genes (quinolones)
- tetracycline-specific efflux pumps, ribosomal protection (tetracyclins)
- multidrug efflux systems, such as the AdeABC pump (tigecycline)
- specific modification of the lipid A component of the outer membrane lipopolysaccharide, proteolytic cleavage of the drug, and activation of a broad spectrum efflux pump (colistin)
Global colistin resistance data

- SENTRY Antimicrobial Surveillance from 2001 to 2011, which included different centres from the USA, Europe, Latin America and the Asia-Pacific region, revealed the colistin resistance of A. baumannii remained at a low level (0.9%–3.3%).
- Most report rates of <7%; however, two reports from Bulgaria and Spain showed high rates of 16.7% and 19.1%, respectively.
- Surprisingly, another report from Spain showed a quite high resistance rate of 40.7%, whose strains were collected from a tertiary care hospital between May 2000 and November 2006.
- Seven of eight reports from Asia reported rates of <12% the highest colistin resistance rate of 30.6% from Korea.

Countries that have reported an outbreak of carbapenem-resistant *Acinetobacter baumannii*

Summary of the distribution and genetic context of the OXA-type enzymes in Acinetobacter baumannii.

OXA-23 Cluster
- Distribution: Europe (widespread), Australia, Tahiti, Noumea, China, Korea, Singapore, Vietnam, United States, Brazil, Libya, Pakistan
- Encoded: plasmid or chromosomal
- Associated IS Elements: ISAb1, ISAb4

OXA-24 Cluster
- Distribution: Spain, Belgium, France, Portugal, United States
- Encoded: chromosomal or plasmid (OXA-40)
- Associated IS Elements: None

OXA-58 Cluster
- Distribution: France, Spain, Belgium, Turkey, Romania, Greece, UK, Italy, Austria, Argentina, Australia, United States, Kuwait, Pakistan
- Encoded: plasmid or chromosomal
- Associated IS Elements: ISAb1, ISAb2, ISAb3, IS18

OXA-51 Cluster
- Distribution: Naturally occurring in A. baumannii therefore global distribution
- Encoded: chromosomal
- Associated IS Elements: ISAb1

Understanding the dynamics of imipenem-resistant Acinetobacter baumannii lineages within Portugal


- A detailed depiction of the evolving epidemiology of MDR A. baumannii in Portugal
- The use of MLST1 among a wide range of typing methods helped in understanding the disease dynamics
Understanding the dynamics of imipenem-resistant
Acinetobacter baumannii lineages within Portugal

• The majority of isolates (77.5%) were obtained from inpatients attending a single general hospital (hospital A), with an endemic situation for IRAB since 2001.
• The remaining isolates were provided by four hospitals in which IRAB had started to spread more recently
• Two isolates collected from distinct outpatients with no previous hospitalization history
• A progressive switching occurred since 2006 where ST98 IRAB carrying $bla_{OXA-24/40}$ has been gradually replaced by ST92 IRAB carrying $bla_{OXA-23}$.
• This new emerging lineage exhibits an extensive multidrug resistance profile
One year later…

Genetic diversity and clonal evolution of carbapenem-resistant *Acinetobacter baumannii* isolates from Portugal and the dissemination of ST118

Manageiro V et al, for the Antimicrobial Resistance Surveillance Program in Portugal

IJAA 2012; 40 (5): 398-403

- ST98 (described so far as endemic in Portugal) and ST92 (which co-existed with ST98 before 2009) appeared to have been gradually replaced by ST118.
- All isolates were non-susceptible to tigecycline; one isolate was also non-susceptible to colistin, making it a step closer to pan-drug resistance.
- 98% were OXA-66 producers.
- Identification of an extensively drug-resistant ST118 and carbapenem-resistant ST92, ST98 and ST118 isolates, both in community and healthcare facilities, demonstrates the menace of *A. baumannii*-associated infections.
The genetic analysis of *A. baumannii* isolates provides valuable data regarding their epidemic distribution that may be helpful for containment of their further spread.

- Carb-R strains: 94% OXA-54 gene(+)

© The Author 2011. Published by Oxford University Press on behalf of the British Society for Antimicrobial Chemotherapy. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com
Sequence type and beta-lactamase content of 174 clinical, carbapenem-resistant A. baumannii isolates during 2010 and 2011 in a tertiary care hospital in central Greece.

Carbapenem resistance was associated mainly with carriage of the blaOXA-23 gene (in 72.4% of the isolates).

During 2011, in our hospital they rapidly ‘replaced’ the previously predominant OXA-58- positive A. baumannii strains.
Hospital Outbreaks and Control Measures

- The propensity for outbreaks of multidrug-resistant A. baumannii has been demonstrated clearly.
- Usually one or two strain types are responsible.
- In New York City, two strain types accounted for >80% of carbapenem-resistant isolates.
- This clearly demonstrates the importance of infection control interventions in response to outbreaks of multidrug-resistant A. baumannii infections.

Factors facilitating the spread of \textit{Acinetobacter baumannii}

- Increased length of hospital stay
- Prior antibiotics
- Mechanical ventilation
- Exposure to patients colonised or infected with \textit{A. baumannii}
- Environmental contamination
- Understaffing
- Poor adherence of staff to hand hygiene

Rosenbaum P, APIC 2010 \textit{Guide to the Elimination of MDR Acinetobacter baumannii Transmission in Healthcare Settings}
Antibiotic pressure and resistance development in *A. baumannii*

In addition to transmission, emergence of resistance occurs in the context of selective pressure from broad-spectrum antimicrobial therapy, such as therapy involving carbapenems (mostly imipenem), quinolones or third-generation cephalosporins.

J Hosp Infect 2005;60:14-18
Clin Infect Dis 2003;36:1268-74
Potential sources from which *A. baumannii* has been isolated in the hospital environment

- Hands of staff
- Ventilators and tubing
- Oxygen analysers
- Bronchoscopes
- Bed frames
- Sinks
- Jugs
- Soap
- Plastic screens
- Bed linen, pillows and mattresses
- Resuscitation bags
- Blood pressure cuffs
- Parenteral nutrition solution
- Gloves
- Humidifiers
- PatientsRespirometers
- Lotion dispensers
- Rubbish bins
- Air supplyBowls
- Hand cream
- Bedside charts
- Service ducts/dust
- Computer keyboards
- Cell phones

Multiresistant Acinetobacter baumannii infections: epidemiology and management.

Garnacho-Montero, Jose; Amaya-Villar, Rosario

DOI: 10.1097/QCO.0b013e32833ae38b

Potential sources of Acinetobacter baumannii in the hospital environment

<table>
<thead>
<tr>
<th>Human reservoirs</th>
<th>Inanimate reservoirs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient colonization</td>
<td>Medical equipment</td>
</tr>
<tr>
<td>Skin</td>
<td>Ventilators and tubing</td>
</tr>
<tr>
<td>Pharynx</td>
<td>Stethoscopes</td>
</tr>
<tr>
<td>Axils</td>
<td>Medical monitors</td>
</tr>
<tr>
<td>Groins</td>
<td>Infusion pumps</td>
</tr>
<tr>
<td>Perineum</td>
<td>Bronchoscopes</td>
</tr>
<tr>
<td>Digestive tract</td>
<td>Resuscitation bags</td>
</tr>
<tr>
<td>Infected patients</td>
<td>Blood pressure cuffs</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Hospital environment</td>
</tr>
<tr>
<td>Tracheobronchitis</td>
<td>Bed frames</td>
</tr>
<tr>
<td>Bloodstream infection</td>
<td>Sinks</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Soap dispensers</td>
</tr>
<tr>
<td>Central nervous system infection</td>
<td>Bed linen</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>Mattresses</td>
</tr>
<tr>
<td>Skin and soft tissue infection</td>
<td>Pillows</td>
</tr>
<tr>
<td>Healthcare workers</td>
<td>Curtains</td>
</tr>
<tr>
<td>Hands of staff</td>
<td>Floor mops</td>
</tr>
<tr>
<td></td>
<td>Rubbish bins</td>
</tr>
<tr>
<td></td>
<td>Computer keyboards</td>
</tr>
</tbody>
</table>
Role of the Clinical Microbiology Laboratory in Providing Surveillance for MDR A. baumannii

- Surveillance for patients colonized with multidrug- or pandrug-resistant A. baumannii is essential for infection control purposes
- The methodology is not well standardized
  - The sensitivity of surveillance cultures was low, even when six different body sites are sampled (nostrils, pharynx, skin, rectum, wounds, and endotracheal aspirates)

Marchaim D, J Clin Microbiol 2007; 45:1551-1555
Molecular studies are very important

- The use of epidemiological typing methods helps further in the delineation of the modes of transmission of *A baumannii* during an outbreak, through the differentiation between sporadic and outbreak strains.
- Phenotypic tests, such as antibiotyping, biotyping, and electrophoretic typing, are not as discriminatory as more sophisticated genotyping methods, including plasmid profiles analysis, pulse field gel electrophoresis, ribotyping, amplified fragment length polymorphism, PCR-based tests, and multilocus sequence typing.
- Additionally, a case-control study can be done to identify potential risk factors for the acquisition of epidemic strains during an outbreak.

Rosenbaum P, APIC 2010 *Guide to the Elimination of MDR Acinetobacter baumannii Transmission in Healthcare Settings*
Efficacious infection control interventions in A. baumannii outbreaks

- Molecular epidemiologic investigations should be conducted to determine clonality of the outbreak.
- Environmental cultures should be used to determine if a common environmental source is present.
- Enhanced environmental cleaning should be performed in order to eliminate the organism from the peripatient environment.
- Enhanced isolation procedures, aimed at optimizing contact isolation (usage of gloves and gowns when dealing with colonized patients or their environment) and improving hand hygiene, should be implemented.
- If single rooms with dedicated staff cannot be provided, cohorting of patients or staff is an alternative.
- Antibiotic restriction policies should be implemented to ensure that “at-risk” antibiotics are not being used excessively.
- Optimally, a case-case control study should be performed to determine risk factors (including antibiotics) for acquisition of MDR A. baumannii.

What if new cases appear despite all measures taken?

• In some cases, despite these efforts, ongoing cases of multidrug-resistant *A. baumannii* infection continue to occur.

• Monitoring adherence to such infection control interventions is also important.

• Although health care worker hand carriage with *Acinetobacter* is typically transient, it may be more prolonged in individuals with damaged skin.

• In some scenarios, closure of wards to new admissions needs to be undertaken.

• Some authors have suggested that eradication of colonization be performed by techniques such as selective digestive tract decolonization or use of topical or aerosolized polymyxins.


Krueger WA *Am J Respir Crit Care Med* 2002; 166:1029–37
Performing the Risk Assessment

• Preparation for the risk assessment requires identifying and obtaining:
  • Administrative support
  • Facility technical support
  • Resources such as laboratory and pharmacy capabilities
  • Infection prevention and control staffing (FTE) and/or hours assigned to infection prevention and control
  • Public health support as applicable
  • Current infection prevention and control interventions (e.g., hand hygiene, contact precautions, etc.)
  • Measurement parameters for the current interventions
  • Comprehensive line list of identified colonized and infected patients
Measures aiming to control patient-to-patient cross-transmission of multidrug-resistant *A baumannii* during institutional outbreaks

Karageorgopoulos and Falagas Lancet Infect Dis 2008;8: 751–62
Containment of an outbreak is a team work!

- The successful management of an outbreak involves the cooperation of all levels of healthcare personnel involved.
- Thus, administrative measures for organising an effective team and providing timely feedback of information regarding the outbreak are fundamental.
- Education of hospital staff on a regular basis and frequent revision of the control measures used are also essential.

Rosenbaum P, APIC 2010 *Guide to the Elimination of MDR Acinetobacter baumannii Transmission in Healthcare Settings*
MULTIFACETED APPROACHES

Successful examples
Long-term control of hospital-wide, endemic multidrug-resistant *Acinetobacter baumanii* through a comprehensive “bundle” approach

Jesús Rodríguez-Baño, MD, PhD, a Lola García, RN, a Encarnación Ramírez, MD, PhD, b Luis Martínez-Martínez, MD, PhD, b Miguel A. Muniain, MD, PhD, a Felipe Fernández-Cuenca, MD, PhD, b Margarita Beltrán, PhD, c Juan Gálvez, MD, a Jose M. Rodríguez, PhD, b Carmen Velasco, PhD, b Concepción Morillo, RN, b Federico Perez, MD, d Andrea Endimiani, MD, PhD, d Robert A. Bonomo, MD, d and Alvaro Pascual, MD, PhD b

Sevilla, Spain, and Cleveland, Ohio

Results

- Colonization/infection was 0.82 cases per 100 admissions (1994-1995) and showed a sustained decrease after implementation of the control program in 1995 to 0.46 in 1996-1997 and to 0.21 in 1998-2003 (P <0.001).

- Coincident with the institution of this program, the rate of bacteremia because of MDR Ab decreased 6-fold during the 8-year observation period.

Conclusions

• A multifaceted program including the detection of colonized patients by means of active surveillance, reinforcement of hand hygiene, environmental investigation and cleaning, and Contact Precautions successfully reduced cross transmission.

• Although active surveillance is time-consuming and costly, it may underscore the educational message and encourage staff participation.

• The daily presence of an infection control professional in units with colonized patients was also crucial to the success of the “bundle.”

Single clone, 12 patients, 9 deaths (7 probably related)

The previous use of quinolones and glycopeptides and an ICU stay were associated with the acquisition of infection or colonization with pan–drug-resistant *A. baumannii*.

**Interventions:** the performance of environmental decontamination of the ICUs involved, an environmental survey, a revision of cleaning protocols, active surveillance for colonization with pan–drug-resistant *A. baumannii*, educational programs for the staff, and the display of posters that illustrate contact isolation measures and antimicrobial use recommendations.

**Conclusions.** “We were not able to identify the common source for these cases of infection, but the adopted measures have proven to be effective at controlling the outbreak”
Protracted Outbreak of Multidrug-Resistant *Acinetobacter baumannii* after Intercontinental Transfer of Colonized Patients

*Infect Control Hosp Epidemiol* 2013;34(2):119-124

Caroline Landelle, PharmD, PhD;¹ Patrick Legrand, MD;² Philippe Lesprit, MD;¹ Florence Cizeau;¹ David Ducellier;¹ Cyril Gouot;¹ Paula Bréhaut;¹ Sophan Soing-Altrach;¹ Emmanuelle Girou, PharmD, PhD;¹ Christian Brun-Buisson, MD²,³

- **Design:** An 18-month outbreak investigation.
- **Setting:** An 860-bed university hospital in France.
- **Patients.** Case patients (i.e., carriers) were those colonized or infected with an MDRAB isolate.
- **Methods.** During the epidemic period, all intensive care unit (ICU) patients and contacts of carriers who were transferred to wards were screened for MDRAB carriage. Contact precautions, environmental screening, and auditing of healthcare worker (HCW) practices were implemented; rooms were cleaned with hydrogen peroxide mist disinfection.
- **One ICU, in which most of the cases occurred, was closed on 4 occasions for thorough cleaning and disinfection.**
Monthly number of new cases of multidrug-resistant A. baumannii (MDRAB) by intensive care unit (ICU) and ward from January 2008 through June 2009.

The outbreak involved 86 patients and evolved in 5 phases, punctuated by closure of ICU A. The outbreak stopped only after all patients who were colonized with MDRAB from wards or discharged from ICUs were transferred to a dedicated isolation unit in May 2009.
Components

- Contact isolation precautions and appropriate hand hygiene, active surveillance, cohorting patients who were colonized or infected with pandrug-resistant *Acinetobacter baumannii*, and environmental cleaning with 1:100 sodium hypochlorite solution. All interventions were continued in period 3, but environmental cleaning solutions were changed to detergent and phenolic agents.

**Table 3. Rate of pandrug-resistant *Acinetobacter baumannii* infection and colonization among intervention intensive care units.**

<table>
<thead>
<tr>
<th></th>
<th>No. of cases per 1000 patient-days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Period 1</td>
</tr>
<tr>
<td>Medical intensive care</td>
<td>1.4</td>
</tr>
<tr>
<td>Surgical intensive care</td>
<td>1.2</td>
</tr>
<tr>
<td>Coronary care</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**NOTE.** Period 1 was the baseline period (1 January 2005 through 31 December 2005). Period 2 was the intervention period (1 January 2006 through 31 December 2006). Period 3 was the follow-up period (1 January 2007 through 31 December 2007).

<sup>a</sup> *P* < .05, compared with period 1.
Rates of pandrug-resistant *Acinetobacter baumanii* infection and colonization in 3 intensive care units

Period 1 was the baseline period, period 2 was the intervention period and period 3 was the follow-up period.

*Clinical Infectious Diseases* 2008; 47:760–7
Cost of surveillance culture versus the monthly cost of hospitalization and antibiotics for treatment of PDR A. baumannii infection.

• The total cost for ASCs was $19,862 for the entire study (~7000 cultures).
• The intervention resulted in a significant reduction in the total cost of antibiotics used to treat PDR A. baumannii infection and in the cost of hospitalization.
• Compared with the costs in period 1, the monthly hospital antibiotic costs to treat PDR A. baumannii infection were reduced in the intervention units in periods 2 and 3 by 36%–42% (P <0.001) and the hospitalization costs for each patient by 25%–36% (P <0.001)
ENVIRONMENTAL CLEANING
Independent risk factors for ICU acquired MDR P. aeruginosa were prior occupant with MDR P. aeruginosa (OR 2.3), surgery (OR 1.9) and prior piperacillin/tazobactam use (OR 1.2)

Independent risk factors for ICU-acquired A. baumannii were prior occupant with A. baumannii (OR 4.2) and mechanical ventilation (OR 9.3)

“We conclude that admission to an ICU room previously occupied by a patient with MDR P. aeruginosa or A. baumannii is an independent risk factor for acquisition of these bacteria by subsequent room occupants”

This relationship was not identified for ESBL-producing GNB.
Why should we target at the inanimate surrounding?

- To assess the desiccation tolerance of *A. baumannii* Jawad et al. compared the survival times on glass coverslips of 22 strains isolated from eight well-defined hospital outbreaks with the survival times of 17 sporadic strains. The overall mean survival time was 27 days, with a range of 21 to 33 days.

- There were no differences in survival times between outbreak and sporadic strains; all investigated *A. baumannii* strains had the ability of long-time survival on dry surfaces and therefore an increased potential for epidemic spread.

- The majority of *A. baumannii* strains had survival times that were considerably longer than those found for *Escherichia coli* and other *Enterobacteriaceae* but similar to those observed for *Staphylococcus aureus*.

- These observations, as well as the previously suggested airborne spread of *Acinetobacter* spp. in hospital wards may explain the occurrence of repeated outbreaks after incomplete disinfection of contaminated dry surfaces.


Is resistance to disinfectants an issue?

- Wisplinghoff et al. recently compared the in vitro activities of various disinfectants, such as propanol, mecetronium ethylsulfate, polyvinylpyrrolidone-iodine, triclosan, and chlorhexidine, against sporadic and epidemic *A. baumannii* strains by using a broth macrodilution method.
- All disinfectants inhibited growth of all *A. baumannii* isolates when concentrations and contact times recommended by the respective manufacturer were used.
- However, with most of the disinfectants tested, a substantial number of viable bacteria remained if contact times were <30 s or if diluted agents were used, as may occur in day-to-day clinical practice.
- **Minor deviations from the recommended procedures leading to decreased concentrations or exposure times may play a role in nosocomial cross-transmission**
Effects of novel copper biocides on healthcare-associated organisms

- Novel topical agents that may be effective for environmental cleaning of *A. baumannii*, including highly charged copper-based biocides, have recently been reported.

- All three copper-based formulations were potently biocidal down to concentrations of 1 ppm for both stationary- and log-phase organisms, and they were all active against *C. difficile* spores.

- At 150 ppm, they achieved a complete (>6 log10) kill of MRSA and ACCB mostly within 1 h.

- This biocidal activity was not achieved by copper sulphate or the inorganic binders used in the formulations.

- All three copper-based formulations and copper sulphate were not cytotoxic to human epithelial cells up to concentrations of 100–200 ppm.

### Table 3. Cleaning of contaminated surfaces using UMF cloths wetted with copper-based formulations or water (control UMF)

<table>
<thead>
<tr>
<th>UMF with Cu formulation (150 ppm)</th>
<th>Inoculum per 100 cm²</th>
<th>cfu on contaminated surfaces detected with contact plates</th>
<th>cfu from UMF cloths after 16 h</th>
<th>Board control cfu</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-clean</td>
<td>Post-clean</td>
<td></td>
</tr>
<tr>
<td>CuAL42</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRSA</td>
<td>$2 \times 10^6$</td>
<td>$&gt;500$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ACCB</td>
<td>$2 \times 10^6$</td>
<td>$&gt;500$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C. difficile spores</td>
<td>$3 \times 10^5$</td>
<td>$&gt;500$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CuPC33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRSA</td>
<td>$2 \times 10^6$</td>
<td>$&gt;500$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ACCB</td>
<td>$2 \times 10^6$</td>
<td>$&gt;500$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C. difficile spores</td>
<td>$3 \times 10^5$</td>
<td>$&gt;500$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CuWB50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRSA</td>
<td>$2 \times 10^6$</td>
<td>$&gt;500$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ACCB</td>
<td>$2 \times 10^6$</td>
<td>$&gt;500$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C. difficile spores</td>
<td>$3 \times 10^5$</td>
<td>$&gt;500$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Control UMF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRSA</td>
<td>$2 \times 10^6$</td>
<td>$&gt;500$</td>
<td>0</td>
<td>$2 \times 10^6$</td>
</tr>
<tr>
<td>ACCB</td>
<td>$2 \times 10^6$</td>
<td>$&gt;500$</td>
<td>0</td>
<td>$2 \times 10^6$</td>
</tr>
<tr>
<td>C. difficile spores</td>
<td>$3 \times 10^5$</td>
<td>$&gt;500$</td>
<td>0</td>
<td>$3 \times 10^5$</td>
</tr>
</tbody>
</table>
Novel materials and compatibility with copper disinfectants

- Microfibre (MF) materials make a significant difference to the effectiveness of surface cleaning and MF mops have been shown to be more effective at microbial removal from surfaces in hospital wards than string mops.
- However, MF cloths and mops become contaminated during cleaning and this can lead to the spread of viable bacteria.
- The novel copper-based biocide CuWB50, which is effective against a wide range of pathogenic bacteria, is, unlike hypochlorite-based disinfectants, also compatible with ultra-microfibre mops and cloths (UMF).

Moore and Griffith, 2006; Nilsen et al, 2002; Wren et al, 2008; Rutala et al, 2007; Bergen et al, 2009; Gant et al. 2007, 20109
 Superior cleaning performance was demonstrated for UMF, which is enhanced with CuWB50, compared with standard cleaning.

(a) bacterial levels (TVCs) and (b) cleaning efficacy (ATP assay). Pre and Post refer to sampling one hour before and after cleaning. All pre versus all post, p < 0.001.

Journal of Infection Prevention September 2011;12(5):188-194
Patients in the medical, surgical, and cardiac surgery ICUs at the University of Maryland Medical Center with a known history of colonization or infection with MDR A baumannii were included.

When a potential participant was to be discharged from their room, environmental samples were collected.

Terminal cleaning implements a “top-down” (high to low surfaces) cleaning method

A quaternary ammonium compound-based

Curtains, infusion pumps, and respiratory equipment are removed from the room
• Even after cleaning, over 25% of rooms remain contaminated, representing a potential source of transmission
• Sites with persistent contamination were: floor, bedside table, call button, door handles, and supply cart
Airborne hydrogen peroxide disinfection

- Before the application of any cleaning method, 187/480 (39.0%) of the sampled environmental sites were found to be contaminated (9 studies)
- After the application of terminal cleaning, 178/630 (28.3%) of the sampled sites were contaminated (6 studies)
- After disinfection with airborne hydrogen peroxide, 15/682 (2.2%) of the environmental sites sampled (range: 0-4.0%) were contaminated (all 10 studies)
Airborne hydrogen peroxide for infection control

• In two studies airborne hydrogen peroxide disinfection contributed to the termination of a *Serratia* spp. outbreak at a neonatal ICU and a polyclonal MRSA outbreak at a 28-bed surgical ward,

• Eradication of persistent MRSA environmental contamination in a 20-bed surgical ward.

• Airborne hydrogen peroxide disinfection of five wards of a 500-bed university-affiliated hospital with the highest incidence of *C. difficile*-associated disease, was related to significant reduction of the incidence of *C. difficile* in the hospital.

Results of environmental microbiologic sampling before and after vaporized hydrogen peroxide (VHP) sterilization of patient rooms

- Time of sterilization is indicated by the *dotted line* and of room repopulation by the *solid line*, with sampling intervals after VHP use indicated on the x-axis.
NOVEL APPROACHES
Antimicrobial properties of copper were already employed in Byzance

...But also to every part of the “Xenona” (municipal hospital) will always be placed one copper-made jar (full of water) and a basin for the doctors in order to wash their hands before and after every handling procedure dealing with one patient, whatever procedure is that.

The Emperor
John B’ Komnenos (1088-1143)
Agia-Sophia-Constantinople

Courtesy of Prof H. Giamarellou
The antimicrobial properties of copper

- (A) Copper dissolves from the copper surface and causes cell damage.
- (B) The cell membrane ruptures because of copper and other stress phenomena, leading to loss of membrane potential and cytoplasmic content.
- (C) Copper ions induce the generation of reactive oxygen species, which cause further cell damage.
- (D) Genomic and plasmid DNA becomes degraded.
Representative frequently touched objects and their respective placements in the ICU
Pre- and post-intervention period comparison (bacterial counts per site)

Bed rails, 94% reduction, p<0.0001

* Bed Rails
* Call Button
* Chair Arms
* Tray Table
* Data Input
* IV Pole

JCM 2012; 50(7) :2217–2223
Pre- and post-intervention period comparison (type of bacteria)

JCM 2012; 50(7) :2217–2223
Microbial Burden

Copper Objects | Non-Copper Objects

<table>
<thead>
<tr>
<th>IV-Pole</th>
<th>Data Input Device</th>
<th>Tray Table</th>
<th>Chair-Arms</th>
<th>Call Button</th>
<th>Bed Rails</th>
</tr>
</thead>
<tbody>
<tr>
<td>56%</td>
<td>67%</td>
<td>58%</td>
<td>34%</td>
<td>41%</td>
<td>46%</td>
</tr>
<tr>
<td>36%</td>
<td>23%</td>
<td>32%</td>
<td>41%</td>
<td>29%</td>
<td>37%</td>
</tr>
<tr>
<td>9%</td>
<td>10%</td>
<td>10%</td>
<td>26%</td>
<td>30%</td>
<td>17%</td>
</tr>
<tr>
<td>32%</td>
<td>56%</td>
<td>41%</td>
<td>10%</td>
<td>15%</td>
<td>18%</td>
</tr>
<tr>
<td>Green</td>
<td>Yellow</td>
<td>Green</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
<tr>
<td>Zero bacteria</td>
<td>Acceptable count</td>
<td>Unacceptable counts &gt;250 CFU/100 cm²</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Antimicrobial activity of copper surfaces against carbapenemase-producing contemporary Gram-negative clinical isolates

Maria Souli¹*, Irene Galani¹, Diamantis Plachouras¹, Theofano Panagea¹†, Apostolos Armaganidis², George Petrikkos¹ and Helen Giamarellou¹‡

¹4th Department of Internal Medicine, Athens University School of Medicine, University General Hospital ‘Attikon’, 1 Rimini Str. 124 62, Chaidari, Athens, Greece; ²2nd Department of Critical Care Medicine, Athens University School of Medicine, University General Hospital ‘Attikon’, 1 Rimini Str. 124 62, Chaidari, Athens, Greece


Pseudomonas aeruginosa

Acinetobacter baumannii
The effect of copper-coated surfaces on the environmental contamination by pathogenic bacteria in a Greek ICU: A comparative trial

M. Souli¹, A. Antoniadou¹, M. Droggari¹, I. Mavrou¹, A. Antonopoulou¹, G. Poulakou¹, E. Papadomichelakis¹, P. Efstathiou², H. Giamarellou³, A. Armaganidis¹, G. Petrikkos¹

¹Attikon University Hospital, Athens, Greece; ²Hellenic Copper Development Institute, Athens, Greece; ³Hygeia Hospital, Athens, Greece

- 24-bed General ICU
- September 2011 until February 2012.
- The bedrails of 6 out of 12 ICU beds, the top and handles of the side table, the iv pole stands, the handles of the accessory side cart and the antiseptic dispenser of each one of these beds as well as the handles of the nurse’s cupboards were coated with copper alloy.
- In the same ICU compartment, coated and similar non-coated surfaces, which served as controls, were sampled 2 or 3 times during the study period.
Of 136 samples taken from copper-coated surfaces, 14 (10.3%) were colonized with a mean of 268±1375 (range 0-13000) CFU/100cm² as compared to 37 of 211 (17.5%, p=0.06) non-copper control surfaces colonized with 1987±13718 (range 0-150000) CFU/100cm².

Pathogenic bacteria isolated were MDR A. baumannii (the predominant microorganism), KPC-producing K. pneumoniae, S. marcescens, P. aeruginosa, E. aerogenes, P. mirabilis, E. faecium, E. faecalis (VRE) and S. dysenteriae.

The copper alloy coating reduced the colonization of highly-touched surfaces by 60-100%.

A trend was noted for fewer copper-coated surfaces to become colonized by pathogenic bacteria.

Replacement of high contact materials with copper could reduce the high burden of environmental contamination by pathogenic bacteria in health-care settings.
In vivo antibiofilm effect of cerium, chitosan and hamamelitannin against usual agents of catheter-related bloodstream infections.


The antibiofilm effect of cerium nitrate, chitosan and hamamelitannin was tested against *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Acinetobacter baumannii* and *Candida albicans* in a mouse foreign body infection model, using polyurethane catheter segments.

Conclusions

- The in vivo antibiofilm effect of cerium nitrate against *C. albicans* and of chitosan against *C. albicans* and *S. epidermidis*, at subinhibitory concentrations, makes them promising alternatives to coat CVCs.
- For all bacterial strains, the highest in vivo antibiofilm efficacy was achieved with hamamelitannin. For *A. baumannii*, this is the first report of in vivo inhibition.
What does the future hold?

Active and Passive Immunization Protects against Lethal, Extreme Drug Resistant-Acinetobacter baumannii Infection
Guanpingshen Luo, PlosOne 2012

- Vaccination of diabetic mice with recombinant OmpA (rOmpA) with aluminum hydroxide adjuvant markedly improved survival and reduced tissue bacterial burden in mice infected intravenously.
Conclusions

• Multifaceted programs based on relevant recommendations have been successful in the termination of outbreaks and epidemics in several settings
• They might need unexpected time and excess resources
• Team work is essential with regular feedback of all stakeholders on the results of the effort
• Political and administrative support is of paramount importance
• Novel approaches related to the eradication of *A. baumannii* from the inanimate environment have gained interest and must be compared to clinical outcomes
THANK YOU