INTENSIVE CARE UNITS AS EPICENTRES FOR ANTIMICROBIAL RESISTANCE DEVELOPMENT

DR JEAN CARLET, (TOP), PRESIDENT, WORLD ALLIANCE AGAINST ANTIBIOTIC RESISTANCE AND
PROFESSOR JAN DE WAELE (BOTTOM), INTENSIVIST, GHENT UNIVERSITY HOSPITAL, BELGIUM

Antimicrobial resistance (AMR) is rapidly increasing to a dangerous level worldwide, both in animals and humans *(1)*. Unfortunately, humans have not been able to protect antibiotics, this precious resource *(2)*, and the environment, both inside and outside the hospital setting, is also a major contributing factor. Effluents coming from hospitals are heavily colonized with high inoculum of multidrug-resistant micro-organisms (MDROs), and contain high concentrations of antibiotics. Although most antibiotics are consumed in the community, hospitals are very important in the emergence of antibiotic resistance because antibiotics are often over-used and because MDROs are easily transmitted from patient to patient via the hands of healthcare professionals and the equipment used. Intensive care units (ICUs) in particular should be deeply concerned by the issue of AMR.

ICUs are epicentres for AMR development

For many reasons, ICUs are the "epicentres" for the selection and diffusion of MDROs, and as such they have an important role in the emergence of AMR, and therefore also in its prevention. Large-scale prevalence studies have shown that up to 70% of ICU patients are treated with antibiotics on a randomly chosen day. The antibiotics used are very often broad-spectrum drugs inducing substantial antibiotic pressure, i.e., the likelihood that AMR may develop. The intestinal microbiome, including the oropharynx, but mostly the distal gut, plays a key role in the "hidden" selection of highly resistant micro-organisms *(3)*. The very high intensity of care in the ICUs dramatically increases the risk of patient-to-patient bacterial cross-transmission via the hands of healthcare professionals (HCP), and the environment. This problem is the same (or even worse) in the step-down units, in which the nurse-to-bed ratio is far lower. Severe infections can occur due to MDROs, including urinary tract infections, central line infections and ventilator-associated pneumonia (VAP). Prolonged, and sometimes repeated, antibiotic exposure selects micro-organisms which are increasingly resistant, particularly in the gut and in the ventilated lungs. In some cases, and in some countries, severe infections from bacteria resistant to every available antibiotic have been reported.

Resistant bacteria can easily spread to the other wards of the hospital, to long-term facilities or to the community when patients are discharged from the ICU, in particular if the colonization of the patient with resistant bacteria is not properly notified to the new care-giver, the general practitioner or outpatient nursing team.

For all the above reasons, ICU physicians and nurses have a very special responsibility in the management of antibiotics and the prevention of the growth and spread of AMR.

Antibiotic resistance levels in ICUs worldwide

Although there are not many international studies on this topic in the literature *(4, 5, 6, 7)*, it is very clear that AMR is consistently increasing in ICUs worldwide. There are huge differences between countries, regions, hospitals or even ICUs within the same facility. In a multicentre European study of 37 ICUs *(4)*, the prevalence of MRSA ranged from 0% up to 100%. Similar differences were noted in a study for ESBL-producing enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter baumanii*. Northern-European countries like the Scandinavian countries – Iceland, the Netherlands, Switzerland, and to a lesser extend Germany – historically have lower antibiotic consumption and AMR levels *(8 ,9)*. In other countries like Italy, Greece, India, Asian countries such as China, North Africa and the Middle Eastern countries, the level of resistance is very high, with prevalences of ESBL- or Carbapenemase-producing enterobacteriaceae above 50%, and sometimes far higher *(9-17)*. Those differences are probably mostly due to an over-consumption of antibiotics, in particular broad-spectrum antibiotics, and to poor hospital hygiene practices. However, other unknown factors may play a role.

In a given country, huge differences could exist in the resistance levels between species. In France, as an example, prevalence of MRSA is still relatively high (although

decreasing over time), but prevalence of vancomycin-resistant enterococci (VRE) is very low *(18)*. There have been only a few epidemic outbreaks with *Acinetobacter baumanii* in France, but no endemics. This might be due to the efficiency of infection control teams, present in each hospital, or to other factors. Another example comes from North African countries, in which MRSA levels are pretty low, although the prevalence of highly resistant Gram-negatives is dramatic. There are certainly many unknown factors explaining those disparities.

Gram-negative bacteria resistant to almost every antibiotic (or, rarely, all of them) are noted more and more frequently in some ICUs, up to as much as a few percent of all pathogens in a Greek study *(19)*. The development of resistance in *Escherichia coli* to colistin via mcr-1 gene has been an important step in the emergence of those truly "omni-resistant" strains *(20)*.

Can we limit and prevent AMR in ICUs?

There are many ways to limit AMR in hospitals, in particular in ICUs and step-down units. The two main actions are antibiotic stewardship (ABS), in order to decrease antibiotic consumption and improve antibiotic management, and infection control programmes, in order to limit cross-transmission of pathogens, in particular MDROs. Other actions can be discussed, most of them targeting the digestive microbiome, such as selective digestive decontamination (SDD) with non-absorbable antibiotics (for all ventilated patients or just to treat an outbreak due to MDROs, probiotics, bacteriocins, bacteriophages or fecal microbiota transplantation (FMT). Data are still rather scarce to define the role of those recent methods.

1) Antibiotic stewardship

This approach is now widely accepted and used worldwide, although some controversies remain *(21, 22)*. The aim of ABS is to improve antibiotic management and reduce antibiotic consumption in the hospital or in a given unit. It includes a bundle of actions such as proper microbiological information, including the MIC of the pathogen, frequent reassessment of antibiotic therapy, de-escalation of antibiotics whenever possible, strict control of the duration of therapy, possibly guided by biomarkers *(23)*, optimized use of the PK/PD properties of the antibiotic, and therapeutic drug monitoring. Such a programme is not easy to implement and is time-consuming. A strong cooperation between intensivists and microbiologists, infectious diseases specialists, pharmacists and nursing teams is fundamental for success. The literature on ABS programmes in ICUs is rich, but unfortunately appropriate studies demonstrating the efficacy of those programmes are still very scarce *(24, 25)*. The available studies are usually monocentric, longitudinal, open, and with historical controls. Randomized studies are necessary, but they are difficult to implement, since it is necessary to randomize units, which may have very different case-mixes. Each element of ABS can be studied in isolation, or the whole bundle can be considered. Other methods like "cycling" or "mixing" have been studied, with controversial results *(26, 27)*. Finally, it is logical to limit the use of antibiotics with a predominant digestive elimination, e.g., ceftriaxone.

2) Infection control programmes

Infection control (IC) represents a key pillar in the fight against AMR, in particular in the ICUs. Preventing the cross-transmission of MDROs must be a daily obsession for each HCP in the ICU, not just the doctors and nurses, but equally, maintenance personnel and visitors. This needs real teamwork, and each member of the team must consider himself or herself as a guardian of IC. There must be dedicated handwashing and disinfection in the unit, in particular for the many consultants, technicians and visitors who "invade" the ICU. There are many IC components to implement in the ICU, and they cannot be detailed in such a short article. But particular attention must be devoted to the care of the skin, the oropharynx, and the rest of the digestive tract in ICU patients. Some specific actions need to be emphasized:

a) Handwashing and disinfection is of paramount importance for every HCP in order to prevent cross-transmission of bacteria, resistant or not, between patients or from patients to the environment via the hands or clothes of HCPs. It has been clearly demonstrated that hand-rub alcoholic solutions are more efficient than soap for most micro-organisms. Global campaigns have been organized in the recent years such as the "Save lives, clean your hands", supported by WHO *(28)*.

b) Screening the patients entering the ICUs to detect MDROs and setting up isolation procedures has been widely used for many years, and is often recommended. Rapid diagnostic methods, in particular for MRSA, may help a lot in this respect. However, the topic remains highly controversial, and much will depend on the local epidemiology. A recent study performed in three European ICUs *(29)* shows that in the context of a high level of hand disinfection and daily antiseptic bathing, screening and isolation was useless in preventing new acquisition of MDROs. Another study *(30)* finds that universal decolonization of the patients was much more effective than screening, isolation and targeted screening (screening, isolation and decolonisation of carriers).

c) Isolation measures are of paramount importance, in particular for MRSA, VRE, carbapenemase-producing bacteria and Acinetobacter spp. among others. In some situations, such as an extensive epidemic outbreak, or in some bacteria (VRE, carbapenemase-producing bacteria) it is necessary to cohort the patients. It is of course labour intensive and costly, but it

is an efficient way to quickly control an outbreak. It might be a way to prevent the occurrence of an endemic in the hospital and the country. The isolation of patients carrying ESBL–procuding enterobacteriaceae is more controversial.

d) Oropharyngeal disinfection with antiseptics is key to reducing the colonization of this organ, including with MDROs, and the risk of pneumonia in ICUs, in particular in ventilated patients (VAP). On top of that, techniques called selective digestive decontamination (SDD) or selective oro-pharyngeal decontamination (SOD) have been studied for many years and are widely used in several countries, in particular, The Netherlands. It consists of applying a paste containing non-absorbable antibiotics (usually polymixin and aminoglycoside) in the oropharynx. For SDD, the same antibiotics are administered in the stomach, and systemic antibiotics are used for three to four days. The two techniques have been shown to decrease the incidence of VAP, and to reduce mortality *(31)*. However, the technique is still very controversial and rarely used in most countries. The main concern here is that SDD or SOD might increase AMR. In fact, surprisingly enough, several very well performed studies have shown that, at least in countries with very low levels of resistance, this resistance was decreased by the two interventions *(32)*. The hypothesis is that the very high levels of non-absorbable antibiotics might prevent the colonization of the oropharynx and the gut with MDROs. In patients receiving SDD, resistance to colistin is stable over years and there is a slow increase in the resistance to aminoglycosides in longitudinal studies *(33, 34)*.

Non-absorbable antibiotics have also been successfully used to treat epidemic outbreaks with MDROs *(35)*.

Additional data and professional consensus is needed, since the use of non-absorbable antibiotics might very well be a very effective way to prevent AMR in ICUs. However, nobody knows what would happen with a broad usage of SDD in countries with a very high level of resistance. A number of large-scale studies are underway and hopefully the role of SOD and SDD will soon be clear.

e) A daily bathing (or cleaning) with antiseptics, in particular chlorhexidine has been shown to decrease colonization with MDROs and hospital-acquired bacteremias, especially with MRSA *(36)*. Although additional studies would have been useful, the technique is now widely used in many ICUs.

f) Special attention should be given to the risk of transmission of bacteria via the faeces during the care of patients, and during the manipulation and cleaning of the basins. Sterile basins must be used, and disposable basins are used in some units.

3) Some other therapies must be explored

FMT has been used successfully in ICU patients when they have developed a very severe colitis due to *Clostridium difficile* *(38)* and in patients with sepsis. It is possible that it could be a way to reconstitute a more normal flora in patients carrying MDROs. No data are available for now on this topic. Probiotics and bacteriocins *(39)* have been also used to modulate gut microbiota in patients with MDROs or recurrent *Clostridium difficile*, but the data are extremely scarce *(40)*. Phage therapy has also been suggested as a potential solution in this setting *(39)*. Methods to extract the genes causing resistance in the bacteria via bacteriophages (CRISPR-Cas nucleases) also look very promising *(41)*.

4) Alternatives to antibiotics

Very few antibiotics have been made available in the last few years and no new antibiotic classes have been developed. Some are in the pipeline, but very few have new mechanisms of action. They will be more than welcome, but alternatives to antibiotics are also another strategy to protect antibiotics and reduce AMR. Unfortunately, very few are available right now. Phage therapy is widely cited in the recent literature, either scientific or lay media, and it is widely used in Russia and Georgia *(39)*. However, there are no randomized studies performed in those countries and the literature remains of very poor quality. A randomized study in patients with infected burns is ongoing. Vaccination is another important way to decrease the prevalence of infectious diseases, and therefore the use of antibiotics. Immunotherapy could help to improve human defences and could be synergistic with antibiotics, but this needs more study. Finally, there are several plants or essential oils which have a powerful antibacterial effect, many of which are used in the traditional medicine, e.g., Chinese medicine. Some of these are currently being studied.

Why is AMR a pressing issue for ICUs around the world?

A recent report from the UK Health Ministry estimates that over the next 35 years, 300 million people will die of AMR infections. It should be expected that – particularly in developed countries – many of these patients will die of severe infections caused by these MDROs in an ICU. This will put a particular burden on the ICU HCPs as it will be hugely challenging to treat AMR infections on the one hand, and prevent the spread to other patients on the other hand. Considering that patients in ICUs are becoming increasingly older, suffer from more, and more severe, comorbidities and may be increasingly more immunocompromised due to more aggressive therapies, the impact of MDRO infections will be enormous, not only in terms of mortality but also in terms of short- and long-term morbidity. This threat of AMR should be incorporated into the planning of financial resources for ICUs in the next decades to allow for appropriate staffing (both in numbers and expertise) as well as other aspects, such as ICU architecture and advanced

care planning for patients with incurable diseases and others.

Conclusion

Intensive care units are epicentres for the emergence and spread of AMR in hospitals. Resistant strains developed in ICUs can be exported to other wards in the hospital, or the community. Antibiotic stewardship and infection control measures are the two pillars of AMR management in ICUs and step-down units, but other methods could very well emerge in the near future. HCP in those units have a unique responsibility in the prevention of AMR, and in the education of other professionals in the hospital. ■

Dr Jean Carlet, MD, is President of the World Alliance Against Antibiotic Resistance (WAAAR). He trained in internal medicine and has been head of the intensive care unit at the Hospital St Joseph in Paris for 25 years. He is Founder and President of the World Alliance Against Antibiotic Resistance (WAAAR) since 2011, which won third prize in the European Union's competition for NGOs active against AMR. In 2015, he was nominated by France's Minister of Health as the President of a Special Task Force for the Preservation of Antibiotics. The Task Force created the national plan and proposed a number of actions to fight against antibiotic resistance. Dr Carlet has published extensively in over a 100 scientific publications on AMR.

Professor Jan De Waele, MD, PhD, is a surgery-trained intensivist with a specific interest in severe infections in critically ill patients. He works at the surgical ICU of the Ghent University Hospital in Belgium. His clinical interests include AMR and antimicrobial stewardship in ICUs. His research activities currently focus on optimizing antibiotic therapy in severely ill infected patients to improve outcomes and combat resistance development. He is active in several societies; he is currently chairing the Infection Section of the European Society of Intensive Care Medicine (ESICM) and is President of the Belgian Society of Intensive Care Medicine.

References

1. Laxminarayan R, Duse A, Wattal C et al. Antibiotic resistance-the need for global solutions. *Lancet Infect Dis.* 2013;13 :1057-98
2. Carlet J, Collignon, Goldmann D et al. Society's failure to protect a precious resource: antibiotics. *Lancet.* 2011 ;378:369-71
3. Carlet J. The gut is the epicentre of antibiotic resistance. *Antimicrobial Resist Infect Control.* 2012;2739: 10.1186/2047-2994-1-39
4. Hanburger H, Arman D, Gill H et al.Surveillance of microbial resistance in European intensive care units: a first report from the Care-ICU programme for improved infection control. *Intensive Care Med.* 2009;35:91-100
5. Vincent JL, Bihari DJ, Suter PM et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European prevalence of infection in intensive care (EPIC) study. EPIC international Advisory Committee. *JAMA.* 1995 ;274:639-44
6. Vincent JL, Rello J, Marshall J et al. International study of the prevalence and outcomes on infection in intensive care units. *JAMA.* 2009 ; 302:2323-9
7. Tabah A, Koulenti, Laupland K et al. Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive cace units : the EUROBACT international cohort study. *Intensive care Med.* 2012;38:1930-45
8. Molstad S, Herntell M, Hanberger H et al. Sustained reduction of antibiotic use and low bacterial resistance : 10-year follow-up of the Swedish STRAMA programme. 2008;8:125-32
9. Grundmann H, Glasner C, Albiger B et al. Occurence of carbapenemase-producing Klebsielle pneumoniae and Escherichia coli in the european survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE) : a prospective, multinational study. *Lancet Infect Dis.*2017;17:153-163
10. EARS-net: http://ecdc.europa.eu/en/healthtopics/antimicrobial-resistance-and-consumption/antimicrobial_resistance/EARS-Net/Pages/EARS-Net.aspx. Visited march 5,2017
11. Logan LK, Braykov NP, Weinstein RA. Extended-spectrum Beta-lactamase-producing and third-generation cephalosporin-resistant Enterobacteriaceae in children : trends in the United States,1999-2011. *J Pediatric Infect Dis Soc.* 2014;3:320-8
12. Logan LK, Renschler JP, Gandra S et al. Carbapenem-resistant enterobacteriaceae in children, United States,1999-2012. *Emerg Infect Dis.*2015;21:2014-21
13. Gandra S, Mojica N, Klein EY et al. Trends in antibiotic resistance among major bacterial pathogens isolated from blood cultures tested at a large private laboratory network in India, 2008-2014. *Int J Infect Dis.* 2016;50:75-82.
14. Hammami S, Dahdeh C, Mamlouk K et al. Rectal carriage of extended-spectrum Beta-lactamases and carbapenemase producing Gram-negative bacilli in intensive care units in Tunisia. *Microb Drug resist.* 2017;10 .1089/mdr.2016.0205 (epub ahead of print)
15. Oteo J, Alcaraz R, Bou G et al. Rates of faecal colonization by carbapenemase-producing Enterobacteriaceae among patients admitted to ICUs in Spain. *J Antimicrob Chemother*. 2015 ;70:2916-8
16. Hurley JC. World-wide variation in incidence of Acinetobacter associated ventilator associated pneumonia: a meta-regression. *BMC Infect Dis.* 2016 ; 16:577
17. Nordmann P, Poirel L. The difficult-to- control spread of carbapenemase producers among Enterobacteriaceae worldwide. *Clin Microbiol Infect.* 2014 ; 20:821-30
18. Bourdon N, Fines-Guyon M, Thiolet JM et al. Changing trends in vancomycin-resistant enterococci in French hospitals,2001-2008. *J Antimicrob Chemother.* 2011;66:713-21
19. Dimopoulos G, Koulenti D, Tabah A et al. Bloodstream infections in ICUs with increased resistance : epidemiology and outcomes. *Minerva Anestesiol.* 2015;81:405-18
20. Yu H, QU F, Shan B et al. Detection of mcr-1 colistin resistance gene in carbapenem-resistant enterobacteriaceae from different hospitals in China. *Antimicrob Agents Chemother.* 2016;60:5033-5
21. Kollef MH, Bassetti M, François B et al. The intensive care medicine research agenda on multi-resistant bacteria, antibiotics, and stewardship. *Intensive Care Med.* 2017;10.1007/s134-017-4682-7 (epub ahead of print).
22. Bretonniere C, Leone M, Milesi C et al. Strategies to reduce curative antibiotic therapy in intensive care units (adult and paediatric). *Intensive Care Med.* 2015;41:1181-96
23. de Jong E, van Oers JA, Beishuizen A et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients : a randomized, controlled,open-label trial. *Lancet Infect Dis.* 2016;16:819-27
24. Singh S, Zhang YZ, Chalkley S et al. A three-point time series study of antibiotic usage on an intensive care unit, following an antibiotic stewardship programme, after an outbreak of multi-resistant Acinetobacter baumanii. *Eur J Clin Microbiol Infect Dis.* 2015;34:1893-900
25. Perez KK, Olsen RJ, Musick WL et al. Integreting rapid diagnostics and antibiotic stewardship improves outcomes in patients with antibiotic-resistant Gram-negative bacteremia. *J Infect.* 2014 ; 69:216-25
26. Merz LR, Warren DK, Kollef MH, Fraser VJ. Effects of antibiotic cycling program on antibiotic prescribing practices in an intensive care unit. *Antimicrob Agents Chemother.* 2004;48:2861-5
27. Warren DK, Hill HA, Merz LR et al. Cycling empirical antimicrobiol agents to prevent emergence of antimicrobial-resitant Gram-negative bacteria among intensive care patients. *Crit Care Med.* 2004 ;32:2450-6
28. Pittet D, Allegranzi B, Boyce J. World Health organization World Alliance for Patient safety first global patient safety challenge core group of experts. *Infect Control Hosp Epidemiol.* 2009;30:611-22
29. Derde LP, Cooper BS, Goosens H et al. Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units : an interupted time series study and cluster randomized trial. *Lancet Infect Dis.* 2014;14:31-9
30. Huang SS, Septimus E, Kleinman K et al. Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med.* 2013;368:2255-65
31. Oostdijk EA, Kesecioglu J, Schulz MJ et al. Effects of decontamination of the oropharynx and intestinal tract on antibiotic resistance in ICUs : a randomized clinical trial. *JAMA.* 2014;312:1429-37
32. Daneman N, Sarwar S, Fowler RA, Cuthbertson BH; suDDICU Canadian Study Group. Effect of selective decontamination on antimicrobial resistance in intensive care units : a systematic review and meta-analysis. *Lancet Infect Dis.* 2013;13:328-41
33. Oostdijk EA, Smits L, de Smet AM, Leverstein-van Hall MA, Kesecioglu J, Bonten MJ. Colistin resistance in Gram-negative bacteria during prophylactic topical colistin use in intensive care units. *Intensive Care Med.* 013;39:653-60

References continued

34. Wittekamp BH, Oostdijk EA, de Smet AM, Bonten MJ. Colistin and tobramycin resistance during long-term use of selective decontamination strategies in the intensive care unit : a post hoc analysis. *Crit Care.* 2015;25:113 doi 10 . 1186/s 13054-015-0838-4
35. Brun-Buisson C, Legrand P, Rauss A et al. Intestinal decontamination for control of nosocomial multi-resistant negative bacilli. Study of an outbreak in an intensive care unit. *Ann Intern Med.* 1989;110:873-81
36. Climo MW, Yokoe DS, Warren DK et al. Effect of daily chlohexidine bathing on hospital-acquired infection. *N Engl J Med.* 2013;368:533-42
37. Wei Y, Yang J, Wang J, Yang Y, Huang J et al. Successful treatment with fecal microbiota transplantation in patients with multiple organ dysfunction syndrome and diarrhea following severe sepsis. *Crit Care.* 2016;20:332
38. Hans S, Shannahan S, Pellish R. Faecal microbiota Transplant : Treatment options for Clostridium difficile infection in the intensive care unit. *J Intensive Care Med.* 2016;31:577-86
39. Rea MC, Alemayehu D, Foss RP, Hill C. Gut solutions to a gut problem: bacteriocins, probiotics and bacteriophage for control of Clostridium difficile infection. *J Med Microbiol.* 2013;62:1369-78
40. Crouzet L, Rigottier-Gois L, Serror P. Potential use of probiotic and commensal bacteria as non-antibiotic strategies against vancomycin-resistant enterococci. FEMS Microbiol Lett. 2015;362(8):fnv012.doi:1093/femsle/fn012 ; epub 2015 Feb8
41. Bikard D, Euler CW, Jiang W et al. Exploiting CRISPR-Cas nucleases to produce sequence-specific antimicrobials. *Nat Biothechnol.* 2014;32:1146-50